COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) IN CANCER

An Evidence-Based Systematic Review of the Efficacy and Safety of CAMs, and the Perceived vs Real Benefits of CAM Use for the Quality of Life and Psychological Adjustment of Cancer Patients Undergoing Cytotoxic Treatment

by

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This thesis is presented for the degree of

Doctor of Philosophy

of

Murdoch University

2014
I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary institution.

........................................

Carlo Pirri
COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) IN CANCER

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ABSTRACT

Complementary and alternative medicine (CAM) continues to evoke fierce debate and divergent views within the medical community. Nevertheless, it remains an attractive and commonly used treatment option for many cancer patients regardless of whether their doctors like it or believe in it. Complementary medicine is used by 14-65% of Australian adult cancer patients (up to 73% in Europe and 91% in the US), and alternative medicine by 8-14%. It is therefore important that clinicians have an awareness of the type of patients that are likely to use CAM, as well as a good understanding of the levels of evidence available for the efficacy and safety of specific complementary and alternative therapies. Two large studies were performed to this end.

Study 1 examined the incidence and type of complementary therapy (CT) use, perceived benefits of use, and the relationship between demographic, clinical or quality of life/psychological factors and use in 200 Australian cancer patients across conventional chemotherapy-based treatment. Overall, 30% of patients reported CT use. CT users were predominantly younger, tertiary educated, possessed comorbid conditions and underwent...
lengthy treatment (.004 ≥ \( p \leq .023 \)). Patients who underwent lengthy treatment (> 6 months) were 3 times more likely to use complementary therapies. Of all CT users, 64% perceived benefit and primarily cited enhanced physical and emotional well-being. CT users, however, did not score significantly better than non-users on any measure of quality of life, physical health or psychological adjustment. CT users generally reported greater psychological distress than non-users across treatment, particularly at pretreatment (baseline). However, with ongoing/new CT use these patients significantly reduced their distress levels to that of non-users by 8 weeks on-treatment (\( p = .042 \)).

Study 2 entailed a systematic review of the benefits and health risks of popular CAMs used by cancer patients. Specifically, the efficacy and safety of over 50 individual CAMs were examined across 363 publications, including over 300 meta-analytic/systematic reviews. Evidence indicated that some CTs are beneficial in reducing disease/treatment symptoms and improving quality of life and psychological adjustment (e.g. relaxation), and in years to come may be integrated into everyday clinical practice. Evidence of potential harm, however, also exists. Nutritional supplements, herbal preparations and other natural therapies may pose direct safety risks because of their potential adverse effects or interactions with conventional anticancer treatments and other medications. Some should not be used by cancer patients under any circumstances irrespective of benefit (e.g. St. John’s wort), while others are beneficial and safe under medical supervision (e.g. valerian). Alternative therapies promoted as “cures” in place of conventional treatments (e.g. laetrile/amygdalin) potentially cause patients the most harm.

Collectively, the studies demonstrated that CTs, at the very least, may enhance the psychological well-being of cancer patients during the early stages of conventional medical treatment. Indeed, CT use by cancer patients may be a clinical marker for psychological
distress, and should trigger clinicians to enquire about physical symptoms and concomitant anxiety and depression. Research, however, indicates that 20-77% of patients do not disclose CAM use to their physicians. Moreover, discussions about CAM are uncommon and are most likely to be initiated by patients rather than physicians, many of whom believe that they cannot effectively communicate with patients about CAM use partly due to having insufficient knowledge about the efficacy and safety of specific CAMs. Patients’ perceptions that CAMs are more “natural” and safer than conventional treatments are problematic. Indeed, they may pose direct safety risks. It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate CAMs, in order to receive benefit while avoiding harm. Additionally, clinicians are strongly encouraged to routinely ask patients about CAM use. Offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments in cancer services can influence patients’ decisions to continue with mainstream care, and help avoid any potential harm that may occur with autonomous CAM use.

Keywords: cancer, complementary and alternative medicine / therapies, quality of life, psychological distress, anxiety, depression, psycho-oncology, cancer treatment, cytotoxic, chemotherapy, radiotherapy, surgery, efficacy, safety, adverse events / effects, drug interactions, systematic review
ACKNOWLEDGEMENTS

There have been many people who have been significant in my long PhD journey – far too many to list individually – but know this, I am grateful for your involvement in my journey and I thank each and every one of you.

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I would like to express my deepest gratitude to the cancer patients and staff at Medical Oncology, Royal Perth Hospital, who made my research possible. Thank you to all the patients who selflessly took the time to complete questionnaires and share the most intimate details of their lives, in the full knowledge that it would not directly benefit them, and during what had to be one of the most difficult and uncertain periods of their existence. You have touched my life immeasurably and I will never forget how much I learned from you all.
I would also like to acknowledge my colleagues and friends at Murdoch University, Royal Perth Hospital, WA Clinical Oncology Group, Cancer Council WA, the Clinical Oncology Society of Australia and Roche Australia, for assisting with the research and providing research/conference funding. I would especially like to thank Lorna Rogers (ex-Roche), Paul Katris (WACOG), Terry Slevin (CCWA), Lawrie Wright (ex-COSA) and Marie Malica (COSA) for their ongoing financial support of the research itself and related conference travel over the years. To Prof. Ian Olver (Cancer Council Australia) and Dr Monica Robotin (Cancer Council NSW), thank you dearly for your invitation to contribute to the CAM in cancer publications in 2011/12 and for your great patience, editorial assistance and mentoring in that time. To the anonymous and third-party reviewers of the publications included in this thesis, thank you for your thoughtful, invaluable critiques and insights. To Prof. Phyllis Butow, Prof. Madeleine King, Dr Angela Ebert, Francis Lee, Man Trac, Jenny Edmonds, Karen Olkowski, Prof. Laurence Hartley and A/Prof. David Leach, thank you for your collegiality and kindness.

To my Murdoch office mates, old and new (Doug, Gaynor, Renee, Steve, Susanne, Gerald, Don, Mei’en, Cath, Eva, Rachael, Lisa, Marie, Anita, Melanie, Alice; Sarah, Corey, Stuart, Rob, Jacquie, Cathy, Olga, Matthew, Nick, Aries), thank you for the camaraderie, friendship and fun memories. Special mentions also go to Khristin Highet (yes, we finally made it!), Caroline Wallis, Beth Gouldthorp, Marco Sturniolo, Lorenz Mattaboni, Bernie O’Hara, George Rebelos, Tony Loretto (RIP) and all my old UWA friends (Dan, Elysia, Jason, Debs, Pete, Michelle, Geoff, Carrie, Jez, Evelina) for their unique brand of moral support, humour and friendship that kept me sane in the final, gruelling stages of my PhD.

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On a parting note, I would like to share with you a collection of quotations that inspired, motivated and otherwise cajoled me towards the finishing line of my long PhD journey:

‘Do not judge me by my successes, judge me by how many times I fell down and got back up again.’

‘The greatest glory in living lies not in never falling, but in rising every time we fall.’

‘I learnt that courage was not the absence of fear, but the triumph over it. The brave man is not he who does not feel afraid, but he who conquers that fear.’

‘It always seems impossible until it’s done.’

— Nelson Mandela, from “Nelson Mandela by Himself” (published 2010) and his autobiography “Long Walk to Freedom” (published 1994)

‘A certain degree of neurosis is of inestimable value as a drive, especially to a psychologist.’

— Sigmund Freud, from “Fragments of an Analysis with Freud” (published 1935)

‘The world ain’t all sunshine and rainbows. It is a very mean and nasty place and I don’t care how tough you are, it will beat you to your knees and keep you there permanently if you let it. You, me or nobody is going to hit as hard as life. But it ain’t about how hard you hit, it is about how hard you can get hit and keep moving forward. How much you can take and keep moving forward. That’s how winning is done!’

— Rocky Balboa, from “Rocky Balboa” (film, 2006), written by Sylvester Stallone

‘No. Try not. Do….or do not. There is no try.’

— Yoda, from “Star Wars-The Empire Strikes Back” (film, 1980), written by George Lucas

‘If you can’t explain it simply, you don’t understand it well enough.’

— Albert Einstein / Anonymous, source unknown

‘As to diseases, make a habit of two things — to help, or at least to do no harm.’

— Hippocrates, from “Epidemics” (Book I, Section XI, written circa 400 B.C.)
LIST OF ORIGINAL PUBLICATIONS

The present thesis comprises the following peer-reviewed publications:


Note on Original Publications

Citations 2-5 above were invited publications that stemmed from conference presentations and related media releases (see page overleaf).

Notes on Formatting and Style

This PhD thesis comprises a number of research publications. The original formatted manuscripts of these publications are reproduced in the thesis chapters that follow in the form in which they were accepted following peer review, and are incorporated into this thesis along with additional text that has been provided to introduce and link together the published works. Consequently, there may be a small degree of repetition and some minor inconsistencies in Anglo/American orthography across the thesis. Nevertheless, it is hoped that the final collated body of work that forms the present PhD thesis represents a cohesive body of research, one which can be readily followed by audiences of various expertise on the subject matter globally.

Notes on Terminology

The terms “doctor” and “physician” are used interchangeably throughout this PhD thesis, often referring to (cancer) specialists and general practitioners alike. In contrast, (cancer) specialists per se are usually referred to as “clinicians”, “cancer physicians” or “oncologists”. Nonetheless, readers should be mindful of the context in which all these terms are used to avoid any uncertainty.
### LIST OF ORAL PRESENTATIONS / SEMINARS


**Note on Oral Presentations / Seminars**

Citations 1, 4 and 6 above relate to an invited conference presentation and two educational seminars that were delivered to oncology health professionals and/or cancer patients.


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Popular CAM Approaches and Evidence for Use

Whole Medical Systems

Homeopathy

Naturopathy

Traditional Chinese Medicine

Mind-Body Techniques

Relaxation

Meditation

Hypnotherapy

Yoga

Tai Chi

Music Therapy

Support Groups

Spirituality, Religion and Prayer

Biologically-Based Practices

Nutritional Supplements (Dietary/Food Supplements)

Antioxidants

Omega-3 Fatty Acids (n-3 Polyunsaturated Fatty Acids)

Shark Cartilage and AE-941 (Neovastat)

Laetrile and Amygdalin (Vitamin B17)

Chinese Herbal Medicine

Astragalus (Astragalus Membranaceus/Mongolicus/
Propinquus, Radix Astragali)

Ginseng (Panax Ginseng/Quinquefolium, Eleutherococcus
Senticosus, Angelica Sinensis)

Ginger (Zingiber Officinale)

Lingzhi / Reishi Mushroom (Ganoderma Lucidum/
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Cancer Physicians’ Concerns and Attitudes Regarding CAM

Efficacy and Safety of CAM

Future Research in CAM and Establishing Research Priorities

Integrative Cancer Care in Australia Today

Integrating Complementary Medicine into Mainstream Cancer Care: Bridging the Gap Between Patients and Doctors and Making the Move from CAM Toward Integrative Oncology

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Methodology (Study 1)

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Study overview
LIST OF ABBREVIATIONS

μg microgram
admin. administration
AE-941 Neovastat®
AIDS acquired immune deficiency syndrome
ALA alpha-linolenic acid
AO antioxidant
BDI-SF Beck Depression Inventory Short Form
BP blood pressure
CAM complementary and alternative medicine
CAT complementary and alternative therapy
chemo chemotherapy
CHM Chinese herbal medicine
CINV chemotherapy-induced nausea and vomiting
COPD chronic obstructive pulmonary disease
COSA Clinical Oncology Society of Australia
CNS central nervous system
CRC colorectal cancer
CRF cancer-related fatigue
CT complementary therapy
CV cardiovascular
CYP cytochrome P-450
CYP450 cytochrome P-450 enzyme
DHA docosahexaenoic acid
EF Emotional Functioning (EORTC QLQ-C30 subscale)
EGCG epigallocatechin gallate
EGFR-TL epidermal growth factor receptor tyrosine-kinase
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
EPA eicosapentaenoic acid
EPO evening primrose oil
EPQ-R Eysenck Personality Questionnaire—Revised
esp. especially
FDA Food and Drug Administration (US)
g gram
G6PD glucose-6-phosphate
GABA gamma-aminobutyric acid
GH global health
GI gastrointestinal
GLA gamma-linolenic acid
HIV human immunodeficiency virus
HIV/AIDS human immunodeficiency virus / acquired immune deficiency syndrome
ICSG internet cancer support group
IES-IS Impact of Event Scale–Intrusion Subscale
incl. including
ISG internet support group
iv intravenous
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MJA</td>
<td>Medical Journal of Australia</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MASCC</td>
<td>Multinational Association of Supportive Care in Cancer</td>
</tr>
<tr>
<td>MBSR</td>
<td>mindfulness-based stress reduction</td>
</tr>
<tr>
<td>NCCAM</td>
<td>National Center for Complementary and Alternative Medicine (US)</td>
</tr>
<tr>
<td>NICM</td>
<td>National Institute of Complementary Medicine (Australia)</td>
</tr>
<tr>
<td>no.</td>
<td>number</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NSCLC</td>
<td>non-small lung cell cancer</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council (Australia)</td>
</tr>
<tr>
<td>PH</td>
<td>Physical Health Uniscale</td>
</tr>
<tr>
<td>PMR</td>
<td>progressive muscle relaxation</td>
</tr>
<tr>
<td>PTSD</td>
<td>post-traumatic stress disorder</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire– Core 30</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>r</td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SCGH</td>
<td>Sir Charles Gairdner Hospital (Western Australia)</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SF</td>
<td>short form</td>
</tr>
<tr>
<td>SJW</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>SPANOVA</td>
<td>split-plot analysis of variance</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin and noradrenaline reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCM</td>
<td>traditional Chinese medicine</td>
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Chapter 1: Complementary and Alternative Medicine Use by Adult Cancer Patients – An Overview

1.1 Introductory Overview and Literature Review

A summary overview detailing the aims and hypotheses of the present thesis and how they are related in the chapters that ensue is presented first (see section 1.2). It is followed by a general overview and literature review for the area of complementary and alternative medicine in cancer underwent peer review, which was published as an invited book chapter in the edited publication, Perspectives on Complementary and Alternative Medicine. The manuscript in the form in which it was published is presented (see p6).

Original Publication

1.2 Summary Overview and Research Aims

Like it or not? Believe in it or not? The simple fact is that the majority of cancer patients will use at least one CAM following diagnosis. In a recent Australian study, two in three people (67%) with cancer used at least one type of complementary therapy (CT) during or after their cancer treatment (Oh et al., 2010). Results from other Australian studies have ranged widely from 14-89% (Wilkinson & Stevens, 2014; Kremser et al., 2008; Sibbritt, Adams, Easthope, & Young, 2003; Correa-Velez, Clavarino, Barnett, & Eastwood, 2003; Begbie, Kerestes, & Bell, 1996). Differences may be due to the methodology (e.g. small sample sizes; most studies are cross-sectional rather than longitudinal and report lower prevalence of use; Horneber et al., 2012; Ernst & Cassileth, 1998), types of CTs included in studies (e.g. those that included prayer and exercise in their definitions of CAM reported higher use, while those that restricted CAM use to certain categories reported lower use; Horneber et al., 2012; Ernst & Cassileth, 1998), or the type of cancer population focused upon (e.g. breast cancer; palliative, elderly or regional populations; Ernst & Cassileth, 1998). Consequently, the purpose of study 1 in the present thesis was to reconcile some of the differences found in previous Australian studies (and those elsewhere) by examining CAM use across cancer treatment and during cancer survival via a prospective, longitudinal, observational study spanning the length of conventional anticancer treatment and acute survival (6 months). Specifically, the aim was to assess the “real world” incidence (or period prevalence) of CT use among cancer patients receiving chemotherapy-related treatment (i.e. chemotherapy ± surgery and/or radiotherapy) in a routine clinical setting. Additionally, the type of CTs used, perceived benefits of use, and the relationship between demographic, clinical or quality of life/psychological factors and CT use were examined (see chapter 2).

No CAM has reliably cured or suppressed any form of cancer thus far (e.g. Deng et al., 2009). Unsurprisingly, this is why doctors generally do not believe in CAM. Doctors believe in scientific evidence, which is the foundation of modern medicine. Patients, however, believe in CAM because they want to believe, they need to believe, in order to maintain hope and feel a sense of empowerment over their own health at a time where they have such little control over the surgery, radiotherapy, chemotherapy and other conventional medical treatments they are being subjected to. Despite generally understanding the meaning of scientific evidence and making use of it in some instances, the basis for cancer patients’ beliefs is more commonly non-scientific (e.g. patient
testimonials, anecdotes from family or friends, expert opinion from general practitioners and pharmacists, the internet and other popular media, gut feelings; Verhoeef, Trojan, Armitage, Carlson, & Hilsden, 2009; White, Verhoeef, Davidson, Gunn, & Cooke, 2008; Verhoeef, Mulkins, Carlson, Hilsden, & Kania, 2007; Pihlak et al., 2014), and is often considered by patients to be as valuable as scientific proof (Verhoeef et al., 2007).

When the patient does not receive positive news or encouragement from his or her doctor, he or she is likely to resort to other sources such as CAM to maintain hope and may withhold this information from their physicians. Indeed, 20-77% of patients do not disclose CAM use to their oncologists (Davis, Oh, Butow, Mullan, & Clarke, 2012). Moreover, discussions about CAM are uncommon and are most likely to be initiated by patients rather than oncologists, many of whom believe that they cannot effectively communicate with patients using CAM partly due to having insufficient knowledge about the efficacy and safety of specific CAMs (Roberts et al., 2005; Hann, Baker, & Denniston, 2003; Schofield, Juraskova, & Butow, 2003; Newell & Sanson-Fisher, 2000; Trimborn et al., 2013). Patients’ beliefs that CAMs are more “natural” and safer than conventional treatments are problematic also. Undeniably, they may pose direct safety risks because of their potential adverse effects or interactions with conventional oncology treatments (e.g. Deng et al., 2009). Alternative therapies promoted as “cures” in place of conventional treatments have the potential to cause patients the most harm, however, when they forego evidence-based cancer treatments that are likely to be more effective. It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies, and be aware of interactions with conventional anticancer therapies, in order to increase the likelihood that patients avoid harm and, where possible, receive benefit should they choose to use CAM. To this end, the purpose of study 2 in the present thesis was to perform a systematic review evaluating the efficacy and safety of several popular CAMs, with a view to increasing the knowledge base of oncologists and associated health professionals and therefore improve the overall care of cancer patients (see chapter 3).
References


Chapter 22

Complementary and Alternative Medicine Use by Adult Cancer Patients: An Overview

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Running Head: CAM Use by Cancer Patients

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Abstract

Complementary and alternative medicine (CAM) continues to evoke fierce debate and divergent views within the medical community, yet complementary medicine is used by 14% to 65% of Australian adults diagnosed with cancer (with estimates as high as 80% to 91% in the US and Europe) and alternative medicine by 8% to 14%. Cancer patients who use CAM are typically female, younger, better educated, and of higher socioeconomic status. While surgery, chemotherapy and radiotherapy have proven increasingly successful but still have limited curative potential, these conventional approaches are generally more invasive, aggressive, and associated with toxicities than CAMs, and tend to take a slower, gentler approach by attempting to bolster constructive forces (e.g. the immune system) rather than battling the destructive forces of growing cancer cells. They focus on symptom control and patients are generally encouraged to be active participants in the management of their illness. This patient-centred approach, which is more easily accessible, contributes to the appeal of CAM. Many CAMs, however, have drawn steadfast opposition from cancer physicians, primarily because they remain unproven in clinical trials and pose potential safety risks and financial or psychological harm of CAM use to their patients. Research indicates that 33% to 77% of patients do not disclose CAM use to their physicians, often because of a perceived negative response. The perception that CAMs are more “natural” and, by association, safer than conventional treatments is problematic. Indeed, they may pose direct safety risks because of their potential adverse effects or interactions with conventional oncology treatments. Alternative therapies promoted as “cures” in place of conventional treatments have the potential to cause patients the most harm. It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies, and be aware of interactions with conventional anticancer therapies, in order to increase the likelihood that patients avoid harm and, where possible, receive benefit should they choose to use CAM.

Key Words: complementary and alternative medicines, interactions, natural
1. Introduction

Complementary and alternative medicine (CAM) continues to evoke fierce debate and divergent views within the medical community. It remains an attractive and commonly used treatment option for many cancer patients, regardless of whether their clinicians like it or believe in it. Consequently, it divides health professionals providing conventional cancer care and CAM practitioners offering unconventional care.

2. Background

2.1 Definitions

The US National Institutes of Health’s National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as ‘a group of diverse medical and health care systems, practices and products that are not presently considered part of conventional medicine’. Complementary and alternative therapies must be distinguished, however. “Complementary therapies” are adjuncts to conventional medical treatment increasingly perceived as an important part of supportive care; they are often used for symptom management and to enhance quality of life (QoL) and overall patient care. “Alternative therapies”, in contrast, are clinically unproven and are used instead of conventional treatments. This is particularly damaging for cancer patients, as delay or outright refusal of conventional treatment often compromises their likelihood of cure or remission. More recently, the term “integrative oncology” has emerged and involves a standard of care for cancer patients that utilises safe, evidence-based complementary therapies in conjunction with conventional anticancer treatments via a multidisciplinary approach designed to evaluate and treat the whole person rather than the disease per se.

2.2 Prevalence and cost of complementary and alternative medicine (CAM) use

In 2004, an estimated 52.2% of the Australian population used CAM, which was at least equivalent to prescription drug use and cost AUD$1.8 billion (approximately four times the public contribution to the Pharmaceutical Benefits Scheme). More recent surveys in 2005/06, however, revealed a significant increase in prevalence to an estimated 67% and out-of-pocket spending of AUD$4.13 billion, with as many visits being made to CAM practitioners as medical practitioners (approximately 68 million each).
CAM use is quite prominent in oncology, with prevalence often being higher in cancer patients than in the general and other chronic disease populations.\textsuperscript{11-15} In adult cancer patients, a systematic review of 21 studies worldwide reported an average prevalence of CAM use of 31.4\% (range: 7-64\%),\textsuperscript{16} while a more recent European survey of 13 countries found an average prevalence of 35.9\% (range: 14.8-73.1\%).\textsuperscript{17} Other studies report even higher prevalence, depending on CAM definitions used and cancer populations studied. For instance, the 2002 Datamonitor Survey encompassing the US and Europe revealed 80\% prevalence amongst adult cancer patients,\textsuperscript{18} while 91\% of US patients reported CAM use (including prayer and exercise) during treatment in another study.\textsuperscript{19} In Australia, CAM use by cancer patients has varied widely from 14.5\%\textsuperscript{20} to 65\%.\textsuperscript{21} More specifically, 22-52\% of medical oncology,\textsuperscript{21-24} 40\% of palliative,\textsuperscript{25} and 46\% of paediatric oncology patients\textsuperscript{26} report CAM use.

3. CAM Use by Cancer Patients

3.1 Profile of CAM users

Studies have consistently shown that cancer patients who use CAM are typically female, younger, better educated, and of higher socioeconomic status than those who do not.\textsuperscript{2,17,24,27-29} This mimics the basic trend observed in the general population.\textsuperscript{30} CAM use is also associated with being married,\textsuperscript{31} medical comorbidity,\textsuperscript{24} advanced cancer,\textsuperscript{31-33} longer disease/treatment,\textsuperscript{24,28} greater symptoms,\textsuperscript{31,87} psychosocial distress and poor QoL,\textsuperscript{24,27,33} and engaging in self-help groups and other active coping strategies.\textsuperscript{32-35}

3.2 Attraction of cancer patients to CAMs and the motivation to use them

The underlying philosophy of most CAMs primarily focuses on health and improving well-being, (e.g. [Cohen et al]) rather than on the disease itself.\textsuperscript{36} Conventional treatments are generally invasive and aggressive, while CAMs tend to take a slower, gentler approach, by attempting to bolster constructive forces (e.g. the immune system), rather than battling the destructive forces of growing cancer cells. Patients are generally encouraged to be active participants in the management of their illness, as opposed to being passive spectators in the case of taking prescribed medical treatment. These ingredients culminate in a highly empowering holistic treatment approach that is tailored to patients and preserves a sense of hope, which makes CAM, like the patient-centred approach \textit{per se}, very attractive.
There are many reasons why cancer patients use CAM. Common reasons include cancer cure or prolongation of life; relief from cancer symptoms and conventional treatment side-effects; to assist conventional treatments; boosting immunological function or energy; enhancing physical, emotional and spiritual well-being, and maintaining a sense of control or hope. Other motivations for patients to use CAM include perceptions that CAMs are natural/non-toxic, beneficial and, at worst, will do no harm; strong encouragement from family, friends, other cancer patients/survivors and the media; congruence with cultural values and beliefs; poor prognosis resulting in limited conventional treatment options; strengthening the body to cope with limited conventional treatments in surgery, chemotherapy and radiotherapy; improving QoL; to prevent recurrence following conventional treatment; high accessibility of CAMs (e.g. due to non-prescription or self-referral); greater individual attention from CAM practitioners; dissatisfaction with some aspects of conventional medical care; and a poor doctor-patient relationship.

4. Patient-Clinician Communication and Decision-Making

4.1 Concerns and attitudes of cancer physicians relating to CAM use

Conventional treatments do not always relieve cancer symptoms adequately, nor do prescribed medications provide total coverage against their side-effects. Some CAMs (e.g. acupuncture, relaxation, massage) have received medical endorsement for use as complementary therapies alongside conventional treatments, due to their proven efficacy in relieving disease symptoms/treatment side-effects or enhancing QoL/psychosocial functioning, as well as the minimal health risks they pose to patients. Other CAMs (e.g. herbs, nutritional supplements, antioxidants), however, have drawn steadfast opposition from oncologists, primarily because they remain unproven in clinical trials (particularly as curative alternative therapies replacing conventional treatments); possessing greater health risks due to adverse interactions with prescribed cancer treatments or medications (e.g. CAM-drug interactions, surgical complications such as bleeding); and as they may delay or reduce the efficacy of conventional treatments such as chemotherapy and radiotherapy and, subsequently, compromise the likelihood of cure/remission and shorten survival time. Additionally, concerns are held that CAMs may inflict financial or psychological harm (e.g. by creating false hope in medically hopeless situations);
precipitate the abandonment of conventional treatment; lead patients to confuse a physician's willingness to discuss and support their decision to use CAMs with actual medical support for them; and result in litigation against physicians in instances of failure if they (appear to) advocate CAM use.58

4.2 Disclosure of CAM use by patients and barriers to open communication between cancer physicians and their patients about CAM

Despite the empirical benefits of some CAMs and greater endorsement of their use as complementary therapies, support is far from universal17 with many oncologists exhibiting dismissive attitudes and negative views towards them.59 Indeed, while one study revealed that cancer patients expected their physicians to be supportive, caring, accepting and non-judgmental about CAM use and to inspire a sense of hope in them,60 several studies have demonstrated that the reality is frequently different.

Oncologists consistently underestimate their patients’ use of CAM.61,62 Discussions about CAM are also uncommon and most likely to be initiated by patients, rather than physicians.63-65 Research has shown that 33-77% of patients do not disclose CAM use to their physicians,66 with one Australian study reporting that 40% of cancer patients did not inform their oncologist.22 Another study has revealed that only 54% of cancer patients disclosed CAM use to their doctor, while medical treatments were discussed with their CAM practitioner in 94% of instances.67 Patients do not tell their doctors for several reasons, including anticipation of a negative response to their CAM use (e.g. fears that physicians will discontinue their health care, will not support their CAM use, or try to dissuade them from using CAM);66-69 the belief that it is unimportant for physicians to know due to perceptions that CAM is entirely natural and safe and irrelevant to the course of conventional treatment;67 perceived inability or unwillingness of physicians to provide useful information about CAM due to inadequate training or bias against CAM use;67 physicians simply not asking about CAM use or appearing disinterested (35% of patient attempts to initiate CAM discussions were ignored by oncologists in one Australian study);66-69 physicians’ emphasis on scientific evidence;69 and patients’ uncertainty about the benefits of CAM.68

Although cancer patients typically do not inform their physicians about their CAM use, patients and their doctors report that it usually enhances their relationship when it is being
discussed and patients exhibit greater satisfaction and treatment compliance. Nevertheless, few oncologists feel comfortable discussing CAM with their patients, with one survey of 291 oncology health professionals revealing that only 34% thought they could effectively communicate with patients using CAM and 42% believing that they lacked the skills to help patients maintain hope. In another survey, cancer physicians and nurses were significantly less likely to instigate CAM discussions with patients than social workers.

Many CAM studies have examined patient perspectives, but few have investigated the barriers to effective communication from oncologists’ viewpoints. Major obstacles to physicians initiating such discussions with patients include the lack of proven efficacy for many individual CAMs in clinical trials, limited time for patient consultations, and a lack of knowledge of specific CAMs (including benefits and adverse effects) preventing them from sufficiently addressing patient questions or concerns. Indeed, an Australian study of 161 oncologists reported self-identified gaps in their knowledge of CAMs used by some patients, and highlighted the need for including education about them in medical training in order to provide adequate advice to patients. Other barriers to effective physician-patient communication about CAM also include limited physician resources for patient referral (e.g. information about qualified CAM practitioners, knowledge of CAM practitioner specialties), and distrust of CAM practitioners to educate them about non-biomedical therapies.

4.3 Making the decision to use CAM alongside conventional anticancer treatment and the information sources and types of evidence used by patients to make such decisions

Cancer patients may make the decision to use CAM upon diagnosis, during conventional treatment, in response to disease progression or recurrence, or during remission/survivorship. In contrast to information needs and decision-making for conventional treatments, relatively little is understood about how information is utilised and evaluated by cancer patients in their decisions about whether to use CAM and which therapies to undertake. The decision to use CAM is a highly personal and individual one (as patients differ in their perceptions of the benefits and risks of available treatment options), and is complex and dynamic in nature.
CAM decisions are influenced throughout the cancer experience by a number of demographic, disease-related psychological and social factors, many of which have been discussed above. Several decision-making models describing the complex interaction between these factors and the cognitive processes underpinning decision-making have evolved from CAM research that has predominantly involved breast and prostate cancer patients. A recent qualitative review of such studies has identified four main stages within the CAM decision-making process of cancer patients: (1) taking stock of treatment options, (2) gathering and evaluating CAM information, (3) making a decision, and (4) revisiting the decision (Figure 1).

Figure 1. Factors involved in the decision-making process utilised by cancer patients to use CAM. Used with publisher’s permission from ‘‘Patient decision-making about complementary and alternative medicine in cancer management: context and process’’ by Lynda G. Balneaves, RN PhD, Laura Weeks, PhD, and Dugald Seely, BSc ND MSc, in Current Oncology, 15 (Suppl 2): S94-S100 (2008).
4.4 Making the decision to forego conventional anticancer treatment in favour of alternative therapies and physician responses to patients making such decisions

A study of CAM use amongst breast cancer patients revealed that few patients distinguish explicitly between conventional treatments and CAMs, and perceive their treatment options as a menu from which to choose a unique treatment protocol or package. Although most cancer patients utilising CAM employ them alongside conventional treatments as complementary therapies (CTs), others decline all conventional treatments and substitute them with alternative therapies. Clinicians often view such choices made by patients as irrational and non-compliant in nature, especially when the proposed conventional treatment is curative. They find such decisions difficult to accept and particularly troubling, given the reduced likelihood of cure and shorter survival time that delay/complete refusal of conventional treatment often confers to patients and the potentially greater health risks, poorer QoL and expense associated with unproven alternative therapies. Clinicians, however, consider CAM to be more likely to help patients treated palliatively than curatively, thus have less difficulty accepting the patient’s decision to decline conventional treatment in favour of alternative therapies in palliative contexts.

How many cancer patients decline conventional treatment is largely unknown, but some researchers and clinicians (particularly in Australia) appear comfortable in dismissing the figure as being very low (1-2%) in the absence of any real supportive evidence. The few studies that have attempted to gauge this, however, suggest that the number is likely to be substantial enough to demand much greater attention and concern than is currently being shown, with prevalence estimates ranging from 8% to 14%.

Given the escalating popularity of CAM, it is quite likely that the prevalence of cancer patients who refuse conventional treatment will increase. Understanding how patients come to such decisions, however, will allow clinicians to offer them the best possible care and guidance that will likely prevent them from discontinuing with conventional cancer care altogether. Fortunately, a number of studies have examined why cancer patients decline conventional treatment and adopt alternative therapies instead. A qualitative review of these studies identified prior negative experiences with conventional medicine, the death of close family or friends to cancer while receiving conventional treatment, pre-existing alternative
therapy use, and a strong belief system invested in the holistic approach as the most important predisposing factors. Factors influencing decisions to refuse treatment following diagnosis include poor doctor-patient communication, psychosocial distress resulting from diagnosis (e.g. fear, anger), perceived severity of conventional treatment side-effects, a strong desire for control in decision-making, great belief in holistic approaches and the mind-body-spirit connection, and beliefs about conventional medicine (e.g. incompatibility with QoL, treatment of symptoms rather than the underlying disease or whole person, reduced capacity for cure) and the causes of cancer (e.g. lifestyle factors such as diet caused their cancer).

Few studies have investigated physicians’ responses to cancer patients making decisions to forego conventional treatment. One study of oncologists and general practitioners, however, found that physicians naturally adopt a goal-orientated medical viewpoint for decision-making, whereas patients rely predominantly on personal values and experiences to make decisions. Consequently, a patient’s decision to decline conventional treatment appears irrational to doctors, especially when the proposed treatment is curative. Besides the distinctions between curable/non-curable disease and rational/irrational treatment decisions, physicians differentiate between patients who assume passive and active roles in decision-making. While most patients are fairly passive decision-makers and follow the medical advice of their doctors, patients who adopt active stances are perceived as being different and may be inclined to forego conventional treatment and seek alternative therapies.

Unsurprisingly, patients who reject conventional treatment in favour of alternative therapies are viewed by some doctors as difficult, irrational, non-compliant, desperate, and in need of more time to reach a sensible decision. In these circumstances, physicians often experience much inner conflict in accepting the patient’s decision and about the role they should play, with interviews of medical and radiation oncologists in one study revealing common themes of uncertainty (e.g. what approach to take in this situation with patients, about their ability to effectively communicate with patients); failure (e.g. to understand the patient or resolve their difference of opinion); helplessness; and concern (i.e. about the patient’s well-being and the implications of his/her treatment decision). The authors concluded that the tendency of physicians to categorise patient decisions as rational or irrational may contribute to their feelings of uncertainty and concern, and that this may interfere with their
ability to respond with appropriate sensitivity and understanding to patients who decline conventional treatment in favour of alternative therapies.79

In the search to make informed treatment decisions, family, friends and CAM practitioners were identified in two qualitative studies as the most valuable sources of support by cancer patients who declined conventional treatment.82,87 Cancer physicians were also cited, but more support was forthcoming from general practitioners within the conventional health realm. Patients who perceived that their oncologist was trying to coerce them into accepting conventional treatment (i.e. by pressuring them, equating alternative therapies to a “death sentence”, or making disparaging remarks about CAM) were more likely to cease conventional cancer care altogether. Conversely, patients highly valued oncologists who could openly communicate and were open-minded enough to support them and provide ongoing follow-up care, despite disagreeing with their decision to decline conventional treatment.

The decision to decline conventional treatment is not necessarily borne from distrust of the health system or the preceding medical care provided by cancer physicians, but may reflect the personal characteristics of individual cancer patients. What clinicians must remember is that treatment decisions are not limited to a single point in time, nor are they absolute. Patients who substitute conventional treatments with alternative therapies want to keep their options open,82 and evidence suggests that some patients ultimately decide to utilise some form of conventional treatment.87 The need for effective, supportive, open-minded/non-judgmental and respectful communication is the most common and important theme identified across the studies in this area.86,88 Understanding what categories of patients are likely to use alternative therapies as surrogates for conventional treatment and what their motivations are is likely to help improve the communication between cancer physicians and their patients, and enhance the overall quality of cancer care offered by oncologists providing conventional treatment.

5. Efficacy and Safety of CAM

Collectively, there is a lack of scientific evidence for the efficacy of CAMs in oncology.16,89-91 A useful distinction, however, is that between cancer cure and cancer care.92 Some CAMs (e.g. mind-body techniques, massage and touch therapies) have proven effective in relieving disease symptoms/treatment side-effects or enhancing
QoL/psychosocial functioning and, thus, are important in caring for cancer patients and alleviating the physical and emotional burden experienced during cancer and its treatment. To date, however, no CAM has proven effective in reliably curing or suppressing any form of cancer. Nevertheless, with the growing popularity of CAM, patients have become increasingly aware that commonly used chemotherapy drugs and other medications used in Western medicine were originally derived from natural sources, hence they are investigating natural products in their search to make informed treatment decisions.

In one population survey, 75% of people agreed that combining conventional medical treatment and CAMs was preferable to using either alone. While use of CAMs may be problematic, they are often perceived by patients as being more “natural” and, by association, safer than conventional treatments. CAMs can directly harm patients via toxic or allergic reactions resulting from their use alone, interactions with chemotherapy agents and prescribed medications, or contaminants in their manufacturing or from the environment (e.g. heavy metals, pesticides, bacteria, fungi). Some herbs, nutritional supplements and other botanical agents, for instance, have toxic and potentially life-threatening effects (e.g. kava, comfrey and black cohosh may cause hepatotoxicity, laetrile/amygdalin cyanide toxicity and dermatitis and high-dose beta-carotene, increases lung cancer incidence and cancer mortality in smokers). Other botanical preparations can interact with chemotherapy and prescription drugs (e.g. St. John’s wort interferes with drug metabolism via the cytochrome P450 pathway and may result in serotonin syndrome or lethargy when taken with antidepressants, as well as reducing the efficacy of chemotherapy drugs, particularly irinotecan and imatinib; botanical agents with oestrogenic properties including red clover, soy and dong quai/female ginseng may interfere with the treatment of hormone-sensitive conditions such as breast cancer and endometriosis); or cause complications during surgery (e.g. garlic, ginkgo biloba and ginseng may increase bleeding; ephedrine alkaloids such as ephedra/ma huang may cause cardiovascular events including hypertension, tachycardia, heart attack and stroke) and radiotherapy (e.g. limited evidence suggests that high-dose supplementation of antioxidants such as vitamin E and beta-carotene during radiotherapy may protect tumour cells along with healthy cells, thus shortening survival of cancer patients).
CAMs may also cause indirect harm to patients. Resultant delays in conventional treatment potentially compromise treatment outcomes, QoL and survival.\textsuperscript{80,81} Clinical trial outcomes, particularly those involving advanced disease patients with poor prognosis, may also be compromised when positive or negative effects of CAM are misattributed to the new conventional treatment being investigated.\textsuperscript{101,102} Financial or emotional burden (e.g. prolonged denial), or the simple squandering of precious, limited time that some patients have left also constitute indirect harm.

Finally, patients may be harmed as a result of the unsafe practices of CAM practitioners with inadequate training and competence, often owing to the absence of self-regulatory bodies and unsatisfactory government legislation protecting health consumers. Furthermore, harm may be exacerbated by regulatory absence or deficiencies in monitoring of the biological potency of herbal crops (causing wide variation in therapeutic efficacy) or the use of incorrect plant species; product standardisation in terms of purity and dosage (resulting in possible substitution/adulteration and incorrect dosing or preparation); and product labelling or advertising.\textsuperscript{103}

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I would like to thank Professor Ian Olver (editor), Professor Peter Drummond and Mr Paul Katris for their comments on early drafts of this chapter. Finally, I would like to thank my loved ones for the patience they showed during the writing of this chapter.

References


2.1 Preface to Study 1

The manuscript describing study 1 underwent peer review and was published in the *Asia-Pacific Journal of Clinical Oncology* as a feature article, which formed the basis of the editorial for that issue. The manuscript in the form in which it was published is presented overleaf. However, a more detailed methodology chapter is located in Appendix A for interested readers. Appendix B also contains the battery of questionnaires used to assess the quality of life and psychological distress of cancer patients in the study. Finally, an alternative version of Table 1 contained in the study 1 manuscript (p.39), which summarises the results of a more complex type of statistical analysis (albeit one that derived identical statistical outcomes), is presented and explained for more discerning readers in Appendix F.

The manuscript presented overleaf has multiple authors. Drs James Trotter and Evan Bayliss suggested the idea for study 1 and helped recruit cancer patients for this study. Together with Paul Katris, they acted as field supervisors and provided consultation throughout the study. Dr Robert Bennett and Professor Peter Drummond acted as academic research supervisors and similarly provided consultation throughout the study. Study design/co-ordination, ethics submissions, patient recruitment, data collection/entry, clinical audits of participants’ medical records, statistical analysis/interpretation and study documentation were all performed by the primary author. Finally, all co-authors provided feedback (including suggestions for improvement) on manuscript drafts and revisions that were brought to their attention for review.

**Original Publication**

Use of Complementary and Alternative Therapies by Western Australian Cancer Patients

Short Title: Complementary and Alternative Therapy Use by Cancer Patients

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Abstract

Background: Many complementary and alternative therapies (CATs) have not been subjected to controlled clinical trials among cancer patients and some may threaten patients’ health and interfere with conventional treatments. Nevertheless, CAT use is becoming increasingly popular and many cancer patients do not discuss it with their physicians. Consequently, we examined the incidence and type of CAT use, perceived benefits of use, and the relationship between demographic, clinical or psychological factors and use in cancer patients who received conventional treatment.

Methods: A heterogeneous cohort of 200 newly-diagnosed cancer patients was recruited from a large Western Australian public hospital. Health-related quality of life, psychological adjustment and CAT use were assessed longitudinally at pretreatment, on-treatment (8 weeks) and post-treatment.

Results: 30% of cancer patients reported CAT use in the course of treatment with nutritional/diet therapies and relaxation therapies most common. CAT users were predominantly younger ($p = .004$), tertiary educated ($p = .016$), possessed medical comorbidities ($p = .023$), and underwent lengthy treatment ($p = .004$). Patients who underwent lengthy treatment (> 6 months) were nearly 3 times more likely to use CATs than those who did not. 64% of CAT users perceived benefit, primarily citing enhanced physical and emotional well-being. CAT users, however, did not score significantly better than non-users on any measure of quality of life, physical health or psychological function. CAT users generally reported greater psychosocial distress than non-users across treatment, especially at pretreatment (baseline). However, with ongoing/new CAT use they significantly reduced their distress levels to that of non-users by 8 weeks on-treatment ($p = .042$).

Conclusion: Complementary and alternative therapies enhanced cancer patients’ psychological well-being during the early stages of conventional treatment only, possibly via a mechanism of empowerment. With patients’ growing interest in CATs, the boundaries between conventional and non-traditional oncology care are becoming less clear. Use of CATs by cancer patients may be a clinical marker for psychosocial distress, and should trigger clinicians to inquire about physical symptoms and concomitant anxiety and depression.

Key words: complementary and alternative therapies, psychosocial oncology, quality of life, adjuvant chemotherapy, cancer treatment.
INTRODUCTION

‘Alternative therapies’ in oncology have been perceived literally as any clinically unproven therapy that is promoted to treat cancer in preference to conventional medical treatments.\(^1\) ‘Complementary therapies’, in contrast, are adjuncts to mainstream cancer treatment, often used for symptom management and to enhance quality of life (QOL).\(^1\) Approximately half of the Australian general population consume complementary and alternative therapies (CATs) every year,\(^3\) resulting in an incidence at least equivalent to prescription drug use\(^3,4\) and costing an estimated AUD$1.8 billion.\(^3\) In adult cancer patients, a systematic review of 21 studies worldwide reported an average prevalence of CAT use of 31.4%.\(^5\) Among Australian cancer patients, 22-52% of medical oncology,\(^6,7\) 40% of palliative,\(^8\) and 46% of pediatric oncology patients\(^9\) report CAT use.

Collectively, there is a lack of scientific evidence for the efficacy of CATs.\(^5,10-12\) Moreover, they are potentially harmful to patients either directly through biological activity\(^1\) or indirectly through delay/refusal of traditional oncology care. Popular complementary therapies (e.g. relaxation, hypnotherapy, aromatherapy, acupuncture) pose minimal risk to patients’ health\(^10,13\) and have proven effective in enhancing psychosocial functioning.\(^14\) Popular alternative therapies (e.g. diet therapies, antioxidants, shark cartilage, coffee enemas, high dose vitamins/minerals and herbal therapies), however, are unproven in controlled trials, hold potentially greater health risks and may negatively interact with conventional treatments.\(^10,13\) Nevertheless, 25-73% of patients using CATs believe they will cure their cancer or prolong their lives,\(^6-9,15,16\) and 74-86% expect them to assist conventional treatments.\(^7,16\) Oncologists, alternatively, consider CATs to be more likely to help patients treated palliatively than those treated curatively.\(^13\) Further, studies suggest that CATs are utilized more in palliative or supportive care than other oncology specialties.\(^17\)

Recent clinical practice guidelines highlight the need for oncologists and general practitioners to be aware of CATs being used or considered by patients, and to encourage them to discuss use.\(^18\) Research shows that 70% or more of individuals who use CATs do not inform their physicians.\(^3,19,20\) One Australian study found that 40% of cancer patients using CATs did not tell their oncologists, possibly due to fear of a negative response.\(^6\)
The psychological well-being of patients is fundamental to holistic cancer care. Research has established that 25-33% of cancer patients experience clinically significant levels of psychosocial distress. In a study of 480 early-stage breast cancer patients, Burstein and colleagues found that complementary and alternative medicine use was independently associated with depression, fear of recurrence of cancer, poorer mental health and sexual satisfaction, and more frequent and intense physical symptoms after 3 months of standard treatment. The authors suggested that women with breast cancer may start using complementary and alternative medicine in response to psychological distress following surgery, and concluded that complementary and alternative medicine use was a clinical marker of psychosocial distress.

Longitudinal cancer research examining the contribution of psychological, clinical and demographic factors in explaining CAT use is scant and limited. Most studies examine few variables and involve homogeneous groups, usually women with breast cancer. What can be said with some certainty, however, is that cancer patients who use CATs tend to be female, better educated, of higher socioeconomic status, and younger than those who do not.

The goals of the present study were to determine the proportion of cancer patients using complementary and alternative therapies in the course of treatment, and the benefits perceived by patients using them. Additionally, the relationships between an expansive range of demographic, clinical, or psychological factors and use of CATs were investigated.

METHOD
A prospective, longitudinal design involving a heterogeneous group of 200 cancer patients was employed. The ethics committees of the participating institutions approved the study. All patients provided written and informed consent.

Patients
Participants were recruited from a consecutive series of 287 eligible cancer outpatients, who were referred to the hospital medical oncology clinic and received multi-modal
treatment at Royal Perth Hospital, Western Australia between September 1997 and December 2002. They were recruited for a larger study evaluating quality of life and psychosocial distress of cancer patients. 200/287 (70%) eligible patients consented and completed baseline questionnaires; 178/200 (89%) patients achieved 8 weeks on-treatment and 153 (76%) progressed to post-treatment. During treatment, 47 patients were withdrawn due to death (15), study ineligibility triggered by changes in medical care (15), study withdrawal (15), and loss to follow-up (2).

Eligibility Criteria
Patients were eligible for the larger study if they met the following criteria: histological confirmation of cancer; age 18 years and over; absence of acute organic psychiatric symptoms; no prior cancer treatment for the current diagnosis (excluding surgery); treatment completely overseen at the hospital following presentation to the medical oncology clinic; and adequate English literacy to complete study questionnaires. Patients were approached just prior to cancer treatment starting and given an explanation of the study and an information sheet to help them decide on participation.

Data Collection
Data concerning demographics and clinical characteristics were collected from patients, oncologists and medical records. Questionnaires were completed by patients at 4 times: pretreatment (start of chemotherapy and/or radiation therapy), on-treatment (8 weeks), post-treatment, and follow-up (6 months). Follow-up data will not be reported, however, as patients reported no change in uptake/relinquishment of CATs in the 6 months following treatment completion.

Questionnaires
Patients were administered the following questionnaires primarily comprising standardized instruments assessing psychosocial distress and QOL:
(1) The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 V2.0.\textsuperscript{26}

The EORTC QLQ-C30 is a cross-culturally validated, self-report measure of quality of life intended for use across a range of cancer diagnoses.\textsuperscript{26,27} It consists of 5 function scales (physical, role, cognitive, emotional, social); 3 symptom scales (fatigue, nausea/vomiting, pain); and 6 single items.

(2) Selby Quality of Life (QOL) Uniscale\textsuperscript{28} and Physical Health (PH) Uniscale.\textsuperscript{26,28}

The Selby QOL Uniscale is a 10-point scale measuring the overall effect of cancer and its treatment on the lives of patients. The PH Uniscale is a 10-point adaptation of the EORTC QLQ 7-point global health scale.

(3) Beck Depression Inventory Short Form (BDI-SF).\textsuperscript{29}

This is an abridged 13-item scale measuring the cognitive-affective aspects of clinical depression while excluding somatic symptoms manifested in medical populations.

(4) Impact of Event Scale- Intrusion Subscale (IES-IS).\textsuperscript{30}

This is a 7-item scale measuring cognitive-emotional distress related to a major stressor, defined as cancer in the present study.

(5) Eysenck Personality Questionnaire – Revised (EPQ-R) – Neuroticism Short Form (SF).\textsuperscript{31}

This is an abbreviated 12-item scale used to measure premorbid levels of neuroticism.

(6) Complementary Therapy Items†.

Patients were asked about the use of CATs since cancer diagnosis: a) ‘Since your diagnosis have you tried any complementary and alternative therapies?’ and b) ‘If yes, please state below what and describe any benefits you get out of them.’ Standard examples of CATs were provided verbally to patients (e.g. dietary changes, vitamin/herbal supplements, meditation, psychological therapy). Two independent trained judges categorized patients’ open-ended responses. Interrater disagreement was resolved by deciding judgments from the first author.
Statistical Analysis
The internal consistency of the multi-item scales administered was calculated using Cronbach’s alpha. Interrater agreement for categorization of patients’ open-ended responses was assessed via Cohen’s kappa. Differences in demographic and clinical characteristics between patients who used and did not use CATs were examined via chi-square analyses. Differences between CAT users and non-users across treatment in quality of life and psychological function were examined via univariate analyses using split-plot analyses of variance/covariance. The level of significance was set at $p < .05$.

RESULTS
Patient Characteristics
Characteristics of the 200 patients are shown in Table 1. The demographic profile of the cohort included 48% male, 52% female, mean age 56 years (SD = 13), 70% married, 47% secondary educated, and 85% resided in the Perth metropolitan area. Primary cancer diagnoses included 29% breast, 28% colorectal and 43% other. Other clinical characteristics included 64% with localized or locally advanced disease, 51% given adjuvant/neoadjuvant treatment (56% surgery plus chemotherapy or chemoradiation), and 74% treated for 6 months or less (excluding any initial surgery). Overall, in terms of sex, age and diagnosis, the sample was quite representative of cancer patients in Western Australia at the time of the study.\(^\text{32}\)

Reliability
All questionnaires demonstrated acceptable internal consistency (EORTC QLQ-C30: 0.68-0.87; other scales: 0.74-0.87) except for the EORTC Pain scale (0.68).\(^\text{33}\) Similarly, interrater agreement was acceptable for classification of CATs used and perceived benefits of their use by patients (85-92% concordance; Cohen’s kappa range = 0.70-0.82, $p$-values < .001).

Association between Complementary and Alternative Therapy Use and Demographic / Clinical Factors
30% (59/200) of cancer patients reported CAT use in the course of treatment. As shown in Table 1, age ($p = .004$), education ($p = .016$), comorbid medical history ($p = .023$) and treatment duration ($p = .004$) were significantly associated with CAT use. More patients
than expected adopted CATs if they were aged 18-39 (46.2%), tertiary educated (39.3%),
possessed a comorbid medical condition (41.3% single; 19.8% multiple), or received more
than 6 months of treatment following medical oncology clinic presentation (6-12 months:
44.7%; > 12 months: 60%). Notably, based on an odds ratio, patients who underwent
lengthy treatments (> 6 months) were 2.95 times more likely to engage in CAT use than
those who did not. Conversely, fewer patients than expected adopted CATs if they were
aged 60 or over (15.1%), primary school educated (10%), or received 6 months of
treatment or less after clinic presentation (23.7%).

Breast cancer patients appeared to be overrepresented among CAT users (39.7%), but the
association of primary diagnosis with CAT use fell short of statistical significance ($p = .064$). Similarly, no significant associations were found between disease recurrence ($p = .562$), disease extent ($p = .478$), treatment goal/intent ($p = .686$), or type of treatment
received by patients ($p = .629$) and CAT use, respectively. Moreover, an analysis of
covariance indicated that primary diagnosis ($p = .32$), disease recurrence ($p = .449$) and
disease extent ($p = .585$) exerted no significant mediating influence on the relationship
between treatment duration and CAT use, which still proved significant after controlling for
the effects of these covariates, $F(2, 181) = 4.68$, $p = .01$.

**Complementary and Alternative Therapy Practices**

Table 2 shows the type of CATs adopted during treatment by 59 cancer patients. At
pretreatment, 53% (31/59) reported using CATs since diagnosis. This increased to 73%
(43/59) by on-treatment (8 weeks), with all 59 patients adopting use by post-treatment.
Furthermore, 53% (31/59) of CAT users tried multiple therapies, 85% (50/59) reported use
more than once during treatment, and only 2% (1/59) relinquished use altogether.

The most frequently reported CAT was nutritional therapy, including the use of food
supplements. This was followed by relaxation/meditation/positive imagery, megavitamins
and minerals, and herbalism. Nutritional therapy involves a diet to treat and prevent illness
and to restore the body to a natural, healthy equilibrium. Patients said that they reduced the
amount of fat in their diet, cut out additives and preservatives and reduced the amount of
<table>
<thead>
<tr>
<th></th>
<th>CAT Users (n=59)</th>
<th>Non-Users (n=141)</th>
<th>All Patients (N=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (26.3)</td>
<td>70 (73.7)</td>
<td>95 (47.5)</td>
<td>.433</td>
</tr>
<tr>
<td>Female</td>
<td>34 (32.4)</td>
<td>71 (67.6)</td>
<td>105 (52.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39yrs**</td>
<td>12 (40.0)</td>
<td>21 (70.0)</td>
<td>33 (16.5)</td>
<td></td>
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<tr>
<td>40-49yrs</td>
<td>14 (37.8)</td>
<td>23 (62.2)</td>
<td>37 (18.5)</td>
<td>.004**</td>
</tr>
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<td>50-59yrs</td>
<td>20 (39.2)</td>
<td>31 (60.8)</td>
<td>51 (25.5)</td>
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<td>60-69yrs**</td>
<td>7 (15.9)</td>
<td>37 (84.1)</td>
<td>44 (22.0)</td>
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<td>70yrs and over**</td>
<td>6 (14.3)</td>
<td>36 (85.7)</td>
<td>42 (21.0)</td>
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<tr>
<td><strong>Marital Status</strong></td>
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<td></td>
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<tr>
<td>Married / Defacto</td>
<td>46 (32.9)</td>
<td>94 (67.1)</td>
<td>140 (70.0)</td>
<td>.244</td>
</tr>
<tr>
<td>Divorced / Separated</td>
<td>6 (20.7)</td>
<td>23 (79.3)</td>
<td>29 (14.5)</td>
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</tr>
<tr>
<td>Widowed</td>
<td>2 (12.5)</td>
<td>14 (87.5)</td>
<td>16 (8.0)</td>
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<tr>
<td>Single, Never Married</td>
<td>5 (33.3)</td>
<td>10 (66.7)</td>
<td>15 (7.5)</td>
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<td><strong>Education</strong></td>
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<tr>
<td>Primary*</td>
<td>2 (10.0)</td>
<td>18 (90.0)</td>
<td>20 (10.2)</td>
<td>.016*</td>
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<td>Secondary</td>
<td>23 (25.3)</td>
<td>68 (74.7)</td>
<td>91 (46.7)</td>
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<td>Tertiary*</td>
<td>33 (39.3)</td>
<td>51 (60.7)</td>
<td>84 (43.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>48 (28.4)</td>
<td>121 (71.6)</td>
<td>169 (84.9)</td>
<td>.742</td>
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<tr>
<td>Rural</td>
<td>10 (33.3)</td>
<td>20 (66.7)</td>
<td>30 (15.1)</td>
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<tr>
<td><strong>Health Insurance Status</strong></td>
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<td></td>
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<tr>
<td>Public</td>
<td>51 (29.8)</td>
<td>120 (70.2)</td>
<td>171 (85.5)</td>
<td>.981</td>
</tr>
<tr>
<td>Private</td>
<td>8 (27.6)</td>
<td>21 (72.4)</td>
<td>29 (14.5)</td>
<td></td>
</tr>
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<td><strong>Primary Diagnosis</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>23 (39.7)</td>
<td>35 (60.3)</td>
<td>58 (29.0)</td>
<td>.064</td>
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<tr>
<td>Colorectal</td>
<td>11 (19.6)</td>
<td>45 (80.4)</td>
<td>56 (28.0)</td>
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</tr>
<tr>
<td>Other</td>
<td>25 (29.1)</td>
<td>61 (70.9)</td>
<td>86 (43.0)</td>
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<td><strong>Comorbid Medical History‡,</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>21 (33.9)</td>
<td>41 (66.1)</td>
<td>62 (32.0)</td>
<td>.023*</td>
</tr>
<tr>
<td>Single Condition*</td>
<td>19 (41.3)</td>
<td>27 (58.7)</td>
<td>46 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Multiple Conditions*</td>
<td>17 (19.8)</td>
<td>69 (80.2)</td>
<td>86 (44.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric History‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Prior History</td>
<td>52 (30.4)</td>
<td>119 (69.6)</td>
<td>171 (88.1)</td>
<td>.54</td>
</tr>
<tr>
<td>Previous History</td>
<td>5 (21.7)</td>
<td>18 (78.3)</td>
<td>23 (11.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No Prior History</td>
<td>44 (29.1)</td>
<td>107 (70.9)</td>
<td>151 (75.5)</td>
<td>.987</td>
</tr>
<tr>
<td>Previous History</td>
<td>15 (30.6)</td>
<td>34 (69.4)</td>
<td>49 (24.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48 (28.4)</td>
<td>121 (71.6)</td>
<td>169 (84.5)</td>
<td>.562</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (35.5)</td>
<td>20 (64.5)</td>
<td>31 (15.5)</td>
<td></td>
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<tr>
<td><strong>Disease Extent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localised Disease</td>
<td>5 (26.3)</td>
<td>14 (73.7)</td>
<td>19 (9.5)</td>
<td>.478</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>29 (26.6)</td>
<td>80 (73.4)</td>
<td>109 (54.5)</td>
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<tr>
<td>Metastatic</td>
<td>25 (34.7)</td>
<td>47 (65.3)</td>
<td>72 (46.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Goal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>5 (21.7)</td>
<td>18 (78.3)</td>
<td>23 (11.5)</td>
<td>.686</td>
</tr>
<tr>
<td>Adjuvant / Neoadjuvant</td>
<td>31 (30.7)</td>
<td>71 (69.3)</td>
<td>102 (51.0)</td>
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<tr>
<td>Palliative</td>
<td>23 (30.4)</td>
<td>52 (69.6)</td>
<td>75 (37.5)</td>
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</tr>
<tr>
<td><strong>Treatment Received</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + Surgery</td>
<td>21 (31.8)</td>
<td>45 (68.2)</td>
<td>66 (33.0)</td>
<td>.629</td>
</tr>
<tr>
<td>Chemoradiation + Surgery</td>
<td>17 (32.1)</td>
<td>36 (67.9)</td>
<td>53 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>10 (21.7)</td>
<td>36 (78.3)</td>
<td>46 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>11 (31.4)</td>
<td>24 (68.6)</td>
<td>35 (17.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Duration‡,</strong>‡,**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6 months**</td>
<td>33 (23.7)</td>
<td>106 (76.3)</td>
<td>139 (74.3)</td>
<td>.004**</td>
</tr>
<tr>
<td>6-12 months**</td>
<td>17 (44.7)</td>
<td>21 (55.3)</td>
<td>38 (20.3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months**</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td>10 (5.4)</td>
<td></td>
</tr>
</tbody>
</table>

1 Patient numbers do not always equal row/column total due to missing data. 2 Treatment duration excludes any initial surgery received prior to medical oncology presentation. * p<.05. ** p<.01 by chi-square analysis of CAT users compared to non-users.
alcohol they consumed. The vitamins and minerals most commonly used were vitamin E and C, selenium, and zinc. Individuals engaging in relaxation/meditation most often used yoga and reiki to reduce feelings of stress and anxiety, as well as to improve their emotional well-being. Herbalism involves using the curative qualities of plants, flowers, trees and herbs to stimulate an individual’s own healing system when the body is ill. Echinacea, milk thistles, herbal teas and promensil (red clover) were the most frequently reported herbal items used.

Nearly two thirds of CAT users (38/59) perceived one or more benefits from their use. Table 3 indicates that the most frequently reported benefits were enhanced physical and emotional well-being (20), immunological functioning (14) and physical energy (8). Fifteen individuals indicated that they had not used CATs long enough to perceive any benefit.

**Table 2**  
Complementary/alternative therapies used by cancer patients (n=59)†

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional Therapy / Supplements</td>
<td>26</td>
</tr>
<tr>
<td>Relaxation / Meditation / Positive Imagery</td>
<td>21</td>
</tr>
<tr>
<td>Megavitamins / Minerals</td>
<td>19</td>
</tr>
<tr>
<td>Herbalism</td>
<td>15</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>5</td>
</tr>
<tr>
<td>Naturopathy</td>
<td>3</td>
</tr>
<tr>
<td>Faith / Spiritual Healing</td>
<td>2</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>

† Some patients used multiple complementary/alternative therapies. Responses total 100.

**Table 3**  
Perceived benefits of complementary/alternative therapy use by cancer patients (n=59)†

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced physical and emotional well-being</td>
<td>20</td>
</tr>
<tr>
<td>Improved immunological functioning</td>
<td>14</td>
</tr>
<tr>
<td>Increased (physical) energy</td>
<td>8</td>
</tr>
<tr>
<td>Reduced feelings of stress (promote relaxation)</td>
<td>4</td>
</tr>
<tr>
<td>Too soon to tell if any benefits have occurred</td>
<td>15</td>
</tr>
<tr>
<td>Did not provide a response</td>
<td>10</td>
</tr>
</tbody>
</table>

† Some patients specified multiple benefits. Responses total 71.
<table>
<thead>
<tr>
<th>Table 4</th>
<th>Cancer patients’ quality of life and psychological functioning in relation to CAT use†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
</tr>
<tr>
<td>Global Quality of Life: Selby QOL Uniscale (Patients)$ – Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>6.6 (2.3)</td>
</tr>
<tr>
<td>Non-users</td>
<td>7.2 (2.0)</td>
</tr>
<tr>
<td>Global Health: Physical Health Uniscale (Patients)$ – Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>7.2 (2.0)</td>
</tr>
<tr>
<td>Non-users</td>
<td>7.4 (1.8)</td>
</tr>
<tr>
<td>Quality of Life: EORTC QLQ–C30 Functional Scales§ – Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>85.6 (23.4)</td>
</tr>
<tr>
<td>Non-users</td>
<td>91.6 (17.5)</td>
</tr>
<tr>
<td>Role Functioning</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>60.9 (36.1)</td>
</tr>
<tr>
<td>Non-users</td>
<td>66.4 (31.7)</td>
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<tr>
<td>Emotional Functioning*</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>74.2 (24.0)</td>
</tr>
<tr>
<td>Non-users</td>
<td>78.5 (20.1)</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>75.5 (20.7)</td>
</tr>
<tr>
<td>Non-users</td>
<td>79.4 (18.4)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>70.3 (28.6)</td>
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<tr>
<td>Non-users</td>
<td>76.5 (29.8)</td>
</tr>
<tr>
<td>Quality of Life: EORTC QLQ–C30 Symptom Scales / Single Items# – Mean (SD)</td>
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<td>Fatigue</td>
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<tr>
<td>CAT users</td>
<td>29.5 (21.2)</td>
</tr>
<tr>
<td>Non-users</td>
<td>29.1 (17.8)</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
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<tr>
<td>CAT Users</td>
<td>12.2 (23.5)</td>
</tr>
<tr>
<td>Non-users</td>
<td>11.7 (23.0)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>CAT users</td>
<td>26.0 (26.4)</td>
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<tr>
<td>Non-users</td>
<td>27.8 (27.7)</td>
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<td>44.8 (38.4)</td>
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<tr>
<td>Non-users</td>
<td>35.2 (36.5)</td>
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<tr>
<td>Appetite Loss</td>
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<td>Non-users</td>
<td>14.5 (26.3)</td>
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<tr>
<td>Depression: Beck Depression Inventory Short Form# – Mean (SD)</td>
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<tr>
<td>CAT users</td>
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<tr>
<td>Non-users</td>
<td>2.2 (2.8)</td>
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<tr>
<td>Cognitive Emotional Distress: Impact of Event Scale– Intrusion Subscale# – Mean (SD)</td>
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<tr>
<td>CAT users</td>
<td>8.0 (7.6)</td>
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<tr>
<td>Non-users</td>
<td>5.3 (5.3)</td>
</tr>
<tr>
<td>Premorbid Neuroticism: EPQ–R Neuroticism Short Form# – Mean (SD)</td>
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<td>CAT users</td>
<td>3.1 (3.0)</td>
</tr>
<tr>
<td>Non-users</td>
<td>3.0 (2.9)</td>
</tr>
</tbody>
</table>

§ Higher scores = healthier functioning. * Higher scores = greater symptomatology/problems. † 47 patients went off-study by post-treatment, thus analysis involved 48 complementary/alternative therapy (CAT) users and 105 non-users. ‡ p-values for between-subjects main effects for CAT use (use vs no use) in split-plot ANOVAs are cited only, as within-subjects effects for treatment stage are secondary. * A significant interaction between Emotional Functioning (EF) and CAT use across treatment was found in split-plot ANOVA tests of within-subjects effects (p=.042); the main effect for EF was not significant (p=.321).
Association between Complementary and Alternative Therapy Use and Health-Related Quality of Life / Psychological Functioning

Consistent with oncologists’ ratings, CAT users reported poorer global quality of life (Selby QOL Uniscale) than non-users across treatment. However, statistical significance was not met in a split-plot analysis of variance (SPANOVA), $F(1, 151) = 3.51, p = .065$ (see Table 4), nor in a split-plot analysis of covariance controlling for patients’ variable treatment durations and starting points for CAT use, $F(1, 149) = 3.24, p = .076$. Similar findings were also observed for cognitive functioning, $F(1, 151) = 3.49, p = .065$. A SPANOVA examining emotional distress (EORTC Emotional Functioning scale) and CAT use revealed no significant main effect for CAT use, $F(1, 151) = .03, p = .859$, but a significant interaction between emotional distress and CAT use over time during treatment, $F(2, 150) = 2.86, p = .043$. Simple effects analyses via a oneway repeated measures ANOVA revealed a significant improvement in emotional functioning of CAT users between pretreatment and on-treatment (74.2 vs 80.1, $p = .042$), but that by post-treatment emotional distress had regressed somewhat to baseline levels (74.2 vs 76.6, $p = 1.0$). As expected, the same analysis uncovered no significant differences in emotional distress across treatment for non-users. Finally, on related measures of depression (BDI-SF) and cognitive-emotional distress (IES-IS), CAT users again consistently reported higher scores than non-users, but results did not reach statistical significance (depression: $p = .176$; cognitive-emotional distress: $p = .184$).

DISCUSSION

30% of the 200 medical oncology patients in this study reported use of a diverse range of complementary and alternative therapies for a variety of reasons. The rate of uptake falls in the 22-52% range reported by such patients in previous Australian studies.\(^6\)\(^7\) CAT use was associated with being younger (18-39 years), tertiary educated, possessing one or more comorbid medical conditions, and undergoing lengthy cancer treatment (> 6 months). These results partially confirm earlier findings that CAT users were younger (use decreasing with age) and more educated,\(^1\)\(^2\)\(^4\)\(^25\) with female gender being a notable omission in the present study.

Patients used CATs in conjunction with chemotherapy, radiation therapy and surgery. While use was not associated with the type of cancer treatment received or its intent, it was
associated with treatment duration. Patients receiving more than 6 months of treatment were nearly 3 times more likely to engage in CAT use than those who did not. Additionally, patients felt that CATs were useful in combating the deleterious physical and psychological side-effects of cancer and its treatment, particularly if lengthy. As in other studies,\textsuperscript{6,9,35} 53\% of CAT users adopted multiple therapies. The CATs chosen were a mix of British and American influences, with psychological and nutritional/megavitamin and mineral approaches, respectively, being most frequently reported. Similar observations were made in another Australian study.\textsuperscript{6}

Significantly, almost two thirds of patients using CATs perceived benefit, mainly citing enhanced physical and emotional well-being, and only one patient relinquished use during cancer treatment. Supportive evidence for benefit, however, was mixed. Compared to non-users, CAT users did not score significantly better on any measure of physical health, quality of life or psychological function. In fact, use of CATs may be clinically significant as a marker for psychosocial distress. Although not statistically significant, CAT users generally reported higher levels of psychological distress/anxiety and depression than non-users across treatment, especially at pretreatment. While emotional distress levels of CAT users significantly declined between pretreatment and on-treatment (8 weeks), no improvements were observed for non-users across treatment. With ongoing/new CAT use, these patients reduced their emotional distress to the more desirable levels experienced by non-users after 8 weeks of cancer treatment (on-treatment). Add to this that most patients adopting CATs had done so by on-treatment, these results together with the recurring theme of personal control of one’s disease in patients’ written comments, suggest that complementary and alternative therapies enhance psychological well-being during the early stages of cancer treatment for patients who struggle to cope at the outset. This process may occur via a mechanism of empowerment rather than any direct biological change initiated by CATs. Randomized controlled trials, however, are required to investigate this further.

Some limitations of this study must be acknowledged. The rate of CAT use in the current sample may not be generalizable to cancer patients Australia-wide. Patients were recruited for a larger study not explicitly targeting CAT use; and were self-selected, English-speaking, chiefly public health patients, and conventionally treated. Also, patients were not screened for pre-existing CAT use prior to diagnosis, nor given any extensive definitions
regarding what CATs were. Despite these shortcomings, the importance of the results of this longitudinal study cannot be ignored. Few, if any, studies have monitored complementary and alternative therapy use in tandem with changes in quality of life and psychological adjustment experienced by cancer patients across treatment.

With the increasing interest of cancer patients in complementary and alternative therapies, the boundaries between mainstream and unconventional oncology care are becoming less clear. It would be valuable for oncologists to possess basic knowledge of specific CATs and their demonstrable benefits or adverse side-effects. However, recent research indicates that oncologists have self-identified gaps in their knowledge of CATs used by some patients, and have suggested a need to consider including education about them in medical training. Currently, complementary and alternative medicine is taught in up to 60% of US medical schools and is a part of conventional medical practice in Europe.34

Sceptics may question the need for oncologists to increase their knowledge of CATs when most remain clinically unproven, but without such knowledge they may be unable to give adequate advice to their patients about possible health risks of their use. As explained in the Australian Clinical Practice Guidelines for Management of Early Breast Cancer, unsupportive and dismissive attitudes are less likely to discourage patients from using potentially harmful and costly complementary and alternative therapies than open and rational discussion. Furthermore, the Australian consumer publication “All about early breast cancer”, produced by the NHMRC National Breast Cancer Centre, urges patients to: ‘discuss with your doctors the complementary and unproven approaches you are using or thinking about using as some unproven approaches are known to adversely affect conventional treatments’ (p.82). Indeed, anecdotal evidence suggested that patients in the present study didn’t do this nearly enough; only 14% (8/59) of those who used CATs were noted in medical records by oncologists as having disclosed their use. Moreover, a minority of these patients also commented to the first author that they didn’t advise oncologists of their CAT use out of fear that conventional treatment would be terminated, or concern that it would strain the doctor-patient relationship.

Ultimately, cancer patients, for the most part, need to feel empowered in helping to control and manage their chronic illness, and feel able to discuss CAT use with their oncologist and
other health professionals. A clinician who genuinely listens and supports patient choice, and whose advice minimizes risk rather than dismisses complementary and alternative therapies is more likely to encourage patients to use them appropriately as an adjunct, rather than as an alternative that replaces conventional medical treatment.

Newly-reported use of complementary and alternative therapies by cancer patients should trigger clinicians to inquire about anxiety, depression or physical symptoms, as recommended in an earlier study.\(^\text{23}\) This may be difficult given the frequent time constraints for consultations in increasingly busy oncology outpatient clinics. Chemotherapy nurses, psychologists, counsellors, and other health professionals may be better-placed to address these issues and ensure provision of valid and reliable information to cancer patients contemplating complementary and alternative therapy use. These consultations could also assist in the identification of patients who may benefit from interventions targeting their physical and psychological needs. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment.

ACKNOWLEDGEMENTS
We are grateful to The Cancer Council Western Australia and Murdoch University for their financial support. We would like to thank Mr Seng Tan and Ms Crystal Laurvick for assisting in preliminary data analysis and Dr Harold J. Burstein for his comments on an early draft of this paper. Finally, we would like to thank the patients and staff at the Department of Medical Oncology, Royal Perth Hospital, as this research would not have been possible without them.

REFERENCES


FOOTNOTES

†In hindsight, it may have been preferable to ask patients to describe not only any benefits they perceived from CAM use, but also any harm or discomfort from CAM use also. Nonetheless, all 200 cancer patients were given an opportunity in multiple study questionnaires (proximal to the CAM questions, Appendix B, p.255) to describe any problem, health-related or otherwise, that they felt was most important in the preceding few weeks. While some patients reported problems relating to conventional cancer treatment, none of the 59 patients (30%) who disclosed CAM use described any associated problems. Furthermore, in a clinical audit of study patients’ medical notes designed to summarise treatment experiences, CAM use was documented by cancer physicians for 10 patients (5%) with only one instance of adverse effects (i.e. a recurrent metastatic melanoma patient receiving palliative radiotherapy reported abdominal pains and flatulence from ingestion of high dose vitamin A and other preparations, and was advised by his oncologist to discontinue CAM use).
Chapter 3: Complementary and Alternative Medicine Used by Patients with Cancer – Evidence for Efficacy and Safety

3.1 Preface to Study 2

The manuscript comprising study 2 underwent peer review and was published as an invited book chapter in the edited publication, *Perspectives on Complementary and Alternative Medicine*. The manuscript in the form in which it was published is presented overleaf. It is followed by a post-publication update of the systematic review that appears in study 2 (comprising a discussion of more recent and newly-located publications *per se* not included in the original review), as well as a commentary article summarising study 2 for health professionals (see sections 3.2 and 3.8, respectively). However, an earlier revision of the manuscript is located in Appendix C. It contains summary tables and material that was otherwise replicated by the authors of other chapters in the edited publication, and subsequently culled due to space restrictions imposed by the publisher. Appendix D also contains a detailed methodology of study 2, which provides more detail regarding the process that underpinned the systematic review performed.

Original Publication

Chapter 3
CAM Used by Patients with Cancer: Evidence for Efficacy and Safety
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Abstract
In Australia the overall prevalence for complementary medicine use is 14% to 65% among Australian adults diagnosed with cancer (with estimates as high as 80% to 91% in the US and Europe), and 8% to 14% for alternative medicine use among adult cancer patients. Given the increasing desire of cancer patients to use CAM, it is important that clinicians have a good understanding of the levels of evidence available for the efficacy and safety of specific complementary and alternative therapies. This systematic review aims to evaluate the efficacy and safety of a range of CAMs in each of five NCCAM/NICM categories used by cancer patients (upon diagnosis, during conventional treatment, in response to disease progression or recurrence, or during remission/survivorship) in Australia and elsewhere. Where possible, evidence from meta-analytic and systematic reviews is utilised. Currently, there is evidence from high quality clinical trials that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving quality of life and psychological functioning. There is evidence of potential harm also. It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies. Additionally, clinicians are strongly encouraged to routinely ask patients about complementary and alternative therapy
use. Offering evidence-based complementary therapies alongside conventional treatments in cancer services can influence patients’ decisions to continue with mainstream care and help avoid any potential harm that may occur with autonomous CAM use.

**Key Words:** complementary and alternative medicines, efficacy, safety, systematic review
1. **Popular CAM Approaches and Evidence for Use**

1.1 **Whole medical systems**

Whole medical systems are complete systems of diagnosis and practice, both developed in Western cultures (e.g. homeopathy), as well as in other cultures (e.g. Traditional Chinese Medicine, Ayurveda).

1.1.1 **Homeopathy**

Homeopathy is based on the proposed law of similars that “like cures like”, whereby low concentrations of substances that cause symptoms in healthy individuals can be used to treat patients with similar symptoms. Homeopathic medicines are generally safe in terms of adverse effects and interactions with conventional treatments. A systematic review of 53 studies found that homeopathic medicines prescribed by trained practitioners in low concentrations are probably safe and unlikely to cause serious adverse events, with the main risks being indirect, stemming from practitioner inexperience (e.g. misdiagnosis).\(^1\)

Systematic reviews of controlled trials have found that homeopathic medicines appeared to improve symptom management during chemotherapy and radiotherapy (specifically chemotherapy-induced stomatitis and acute radiotherapy-induced dermatitis).\(^2\) While producing encouraging preliminary evidence, the authors of both reviews expressed concern about the general lack of evidence and the clinical heterogeneity of identified homeopathy studies and cautioned that further research was required before any definitive recommendations on use by cancer patients could be made.

1.1.2 **Naturopathy**

Naturopathy is an alternative medical system based on the core beliefs that nature has the ability to heal and that the human body has the vital ability to maintain and heal itself. Naturopaths favour natural remedies and minimally-invasive approaches in preference to surgery and drugs. Practitioners use a wide variety of treatment modalities, including dietary and lifestyle changes (e.g. eating more whole and unprocessed foods, abstaining from alcohol and sugar, stress reduction); using vitamins, minerals and nutritional supplements; herbal medicine; homeopathy; mind-body techniques (e.g. meditation, yoga, counselling); and manipulative and body-based therapies (e.g. hydrotherapy, physical...
exercise). Given the overlap of naturopathic remedies with other categories of CAM, they will be reviewed in their respective sections below.

### 1.1.3 Traditional Chinese medicine

Traditional Chinese medicine (TCM) is based upon the concept that the human body is a dynamic universe of interconnected energy systems and aims to maintain balance, harmony and order of these systems to ensure healthy body functioning. TCM treatments include acupuncture and related techniques (e.g. acupressure, moxibustion), Chinese herbal medicine, massage (e.g. tui na, cupping), exercise and breathing techniques (e.g. Qigong), and dietary and lifestyle advice.

TCM is predominantly used by cancer patients to improve immune function, for symptom management (i.e. of general constitutional symptoms such as fatigue, pain and depression, and for specific symptoms such as gastrointestinal distress, or appetite loss) and overall well-being, as well as to enhance the effects of conventional treatments in chemotherapy and radiotherapy. In a review of randomised controlled trials (RCTs) and observational studies of TCM in supportive cancer care, the authors concluded that overall there was sufficient preliminary evidence to suggest that further quality clinical trials were warranted to evaluate the effects on QoL and survival of integrating TCM into conventional oncology care (see below for discussion of specific TCM treatments).

### 1.2 Mind-body techniques

Mind-body techniques involve individuals learning coping strategies to deal with emotional distress that may be manifest in physical symptoms. Techniques include practitioner-administered therapies such as hypnotherapy and mindfulness-based stress reduction, and self-help strategies such as relaxation, meditation and creative therapies (including art, music and dance therapy). Some techniques that were considered CAM in the past have become mainstream (e.g. patient support groups), but they are discussed below nonetheless, because they complement conventional anticancer treatment.

#### 1.2.1 Relaxation

Relaxation techniques originated in the early 1900s in the U.S. and Europe. They are designed to elicit a state of mental and physical relaxation, most commonly by focusing
attention on the sensations associated with systematically tensing and relaxing muscle
groups, as in progressive muscle relaxation (PMR), or to achieve a hypometabolic state of
reduced sympathetic arousal (e.g. via autogenic training, PMR augmented with
diaphragmatic breathing and/or guided imagery). Relaxation techniques often involve
diaphragmatic or deep breathing (slow, deep rhythmic breathing) to aid in the release of
muscle tension, and may incorporate guided imagery/visualisation (evoking images, usually
sensory or affective) to calm the mind. Relaxation is generally safe and adverse events are
rare.

Turning to efficacy, a meta-analysis of 15 RCTs involving patients undertaking acute non-
surgical cancer treatment (chemotherapy, radiotherapy, bone marrow transplantation,
hyperthermia) revealed that relaxation exerted significant positive effects on nausea, pain,
physiological arousal (blood pressure, heart rate), anxiety, depression and hostility.4 A
more recent meta-analysis of 25 controlled trials and observational studies also found
reasonably strong evidence for the efficacy of relaxation-based interventions in reducing
cancer pain,5 while recent systematic reviews derived some support that relaxation reduced
pain,6 nausea and vomiting7 and anticipatory nausea and vomiting,8 respectively.

1.2.2 Meditation
Meditation is an ancient Eastern practice that has been popularly adopted worldwide. It
involves training the mind to focus on breathing or a specific object/image in an effort to
free it of all thought (concentrative meditation), or to focus on sensations experienced in the
present moment in a non-judgmental and accepting manner, to establish a stable, non-
reactive awareness to the physical or psychological symptoms associated with them
(mindfulness meditation).9 Most meditation practices were developed within a religious or
spiritual context and the ultimate goal is to achieve some form of spiritual/personal growth
or transcendental experience and to find a system of values and philosophy of life, whereas
many approaches in behavioural medicine (e.g. relaxation, biofeedback) are designed as
treatments for particular disorders.10 There are many forms of meditation (e.g. Sahaja yoga
meditation, Vipassana meditation), but the two most researched practices are mindfulness
and transcendental meditation [the latter involves a silent word or phrase (a mantra) being
repeated in order to calm (and ultimately transcend) the ordinary flow of internal mental
dialogue].11
Meditation is generally safe and serious adverse events are rare, but it is not without some side-effects. Common adverse effects include relaxation-induced anxiety and panic, restlessness, frustration, paradoxical increases in tension, depersonalisation or derealisation (which can recur after meditation), antisocial behaviour and flattened affect. \(^{12,13}\) Other adverse effects during and after meditation may include reduced motivation, boredom, difficulty in returning to normal life after meditation retreats, pain, impaired reality testing, disorientation, feeling “spaced out”, depression, other psychological sequelae and feeling addicted to meditation. \(^{12}\)

In any case, most studies reporting safety concerns about meditation have involved transcendental or Vipassana meditation and most side-effects have been observed in longer-term retreats (e.g. 10 days) and/or intensive meditation (e.g. 3 hour sessions), which are not formally recommended for “novice” patients of some meditation practices such as mindfulness. \(^{14,15}\) Moreover, only 7.4% of long-term meditators in one study reported severe adverse effects. \(^{12}\) Nevertheless, meditation practices (transcendental or Vipassana meditation, in particular) should be used with caution or are best avoided in cancer patients with (a history of) psychosis, personality/bipolar/dissociative/hypochondrial/somatisation disorders, or with physical exhaustion. \(^{14-16}\)

A meta-analysis of 3 RCTs and 7 observational studies suggested that mindfulness-based stress reduction (MBSR) may improve breast cancer patients’ psychological adjustment to illness (i.e. ameliorating anxiety, stress, fatigue, general mood and sleep disturbance), but it found less convincing evidence to support improvement in physical health. \(^{17}\) Additional larger RCTs involving other cancer populations were recommended. Similar conclusions were also drawn in recent systematic reviews involving cancer patients using MBSR or mindfulness meditation alone. \(^{6,18,19}\)

1.2.3 **Hypnotherapy**

Hypnotherapy is a psychological approach that induces a state of aroused consciousness in which suggestions are made to an individual to facilitate behaviour change or symptom relief. An induction procedure, often involving relaxation/imagery techniques, is used prior to suggestion. The efficacy of hypnotherapy is associated with an individual’s level of suggestibility, particularly in achieving long-term symptom relief. \(^{20}\) Hypnotherapy is
generally safe when administered by qualified practitioners, but some individuals might experience transient side-effects during or after hypnosis. These adverse effects include headaches, drowsiness, confusion, dizziness, or nausea and, less frequently, anxiety or panic; they occur in 5% to 31% of individuals who undertake hypnotherapy. Serious adverse events are rare and typically involve exacerbation of psychological symptoms, which is usually caused by the misapplication of hypnotherapeutic techniques or poor clinical practice (e.g. not preparing patients sufficiently). Nevertheless, the World Health Organization and others caution against the use of hypnotherapy in individuals with (a history of) psychosis, personality disorders or organic psychiatric conditions.

A meta-analysis of 6 RCTs (one in adults, five in children) has suggested that hypnotherapy is effective in reducing anticipatory and chemotherapy-induced nausea and vomiting in paediatric patients alone. Furthermore, a more recent systematic review found that hypnotherapy improved cancer pain without exception in a small number of controlled and observational studies; and systematic reviews of RCTs and observational studies have demonstrated that hypnotherapy is a potentially valuable treatment for acute procedural pain and distress in adult and paediatric cancer patients, although large RCTs are needed.

### 1.2.4 Yoga

Yoga is a series of practices that incorporate eight disciplines, including physical poses and postures, breath control and meditation, with the goal of uniting the mind, body and spirit for improved physical/mental health and self-awareness. There are many types of yoga, with Hatha yoga (a gentle form most commonly practiced in Western countries) and Tibetan yoga being the most studied in recent years. Yoga has been well-tolerated in studies and no serious adverse effects. Nevertheless, yoga should be avoided or used in a gentler, modified form by individuals with balance problems; uncontrolled hypertension, symptomatic anaemia, postural hypotension; infection or significant thrombocytopenia; certain eye conditions (e.g. glaucoma); severe osteoporosis and bone injury, vertebral damage or cervical spondylosis; artificial joints or prothetic devices (e.g. infusaport, colostomy bag), pregnancy; and psychosis.
Two systematic reviews of RCTs and observational studies provide preliminary support for the efficacy of yoga interventions in cancer patients and survivors.\textsuperscript{28,29} Positive effects were reported for a range of outcomes including sleep quality, mood, stress and overall QoL, but more RCTs are needed.

1.2.5 Tai chi
Sometimes referred to as “moving meditation”, tai chi is derived from TCM and incorporates slow movements and postures (similar to aerobic exercise), controlled breathing and meditation. Tai chi appears to be generally safe and no serious adverse effects have been reported in cancer and other chronic disease populations.\textsuperscript{30,31}

Tai chi has been used by cancer patients to improve QoL, mood, flexibility, and balance.\textsuperscript{31} Two systematic reviews of controlled studies in supportive breast cancer care, however, have found insufficient evidence for the positive impact of tai chi on physical or psychological outcomes and QoL in patients.\textsuperscript{30,31} Large RCTs involving breast and other cancer populations are required.

1.2.6 Music therapy
Music therapy is designed to facilitate communication and achieve therapeutic goals through the creative use of music alone or in combination with relaxation/imagery techniques. A recent meta-analysis of 183 studies across 11 medical specialties (with a heavy emphasis on cancer patients) revealed that music therapy resulted in significant improvements in pain, well-being, mood, and nausea and vomiting.\textsuperscript{32} Nevertheless, more large RCTs are required, although music therapy could be supported for use in cancer patients in the interim given its association with few (if any) adverse events.

1.2.7 Support groups
Support groups enable patients at any stage of their cancer experience to gain emotional support from others with similar experiences (and to reciprocate in kind) by sharing. Cancer support groups include a variety of different approaches (e.g. psychotherapy, psychoeducation, cognitive-behavioural therapy), types (e.g. face-to-face, telephone or internet support) and settings (e.g. community centres or hospitals, the patient’s home) encompassing health professional-led support groups and self-help groups.
A meta-analysis of 20 RCTs has suggested that participation in professional-led support groups results in significant improvements in cancer patients’ emotional well-being (depression, anxiety), adjustment to illness, QoL and marital satisfaction, but not survival. Similarly, a more recent systematic review of 32 RCTs and 12 descriptive studies revealed that professional-led support groups produced positive effects in psychosocial functioning (less social isolation, felt more understood and hopeful) and morale and other QoL dimensions, but not improved survival. Further RCTs of professional-led support groups involving different cancer populations, preferably in community settings, are required.

Benefit from peer/volunteer support programmes, however, is less apparent for cancer patients. A systematic review of 16 controlled trials and 26 descriptive studies indicated a high level of satisfaction with individual/group peer support programmes, but mixed evidence for psychosocial benefit. A systematic review of 10 controlled trials and 10 descriptive studies also found a high level of satisfaction among participants in individual volunteer support programmes, but very limited evidence for psychosocial benefit given the lack of RCTs performed. Again, more large RCTs involving different cancer populations are needed.

1.2.8 Spirituality, religion and prayer

Spirituality and religion are overlapping concepts that involve a search for the sacred, in which individuals seek to discover, hold on to, and, when necessary, transform whatever they hold sacred in their lives. Spirituality differs from religion in that religion is a search for significance in ways related to the sacred and, in instances of popular usage, places spirituality within the context of beliefs, values and practices of an organised institution.

A systematic review of 7 longitudinal and 10 cross-sectional studies found some evidence for improved adjustment to illness or reduced distress of religious/spiritual coping with cancer, but could not draw any firm conclusions. A more recent review of 4 longitudinal and 36 cross-sectional studies drew similar conclusions regarding spirituality and emotional well-being in cancer patients. Further large longitudinal studies are required.

Researchers have argued that prayer can be separated from religion in the same way that related activities such as meditation have. A systematic review of 7 prospective cohort
studies, 14 cross-sectional studies and 3 qualitative studies involving hospitalised populations (including cancer patients) found a positive association between private prayer and emotional well-being (anxiety, depression), optimism and functioning, respectively, in patients with religious faith who engage in regular devoted prayer, and some evidence that prayer out of desperation (e.g. in response to pain, poor prognosis or postoperative trauma) in the absence of faith is associated with poorer emotional well-being and functioning. More rigorous studies involving cancer patients across different religions are needed, however.

Studies examining the effects of intercessory prayer on well-being are rarer and reported in another chapter of this book. Additionally, a systematic review of 17 epidemiological studies (including a subgroup analysis of 11 studies adjusted for demographic and lifestyle factors) revealed no significant reduction in cancer risk among members of Christian communities compared to the general population, and concluded that a healthy lifestyle was the most important mediating factor in explaining any correlation observed between religious membership and cancer risk. Finally, two meta-analyses of randomised trials involving medical populations (including leukaemia patients) have found insufficient evidence that distant intercessory prayer has any beneficial effects on clinical outcomes (health, mortality, hospital re-admission).

1.3 Biologically-based practices
Biologically-based practices involve supplementing a person’s normal diet with additional extracts, nutrients, herbs and/or certain foods. Examples include, nutritional supplements, herbal and other plant-based preparations (botanicals), animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics and probiotics (live bacteria often found in whole grains, yoghurt and functional foods), whole diet therapies, functional foods, and other so-called natural therapies (e.g. shark cartilage for cancer treatment).

1.3.1 Nutritional supplements (dietary supplements, food supplements)
Nutrients in dietary supplements may include vitamins, minerals, herbs or other plant-based substances (botanicals), amino acids, fatty acids, and substances such as enzymes. Nutritional supplements may be extracts or concentrates sold as tablets/capsules, liquids, or powders.
1.3.1.1 *Antioxidants*

Free radicals are unstable molecules produced when the body breaks down food, or is exposed to environmental influences (e.g. tobacco smoke, radiation). While free radicals are essential for various biological functions including the removal of damaged cells, they are also highly reactive and can damage healthy cells via oxidation. Excessive free radicals may play a role in the development and progression of certain diseases, such as cancer, cardiovascular disease and liver disease.\(^{48}\) Antioxidants neutralise free radicals and may protect cells in the body from damage caused by oxidative stress.\(^{49}\) Broadly, antioxidants take the form of nutrients [e.g. vitamins C (ascorbic acid) and E (alpha-tocopherol); minerals such as selenium and zinc] and non-nutrients (e.g. phytochemicals such as lycopene, beta-carotene and indole-3-carbinol; zoochemicals in red meat and fish products). Whilst present in food and beverages, they are commonly taken as nutritional supplements (capsules/tablets, powders) alone or in combination with vitamins and minerals.

Proponents argue that antioxidants are beneficial to cancer patients because they enhance the efficacy of chemotherapy, as well as alleviate treatment toxicity and thus allow patients to tolerate full courses of chemotherapy and/or radiotherapy with fewer dose reductions.\(^{50}\) Others are concerned that antioxidants may not only reduce the efficacy of some chemotherapy agents and radiotherapy, but may protect cancer cells as well as healthy cells from oxidative damage.\(^{51}\)

A recent systematic review of 33 RCTs found that concurrent use of antioxidants with chemotherapy resulted in reduced toxicity in the majority of studies (which involved mostly advanced or recurrent cancer patients), and that patients in 5 studies completed more full doses of chemotherapy or had fewer dose reductions when receiving antioxidants than control patients.\(^{52}\) Similarly, another review suggested that antioxidants may mitigate the adverse effects of radiotherapy,\(^{53}\) while a meta-analysis of 14 RCTs showed that amifostine (a synthetic antioxidant) significantly reduced the side-effects of radiotherapy.\(^{54}\) In contrast, however, a systematic review of 22 controlled trials and observational studies involving breast cancer patients found insufficient evidence that individual antioxidant supplements reduced toxicity during conventional breast cancer treatment.\(^{55}\) Other systematic reviews have also revealed insufficient evidence that selenium supplementation alleviates chemotherapy- or radiotherapy-induced toxicity or postoperative side-effects in cancer patients.\(^{56}\)
patients,\textsuperscript{56} or that selenium or lycopene supplementation relieves symptoms in prostate cancer patients.\textsuperscript{57,58} Similarly, a systematic review of 6 controlled trials found inconclusive evidence that coenzyme Q10 (synthetic antioxidant) reduced chemotherapy-induced toxicity.\textsuperscript{59} Further large, well-designed RCTs are advised.

The formation of free radicals is the primary mechanism by which radiotherapy and many chemotherapy drugs act in destroying cancer cells. One systematic review of 21 randomised trials and 31 observational studies of antioxidants and chemotherapy observed such great diversity across studies (study design, cancer diagnoses, chemotherapy regimens, type/dose/schedule of antioxidant supplementation) that definitive conclusions could not be made about the efficacy and safety of antioxidant supplementation.\textsuperscript{60} Similarly, a systematic review of 22 controlled trials and observational studies could not draw any conclusions regarding the effects of antioxidants during breast cancer treatment (chemotherapy, radiotherapy and/or hormonal therapy) on tumour response, survival or recurrence,\textsuperscript{55} nor could the authors in a systematic review of lycopene supplementation in prostate cancer patients.\textsuperscript{58} Another review of 44 randomised trials, however, went further and concluded that concurrent use of antioxidants with chemotherapy and/or radiotherapy should be discouraged, due to the possibility of tumour protection and reduced survival, despite limited evidence of these negative outcomes during radiotherapy and limited evidence that some antioxidant supplements may actually enhance the efficacy of chemotherapy.\textsuperscript{61} In contrast, a systematic review found that the great majority of 19 RCTs demonstrated either statistically significant or non-significantly greater survival and/or treatment response for concurrent use of antioxidants with free radical-generating chemotherapy, in patients with predominantly advanced or recurrent cancer.\textsuperscript{62} Additionally, no evidence was found that antioxidant supplementation reduced the efficacy of chemotherapy. Again, further large, well-designed studies are recommended.

More unequivocal, though, were the results of three meta-analyses. One meta-analysis of 7 RCTs (with no evidence of heterogeneity) found that amifostine (a synthetic antioxidant) had no effect on tumour response in locally advanced non-small cell lung cancer in patients treated with radiotherapy ± chemotherapy.\textsuperscript{63} Another meta-analysis and systematic review of 38 studies found no support that vitamin E or C supplementation helped treat or prevent cancer.\textsuperscript{64} The third meta-analysis of 10 unblinded RCTs (with no evidence of
heterogeneity), however, demonstrated consistent positive effects on 1-year survival across melatonin dose and diagnosis for advanced solid tumour patients receiving melatonin alone or combined with cancer treatment.65

In regard to chemoprevention, a meta-analysis of 22 RCTs indicated no evidence for the primary or secondary prevention of cancer through use of antioxidant supplements.66 Another meta-analytic and systematic review of 12 RCTs (predominantly high quality) revealed that antioxidant supplementation did not significantly reduce total cancer incidence or mortality or any site-specific cancer incidence in primary prevention.67 Similarly, meta-analytic and systematic reviews do not support the supplementation of antioxidants (vitamins A, C, E; selenium; beta-carotene) alone or in combination to prevent colorectal cancer or gastrointestinal cancers;69 of vitamin C or E individually to prevent cancer overall,64,67,70,71 or of vitamin C or E, folate or beta-carotene individually to prevent lung cancer.72,73 Vitamin E and selenium may have preventative effects for prostate cancer and gastrointestinal cancers or cancer in men, respectively, although confirmation is required in further RCTs.67,69,70

Despite the lack of clinical trial data, antioxidants in foods are generally considered safe and few studies of antioxidant supplements have reported adverse effects. Common minor adverse effects include mild diarrhoea and gastrointestinal upset for vitamin C,74 and carotenodermia (yellowish discoloration of the skin) following heavy, chronic intake of beta-carotene.69 However, high-dose beta-carotene appears to increase lung cancer incidence and cancer mortality among smokers;67,75 antioxidant supplementation may increase the risk of bladder cancer;66 and high vitamin E supplementation may increase bleeding in individuals with drug-induced vitamin K deficiency.74 Given the lack of long-term safety data, antioxidant supplementation during cancer treatment is not recommended without guidance from the treating oncology team.

1.3.1.2 Omega-3 fatty acids (n-3 polyunsaturated fatty acids)

Omega-3 fatty acids [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA)] influence many physiological functions, including fertility, cell division, angiogenesis, apoptosis and immune cell function, thus suggesting they may protect against cancer or alter the response to cancer treatment.76,77 Omega-3 fatty acids are
found naturally in fish, fish oil, vegetable oils (mainly canola and soybean), walnuts, wheat germ, and other foods or as supplements. They are also available as nutritional supplements in fish oil preparations in both capsule and liquid form. EPA and, to a lesser extent, DHA have demonstrated anti-cancer and anticachectic effects in human studies.\textsuperscript{78,79}

A meta-analytic and systematic review of 38 studies, involving 20 different prospective cohorts across 7 countries with different demographics, revealed that data across 11 different types of cancer suggested that nutritional supplementation with omega-3 fatty acids is unlikely to prevent cancer.\textsuperscript{80} Additionally, a recent meta-analysis of 5 prospective studies found a weak protective association between high dietary ALA intake (1.5g/day) and prostate cancer risk.\textsuperscript{81} In contrast, two other recent meta-analyses of prospective and case-control studies revealed that high intake or blood level of ALA (but not EPA or DHA intake) is weakly associated with an increased risk of prostate cancer.\textsuperscript{82,83} Clearly, further \textit{in vitro} and epidemiological studies are needed.

Many advanced cancer patients develop cachexia and treatment of associated weight loss and other symptoms has proven difficult. More recently, novel approaches have included the use of fish oils containing EPA and DHA. A Cochrane meta-analytic review of 5 RCTs found insufficient data to establish whether oral EPA was better than placebo in improving symptoms associated with cachexia in advanced cancer patients.\textsuperscript{78} Similarly, a meta-analytic and systematic review of 19 studies demonstrated no effect of omega-3 fatty acids on weight loss, nutritional status, postoperative complications, mortality or length of hospital stay after surgery for upper gastrointestinal cancers.\textsuperscript{80} A more recent systematic review of 17 clinical trials and prospective studies, however, suggested that dietary or supplemental intake of omega-3 fatty acids (EPA and/or DHA; 1.5g/day) for prolonged periods (8 weeks) by advanced cancer patients is associated with improved clinical (nutritional status, tolerance, survival, hospital stay), biological and QoL outcomes.\textsuperscript{79} Further large RCTs are recommended. Finally, omega-3 fatty acids are generally well-tolerated and cause few adverse effects in low to moderate doses. Gastrointestinal symptoms (e.g. diarrhoea, heartburn, bloating, nausea) are the most common side-effects.
1.3.1.3 Shark cartilage and AE-941 (Neovastat)

Shark cartilage use by cancer patients became popular in the 1980s after several poor quality studies claiming “miracle” cancer cures were reported by the US media, many of which were generated by a single manufacturer (Lane Labs-USA, producer of BeneFin). Use of shark cartilage in cancer patients originally stemmed from and has been perpetuated by the popular belief that sharks do not develop cancer because of the high proportion of cartilage in their body (about 6% by body weight). Scientifically, this has been shown to be untrue (several tumours in sharks have subsequently been detailed in a review article).

Shark cartilage preparations are not standardised and there is no generally accepted recommended dosage or duration for administration. The only standardised source of shark cartilage is Neovastat (AE-941, manufactured by AEterna Zentaris), a matrix metalloproteinase inhibitor specifically developed as a highly purified liquid shark cartilage extract for evaluation in clinical drug trials. Generally, shark cartilage is well-tolerated. The most common adverse effects reported are gastrointestinal symptoms (nausea, vomiting, stomach upset, constipation, diarrhoea, flatulence) and taste alteration.

While some preclinical studies of shark cartilage and preliminary clinical studies of Neovastat have demonstrated anti-angiogenic and anti-cancer properties, and it has been observed that cartilage lacks blood vessels and that human cancer rarely invades cartilage, no controlled study has demonstrated that crude cartilage extracts are beneficial in the treatment of cancer in humans (or animals). In a double-blind RCT of 83 incurable breast and colorectal carcinoma patients (with good performance status and organ function), no differences in overall survival or QoL were observed between patients receiving standard conventional care (including chemotherapy for some patients) with powdered liquid shark cartilage extract (BeneFin nutritional supplement, 3-4 times daily until unacceptable toxicity developed) versus standard conventional care with placebo. These results mirrored those of a previous uncontrolled phase I/II trial involving 60 advanced cancer patients.

Larger RCTs involving the use of Neovastat in cancer patients have been similarly disappointing. In a double-blind RCT of 305 metastatic renal cell carcinoma patients refractory to immunotherapy, no survival advantage was observed in patients treated with
Neovastat versus placebo. More recently, a comprehensive double-blind RCT of 379 locally advanced non-small cell lung cancer patients (newly-diagnosed, unresectable and previously untreated) found no differences in overall survival, tumour response rates, time to disease progression and progression-free survival between patients receiving chemoradiation with Neovastat (120ml orally, twice daily until disease progression or unacceptable toxicity developed) versus chemoradiation with placebo. It was concluded that the results do not support the use of shark cartilage-derived products for lung cancer patients, and this has prompted the pharmaceutical manufacturer of Neovastat to cease clinical development.

1.3.1.4 Laetrile and amygdalin (Vitamin B17)

Laetrile has been popularly used by cancer patients worldwide since the 1970s in the hope that it might cure or slow the growth of cancer. The term “laetrile” is an amalgam of laevorotatory and mandelonitrile, which is used to describe a purified form of amygdalin (cyanogenic glycoside plant compound). Amygdalin is found in the stones of many fruits and nuts (e.g. almonds, cashews). Laetrile may be taken as an oral supplement (dubbed vitamin B17, although it is not a real vitamin), or injected intravenously, intraperitoneally or intramuscularly. Despite frequent interchangeable use, the intravenous form of laetrile (D-mandelonitrile-beta-glucuronide) is a US patented semi-synthetic derivative of amygdalin, while laetrile produced in Mexico (D-mandelonitrile-beta-gentiobioside) is usually amygdalin naturally produced from crushed apricot stones.

Laetrile/amygdalin is typically used as an adjunct to conventional anticancer treatments or in combination with other alternative therapies, such as metabolic therapy. In vitro studies suggest that amygdalin has anti-cancer properties, but no RCTs have been performed of amygdalin or laetrile in humans. A limited uncontrolled phase II trial, performed by the US National Cancer Institute in 1982, found that 95 of 178 (53%) of mixed, non-metastatic cancer patients experienced disease progression and only 1 patient exhibited a partial tumour response (lasting 10 weeks) following 21 days of intravenous laetrile plus oral maintenance therapy combined with metabolic therapy (pancreatic enzymes, high vitamin doses, dietary changes employed by metabolic practitioners). Furthermore, all remaining patients experienced disease progression within 7 months post-treatment, and no significant
difference in survival was observed compared to historical controls who had inactive or no treatment.

Better evidence, however, is offered by a systematic review of 36 studies (25 case reports, 6 best case series of case reports, 3 non-consecutive case series, 2 consecutive case series) involving 352 cancer patients treated with laetrile/amygdalin.\textsuperscript{95} Despite the likelihood of positive bias in case reports, only 3.1\% of patients reportedly had a complete response and 9.4\% had a partial response (although some of these patients may have received conventional treatments and no detailed follow-up information was reported for complete response patients), while 36.4\% exhibited disease progression; symptomatic benefits were also reported in 22.9\% of cases. The authors concluded that the claim that laetrile has beneficial effects for cancer patients is not supported by sound clinical evidence.

Possible adverse effects of laetrile/amygdalin are of particular concern, given the belief that cyanide produced when it is broken down, kills cancer cells. In the aforementioned systematic review, 14.4\% of patients experienced adverse reactions consisting mainly of nausea, vomiting, headache, fever and abdominal pain.\textsuperscript{95} The most important concern with toxicity, however, involves several reports of cyanide poisoning (including deaths) from the use of laetrile/amygdalin by cancer patients in North America in the 1970s and 80s, which prompted the US to ban its use.\textsuperscript{95}

1.3.2 Chinese Herbal Medicine

Chinese herbal medicine (CHM) is a key part of TCM and is used to normalise imbalanced energy that runs through invisible meridians in the body. CHM includes any mixture of herbs (mainly plant-based, but also including minerals or animal extracts) and decoction (liquid extraction of boiled herbs), which may take the form of tablets/capsules, powders, tonics, lotions and pastes. There are a number of issues associated with the safety and quality of CHMs, including herb-drug interactions [via induction or inhibition of enzyme systems (e.g. cytochrome P450) or by affecting efflux proteins (e.g. P-glycoprotein)], resulting in a reduced efficacy or increased toxicity of chemotherapy and prescription medications; direct (pharmacological) or indirect (e.g. free radical-mediated) toxicities; allergic responses; contamination with heavy metals, pesticides, micro-organisms or other impurities; deliberate substitution or adulteration with prescription or non-prescription
drugs (e.g. corticosteroids, hormones, salicylates, antihistamines, caffeine); and reactivation of viruses or disease (e.g. hepatitis B or C, herpes simplex, varicella zoster, tuberculosis). The safety and quality of CHMs are regulated by the Therapeutic Goods Administration (TGA) in Australia, but limitations of The Therapeutic Goods Act 1989 do not subject individual practitioners to the standards that companies selling CHMs are required to meet. Consequently, practitioners can import raw herbs that may not meet the TGA standards and legally dispense them over the counter, without registering with the TGA.

1.3.2.1 Astragalus (*Astragalus membranaceus, Astragalus mongolicus, Astragalus propinquus, Radix astragali*)

Astragalus is usually combined with other Chinese herbs, particularly as part of an immune-enhancing herbal regimen known in TCM as Fu Zheng therapy. It is typically administered as a dried root, a powder or in a decoction, although it may be given by intraperitoneal injection also. Human and *in vitro* studies have demonstrated the immunostimulatory properties of astragalus polysaccharides and triterpinoid saponins in both healthy individuals and cancer patients (e.g. by stimulating macrophage and natural killer cell activity, and inhibiting T-helper cell type 2 cytokines), as well as anti-cancer activity.

In China, astragalus-based Chinese herbs (e.g. Jin Fu Kang) combined with platinum-based chemotherapy is a standard treatment for non-small cell lung cancer. A meta-analysis of 34 Chinese RCTs found evidence that astragalus-based herbal medicine (oral Jin Fu Kang, Aidi injection, other preparations) may enhance the treatment outcomes (improved survival, tumour response and performance status) and reduce the toxicity (leukopenia, haemoglobin toxicity) of standard platinum-based chemotherapy for advanced non-small cell lung cancer patients. Similarly, a more recent meta-analysis and systematic review of 45 RCTs revealed that oral astragalus-based herbal medicine enhanced complete/partial tumour response, survival rates and symptom control (abdominal pain, fatigue, appetite loss), and reduced the risk of disease progression (for astragalus alone also) in unresectable liver cancer patients receiving transcatheter arterial chemoembolization. Another systematic review of 14 Chinese RCTs suggested that Aidi injection improved the tumour response and QoL of non-small cell lung cancer patients receiving chemotherapy involving vinorelbine and cisplatin injections or cobalt-60 (but not etoposide or paclitaxel combined
with cisplatin injections). Finally, a Cochrane meta-analytic review of 4 RCTs involving colorectal patients suggested that astragalus (huang qi) compound decoctions as an adjunct to chemotherapy may decrease chemotherapy toxicity (nausea and vomiting, leukopenia) and stimulate immunocompetent cells. The authors in each review, however, concluded that larger, more rigorous RCTs were needed to confirm these benefits given the poor quality of the studies examined.

Attributing specific adverse events or drug interactions to astragalus is difficult, however, given that it is predominantly used in combined herbal preparations. Nevertheless, side-effects of oral astragalus-based preparations reported in two phase II studies involving incurable cancer patients receiving standard care (including chemotherapy and radiotherapy) and incurable non-small lung cancer patients undergoing adjuvant chemotherapy with paclitaxel, included grade 3 lymphopenia, grade 3/4 hyperglycaemia and grade 1/2 gastrointestinal symptoms (e.g. diarrhoea, dyspepsia). Finally, direct ingestion of certain toxic astragalus plants (locoweed) containing swainsonine and selenium may cause neurological symptoms, some of which are irreversible.

1.3.2.2 Ginseng (Panax ginseng, Panax quinquefolium, Eleutherococcus senticosus, Angelica sinensis)

While the immunostimulatory properties of ginseng (and its ginsenosides) in recent reviews have suggested a possible role as an adjuvant or immunotherapeutic agent, to enhance immunological function and improve QoL in cancer patients during chemotherapy and radiotherapy, RCTs are yet to be performed to confirm these benefits. Ginseng is associated with a relatively low incidence of adverse events, with reports being attributed to adulterated or contaminated preparations. Common side-effects of ginseng include insomnia if taken in the evening, and agitation/overstimulation if excessively used. Possible contraindications of Asian ginseng (Panax ginseng) and American ginseng (Panax quinquefolium) include hypertension, diabetes, coagulation disorders and surgery, and use of anticoagulants (e.g. warfarin) or antiplatelet medications (aspirin), phenelzine (monoamine oxidase inhibitor antidepressant), hypoglycaemics, oestrogens, corticosteroids or alcohol. Possible contraindications of Siberian ginseng/eleuthero (Eleutherococcus senticosus) include cardiovascular disease, and concomitant use of digoxin (heart drug) and antihypertensive medications. Finally, ginseng, particularly dong quai/female ginseng
(Angelica sinensis), has oestrogenic effects, which may interfere with the treatment of hormone-sensitive conditions, such as breast cancer (e.g. hormonal therapy) and pregnancy.116

1.3.2.3 Ginger (Zingiber officinale)
Ginger may be used by cancer patients to alleviate postoperative and chemotherapy-induced nausea and vomiting, as well as gastrointestinal symptoms including diarrhoea. A meta-analysis of 5 RCTs demonstrated that a fixed dose of ≥1g of ginger is more effective than placebo in reducing acute postoperative nausea and vomiting.117 Studies examining the efficacy of ginger for chemotherapy-induced nausea and vomiting, however, have produced mixed results and are still in their infancy.118 More RCTs comparing ginger to current antiemetics are required.

Ginger causes few adverse effects when taken in small doses. Gastrointestinal symptoms (e.g. heartburn, bloating, flatulence) are the most common side-effects. Additionally, ginger inhibits thromboxane synthase (platelet enzyme) and platelet aggregation, thus the risk of bleeding is increased in individuals taking anticoagulant/antiplatelet medications (e.g. warfarin, aspirin), those with coagulation disorders and surgical patients.113

1.3.2.4 Lingzhi/Reishi mushroom (Ganoderma lucidum, Ganoderma tsugae)
Lingzhi is a traditional medicinal mushroom that has been used extensively in cancer treatment in Asia. Lingzhi polysaccharides have demonstrated anti-cancer and immunostimulatory properties.119 Reviews of preliminary clinical data suggest that Lingzhi extracts or powders may have some potential in cancer treatment, but more rigorous RCTs are required.119,120 Adverse effects from medicinal mushrooms are rare. Dry throat and nose and gastrointestinal symptoms are the most common side-effects of Lingzhi. Caution is warranted, however, as Lingzhi causes platelet inhibition, thus the risk of bleeding is increased in individuals taking anticoagulant/antiplatelet drugs (e.g. warfarin, aspirin), those with coagulation disorders and surgical patients.121 Additionally, Lingzhi can increase antioxidant capacity and may interact with chemotherapy agents that rely on free radicals.122
1.3.2.5 Green tea (*Camellia sinensis, Thea sinensis*)

Green tea and its extracts have a long history of use as a traditional cancer treatment in Asian cultures. Polyphenols in green tea known as catechins, particularly epigallocatechin gallate (EGCG), have demonstrated anti-cancer, antioxidant and chemopreventive properties. The US Food and Drug Administration (FDA) in a review of studies concluded that there is no supportive evidence for green tea decreasing the risk of gastric, lung, colorectal, oesophageal, pancreatic, ovarian and combined cancers, but weak evidence for decreased risk in breast and prostate cancer. Similarly, more recent systematic reviews have suggested that green tea may reduce cancer risk and slow or prevent progression in cancer patients, but found the overall evidence to be inconclusive and counselled that use of green tea alone to treat cancer may be ill-advised given its limited cytotoxic effects. Further large prospective cohort studies and RCTs are recommended.

Green tea is generally safe when consumed in moderate amounts (3-9 cups per day). Excessive consumption (5-6 litres per day) may cause gastrointestinal and central nervous system disturbances (e.g. nausea, insomnia, irritability, frequent urination, cardiac arrhythmia), however, predominantly as a result of the caffeine content, rather than the tannin content of green tea. Finally, EGCG and other polyphenols in green tea are potent blockers of boronic acid-based proteasome inhibitors and can reduce the efficacy of bortezomib during chemotherapy for multiple myeloma and mantle cell lymphoma.

1.3.2.6 Ginkgo (*Ginkgo biloba, EGb 761*)

Ginkgo is one of the most popular herbal medicines worldwide; it is used for a wide range of conditions including cardiovascular disease, stress, neurodegenerative diseases such as Alzheimer’s, cognitive impairment including memory loss and psychiatric disorders such as schizophrenia, as well as cancer. Ginkgo is contained in the leaves and seeds of the ginkgo tree and is available as a standardised extract (EGb 761), taken orally or, rarely intravenously. Amongst others, the flavonoids and the terpenoids (gingkolides, bilobalide) of ginkgo have been reported to have anti-cancer, antioxidant, cardioprotective, antiplatelet, stress-alleviating, cognitive-improving and sexually-enhancing effects. Nonetheless, RCTs are yet to confirm these benefits in cancer patients.
Side-effects of excessive ginkgo consumption include headache, gastrointestinal disturbances (e.g. nausea, diarrhoea), dizziness, palpitations, convulsions (due to 4-methoxypyridoxine in ginkgo seeds), allergic skin reactions (by handling ginkgo seeds), and anaphylaxis-like reactions (intravenous administration only). Additionally, ginkgo enhances anticoagulant/antiplatelet activity and increases the risk of bleeding.

1.3.3 Western herbal medicine

Western herbal medicine (WHM) includes any mixture of herbs that are primarily native to Europe, which may take the form of tablets/capsules, infusions (teas), concentrated liquid extracts (requiring dilution) and lotions. WHMs share the same safety and quality issues associated with TCMs.

1.3.3.1 St. John’s wort (Hypericum perforatum)

St. John’s wort (SJW) is well-known for its antidepressant activity. While a Cochrane meta-analytic review of 29 RCTs suggests that SJW has similar efficacy to standard prescription antidepressants and fewer side-effects, numerous herb-drug interactions preclude its safe use in cancer patients and other populations. In fact, SJW is the most implicated herbal product in herb-drug interactions reported in the literature to date. Human studies suggest that SJW can interact with medicines by affecting drug metabolism (via induction of cytochrome P450 enzymes, particularly cytochrome P450 3A4, and P-glycoprotein) or levels of neurotransmitters (primarily serotonin). Consequently, SJW is contraindicated with the use of opioids, anaesthetics (e.g. fentanyl and propofol), benzodiazepines (e.g. midazolam) and anticoagulants (e.g. warfarin) in surgical patients, and opioid use for cancer pain in (palliative) patients (e.g. morphine, fentanyl). Additionally, SJW taken in combination with other antidepressants by cancer patients may result in reduced efficacy of the antidepressants or serotonin syndrome [cognitive, autonomic and somatic effects ranging from mild symptoms (e.g. hypervigilance, agitation, muscle twitching) to severe symptoms (e.g. tachycardia and hypertension that may lead to shock and death)]. Finally, SJW can reduce the efficacy of imatinib during chemotherapy for chronic myeloid leukaemia, gastrointestinal stromal tumours and other malignancies, while having the same effect accompanied by greater myelosuppression in advanced colorectal and lung cancer patients receiving irinotecan.
1.3.3.2 Garlic (*Allium sativum*)

Garlic has had a long history of use worldwide for general health, as well as in a variety of conditions including infections and cancer. Garlic can be eaten raw or cooked, may be dried or powdered and used in tablets/capsules, or taken in the form of oils and liquid extracts. Amongst others, garlic has been reported to have antimicrobial, antithrombotic, immune-enhancing, and anti-cancer/chemopreventive effects. A meta-analysis of 18 observational studies suggested that high consumption of raw and/or cooked garlic (but not garlic supplements) may be associated with reduced risk of colorectal and gastric cancers, although a review of intervention studies was recommended given that many of the studies identified did not control for dietary differences. A more recent meta-analysis of 2 small RCTs and 8 observational studies also found an inverse relationship between high garlic intake and colorectal cancer risk, despite great heterogeneity of measures of intake and lack of control for dietary differences. In contrast, a recent large RCT found that long-term garlic supplementation has no beneficial effects on the incidence of gastric cancer or the prevalence of precancerous gastric lesions. Further large prospective cohort studies and RCTs are needed.

Garlic appears to be generally safe, but may cause mild to severe gastrointestinal symptoms (stomach upset, heartburn, bloating) and allergic reactions (e.g. contact dermatitis, garlic burns and anaphylaxis resulting in possible death with topical or oral use). Human clinical trials using well-established probe drugs have demonstrated that oral garlic inhibits cytochrome P450 2E1 enzymes (but not 1A2, 3A4 or 2D6 enzymes), which may reduce the efficacy of chemotherapy involving dacarbazine (metastatic melanoma, Hodgkin’s lymphoma and other malignancies) and other drugs (e.g. anaesthetics). Finally, due to its anticoagulant properties, garlic should be avoided by patients undergoing surgery and should be used with caution by those taking anticoagulant/antiplatelet medications (e.g. warfarin, fluindione, aspirin).

1.3.3.3 Kava (*Piper methysticum*)

Kava, a psychoactive substance, is derived from the pepper plant and has been traditionally consumed as a beverage in cultural practices of Pacific countries. It has gained popularity in Western countries in recent years as a medicinal herb because of its anxiolytic, stress-relieving and sedative properties. The roots and rhizomes of kava are used to prepare
beverages, extracts, tablets/capsules, and topical solutions. Complementary medicine practitioners commonly prescribe kava for anxiety, sleep disorders and menopausal symptoms. A recent Cochrane meta-analytic review of 7 RCTs suggests that kava extract (60-280mg of kavalactones) is a safe, effective treatment for anxiety in the short-term (1-24 weeks) compared to placebo, but recommended that more rigorous studies be performed to clarify uncertainties about long-term efficacy and safety.144

Possible adverse effects of kava are of concern. Chronic and/or heavy use (300-400g per week) may cause appetite loss, leading to malnutrition and weight loss, shortness of breath, skin conditions (e.g. dry, scaly skin; yellow or white ulcer-like lesions known as kani or kava dermopathy), blood and metabolic abnormalities, loss of muscle control (ataxia/dystonia), and pulmonary hypertension.145 The most important concern with toxicity, however, involves several reports of hepatotoxicity (including those resulting in death and liver transplants) from use of concentrated kava extracts (but not beverages) in Europe and North America, which prompted several European countries to ban its use in 2002 and other countries (including Australia and the US) to issue health warnings to healthcare professionals and consumers advising of the potential (albeit rare) outcome of severe liver injury.146

1.3.3.4 Valerian (Valeriana officinalis)

Valerian, although native to Europe and Asia, grows in most parts of the world and has a long history of use as a sedative for sleep disturbance. The roots and rhizomes of valerian can be prepared to make supplements including capsules/tablets and liquid extracts, as well as infusions (teas). Short-term use (≤ 4-6 weeks) of valerian in recommended doses is generally well-tolerated. Common side-effects include central nervous system (e.g. headache, nervousness, dizziness) and gastrointestinal symptoms (notably diarrhoea, but also nausea, heartburn and epigastric pain).147 As with conventional sleep medications, chronic use of valerian (≥ 2-4 months) may result in insomnia, as well as withdrawal effects (e.g. delirium, tachycardia) if also used heavily.148

Valerian is often used for the treatment of insomnia, fatigue and anxiety/stress, which are common symptoms experienced by cancer patients. A Cochrane review found only one small RCT evaluating the treatment of anxiety disorders using valerian and recommended
that more, larger RCTs be performed before drawing any conclusions about its efficacy for anxiety.\textsuperscript{149} One systematic review of 29 controlled trials found no significant differences between valerian pills and placebo, overall, in healthy individuals or in individuals with general sleep disturbances or insomnia.\textsuperscript{150} A more recent meta-analysis of 18 RCTs, however, found that valerian resulted in significant improvement in subjective measures of sleep quality, but that the effect was not mirrored in objective sleep measures.\textsuperscript{147} Further RCTs are required. Overall, short-term use of valerian could be considered for some cancer patients (e.g. non-surgical patients who prefer not to take conventional sleep medications), particularly given there is no evidence of potential interactions with chemotherapy agents.

\subsection*{1.3.3.5 Evening primrose oil (\textit{Oenothera biennis})}

Evening primrose, although native to North America, grows in Europe and parts of the southern hemisphere. Flowers and seeds are pressed to make evening primrose oil (EPO) that contains gamma-linolenic acid (GLA), an omega-6 essential fatty acid believed to be the active ingredient. EPO is commercially available in capsule or liquid form and is widely used to treat menopausal symptoms, premenstrual syndrome and chronic mastalgia (breast pain associated with menstruation).\textsuperscript{151}

Breast cancer patients may experience symptoms of (premature) menopause (e.g. hot flashes, night sweats, vaginal dryness) as a result of chemotherapy, which may be exacerbated by therapy with tamoxifen in patients with hormone-receptor positive (HR+) tumours.\textsuperscript{152} Non-hormonal therapies in the form of herbal medicines such as EPO have become a popular alternative for women (including breast cancer survivors) for the treatment of menopausal symptoms, particularly since health risks were cast over prolonged use (> 5 years) of hormone replacement therapy by the Women’s Health Intervention study published in 2002.\textsuperscript{153} The menopausal benefits of EPO, however, have yet to be confirmed in RCTs involving postmenopausal women or breast cancer patients.\textsuperscript{154,155} Few studies examining the safety of EPO have been conducted either. Common adverse effects include headache and gastrointestinal symptoms (e.g. stomach upset, nausea, mild diarrhoea).\textsuperscript{156} Limited evidence suggests that EPO may lower the seizure threshold and increase the risk of seizures in individuals taking phenothiazines (e.g. fluphenazine).\textsuperscript{151} Finally, despite the absence of reported herb-drug interactions of EPO, it may be prudent to monitor use by patients receiving chemotherapy.\textsuperscript{141}
1.3.3.6 Black cohosh (*Actaea racemosa, Cimicifuga racemosa*)

Black cohosh, a member of the buttercup family, was traditionally used by the North American Indians and in 19th-century America for a variety of conditions ranging from gynaecological disorders to rheumatism, but has more recently been adopted for use in Europe and Western countries for the treatment of menopausal symptoms and dysmenorrhoea. The roots and rhizomes of black cohosh are commonly used fresh or dried to make infusions (strong teas), capsules, solid extracts used in pills, or liquid extracts.

Like evening primrose oil, black cohosh is used by breast cancer survivors for the treatment of menopausal symptoms. Alternatively, prostate cancer patients may use black cohosh to control hot flushes after surgical or medical castration (e.g. hormonal ablation). Systematic reviews of RCTs, however, have found inconclusive evidence to support the use of black cohosh for menopausal symptom relief in peri-/post-menopausal women and breast cancer patients. More rigorous RCTs of longer duration (> 6 months) are needed.

Black cohosh appears to be relatively safe despite reports that it may be associated with hepatotoxicity. The most important safety concern with black cohosh, however, is the fear that it has oestrogenic effects and may promote breast or uterine cancer in women. Early studies suggested an oestrogenic mechanism of action for black cohosh, but this may have been due to phyto-oestrogen contamination. More recent in vitro and human studies of unadulterated black cohosh extracts, though, have demonstrated no oestrogenic activity. Nevertheless, women with oestrogen-dependent cancers may want to avoid black cohosh until its long-term effects on breast or uterine tissue are more clearly established in epidemiological studies. Finally, no herb-drug interactions have been reported for black cohosh.

1.3.3.7 Echinacea (*Echinacea purpurea, Echinacea angustifolia, Echinacea pallida*)

Echinacea is an immunostimulant commonly used by cancer patients to boost their immune system and to prevent or treat upper respiratory tract infections. RCTs are yet to confirm these benefits in cancer patients, however. Short-term use of echinacea is relatively safe, although there is some concern about allergic reactions including rashes, increased asthma and, in rare cases, anaphylaxis. Echinacea use is contraindicated in individuals with asthma or atopy (a genetic tendency towards allergic reactions), given greater risk of an
allergic reaction. Currently, there are no verifiable reports of herb-drug interactions for any echinacea products.

1.3.3.8 Milk thistle (Silybum marianum, Carduus marianum)
The principal constituent of milk thistle is silymarin, which is a mixture of flavonolignans (silychristin, silydianin, silybin and others) isolated mainly from the seeds (fruit) of the plant. The seeds are used to prepare capsules, extracts, and infusions (strong teas). Evidence suggests that milk thistle has hepatoprotective, anti-cancer, tissue-regenerative, hypoglycaemic and cardioprotective properties. Milk thistle is being increasingly used by cancer patients for liver protection during chemotherapy and for detoxification between chemotherapy cycles or after chemotherapy, as well as an adjuvant treatment and chemopreventive agent.

A Cochrane meta-analytic review of 13 RCTs involving alcoholic and/or hepatitis B or C liver disease patients found significant benefits of milk thistle on mortality or hepatic complications across low quality trials alone, but not across all trials or high quality trials alone. High quality RCTs involving liver disease patients (including those with chemotherapy-induced hepatotoxicity) are needed. Reviews of preclinical studies and preliminary clinical trials also suggest that milk thistle extract may potentiate the antitumour action of certain chemotherapy drugs (e.g. doxorubicin, cisplatin) and radiotherapy and have chemopreventive potential (e.g. skin cancer, colorectal cancer), but rigorous RCTs are required to establish its efficacy and safety as an adjuvant or chemopreventive treatment.

Finally, reviews have established that the chronic use (≤ 41 months) of milk thistle is generally safe and well-tolerated in recommended doses. Gastrointestinal problems are the most common complaint, but are infrequent. Allergic reactions, ranging from itchiness to eczema and anaphylaxis, are rare. Large doses (> 1.5g/day) may cause diarrhoea, and very high doses (10-20g/day) can result in asymptomatic hepatotoxicity (hyperbilirubinaemia) in cancer patients. Drug interactions do not appear to be problematic either, although further study of milk thistle at higher doses is required.
1.3.3.9 European mistletoe (*Viscum album L.*)

Mistletoe has a long tradition of folk remedy use in Europe, but has been used extensively in recent years in adjuvant cancer treatment or as a standalone alternative therapy, by and large, in German-speaking countries (Switzerland, Austria, Germany). Its use in cancer treatment stems from anthroposophic medicine developed in the early 1900s, which approaches disease as an imbalance in the biological organism and utilises treatment strategies designed to restore this balance. Anthroposophic doctors believe that regular injections of mistletoe will inhibit or stop tumour growth and improve QoL in cancer patients. The stem and leaves of the semi-parasitic mistletoe plant are used to make commercial preparations (e.g. extracts, pressed sap) that are often administered by subcutaneous injection (near or directly into the tumour), but may be taken orally, intravenously or intrapleurally.

*In vitro* studies indicate that mistletoe or its main constituents (lectins, viscotoxins, polysaccharides, alkaloids) have anti-angiogenic, anti-cancer and immunostimulatory properties. In 2003, a systematic review of 10 RCTs found some benefits of mistletoe extract as adjuvant or standalone treatment for cancer patients, particularly in relation to QoL, across low quality trials alone; however, no benefits in terms of QoL, survival and other outcomes were demonstrated in higher quality trials. In contrast, another systematic review in 2003 involving 16 RCTs and 7 quasi-/non-randomised controlled trials of mistletoe preparations revealed that 12 studies exhibited significantly positive results on at least one clinically-relevant outcome measure, 7 studies indicated a positive trend on at least one measure, 3 showed no significant results and 1 demonstrated a negative trend. In 2007, a systematic review of 16 RCTs and 9 non-RCTs involving mistletoe use as adjuvant or standalone treatment found arguable benefits for cancer survival, but better evidence for the efficacy of anthroposophic mistletoe preparations in improving QoL and reducing toxicity of conventional treatments. Despite similar observations, a 2008 Cochrane meta-analytic review of 21 RCTs found weak evidence to support that mistletoe extract improves survival and QoL or reduces the adverse effects of chemotherapy and radiotherapy, although the conclusions for QoL were qualified by stating that a small number of higher quality trials suggested possible benefits for breast cancer patients during chemotherapy.
Seeking to minimise the problems of previous reviews (e.g. heterogeneity), a more recent systematic review limited to 18 RCTs and observational studies\textsuperscript{180} found inconsistent evidence for the efficacy of mistletoe preparations as adjuvant or standalone treatment in increasing cancer survival and tolerance to chemotherapy and radiotherapy, but concluded that there was clear evidence for enhanced QoL and that these benefits were not limited to specific mistletoe preparations or cancer populations. The latest systematic review (26 RCTs, 10 non-RCTs) has further confirmed the QoL benefits also.\textsuperscript{181} Nevertheless, more high quality prospective trials are needed to consolidate the positive QoL effects of mistletoe preparations in cancer patients.

Mistletoe preparations are usually well-tolerated and that serious adverse effects are rare (cf. mistletoe plants and berries, which are poisonous) when used as directed under the supervision of health professionals.\textsuperscript{179,180} Depending on the dose, local reactions (e.g. pruritus, erythema or induration at the injection site) have been observed in 0.9-43\% of cancer patients\textsuperscript{182} and systemic reactions (e.g. headaches, fever, influenza-like symptoms) in up to 10\% of patients.\textsuperscript{179} Allergic reactions (e.g. breathing difficulties, anaphylaxis) have been reported, but are rare (< 1\%).\textsuperscript{182} Also, long-term use of mistletoe extracts may reduce T-cell function in cancer patients without local reactions, thus use should be suspended periodically to allow T-cell reactivity to recover.\textsuperscript{183} Finally, herb-drug interaction studies involving mistletoe use in cancer patients are required, given their virtual non-existence.

1.4 \textit{Manipulative and body-based practices}

Manipulative and body-based practices focus primarily on body structures and systems including bones and joints, soft tissue, and the circulatory and lymphatic systems.\textsuperscript{184} They involve manipulation or movement of one or more parts of the body in order to heal the body and achieve good health. Examples include massage, acupuncture/acupressure, chiropractic and osteopathic manipulation, tui na, reflexology, and Bowen therapy. There is considerable variation in the level of formal training and approaches taken by practitioners both across and within modalities (e.g. chiropractic and osteopathic manipulation primarily involve rapid movements, whereas massage therapy involves slower application of force). Despite this heterogeneity, manipulative and body-based practices share some common principles (e.g. the human body is self-regulating, parts of the body are interdependent) and features (e.g. therapies tend to be tailored to the specific needs of patients).
1.4.1 Massage therapy

Massage therapy involves the systematic manipulation of soft tissues of the body; examples include Swedish massage, aromatherapy, shiatsu, reflexology and acupressure. The common goal of most massage techniques is to promote relaxation and general well-being. Overall, therapeutic massage administered by trained practitioners is very safe. Two reviews, one focusing on cancer patients, found few reported adverse events. While there is no evidence that massage therapy can spread cancer, applying direct pressure over known tumours is best avoided. Reduced pressure and/or avoidance of direct or deep tissue massage is also advisable for cancer patients with coagulation disorders (and those using anticoagulant/antiplatelet medications, such as warfarin and aspirin), bone metastases or severe osteoporosis, open wounds or radiation dermatitis, and prosthetic devices (e.g. infusaport, colostomy bag, stents). Additionally, caution is advised with use of aromatherapy essential oils in cancer patients with renal or liver disorders, and direct application should be avoided in those with wounds, skin conditions or allergies to essential oils.

A Cochrane meta-analytic review of 8 RCTs found limited evidence for short-term benefits of massage/aromatherapy on anxiety in cancer patients, but inconclusive results for other symptoms. More recent systematic reviews of RCTs and observational studies have also suggested that massage may alleviate anxiety, as well as other symptoms such as pain, nausea, depression and stress. Larger RCTs are required, but massage therapy should be supported for use by patients in the interim given the encouraging evidence for symptom control and safety.

1.4.2 Acupuncture

Acupuncture, a key aspect of TCM, is a family of procedures that involves the application of needles, pressure, heat and other treatments to the skin at particular sites called acupuncture points for therapeutic purposes. Acupuncture performed by competent and experienced practitioners is safe.

Systematic reviews revealed that there is no convincing evidence that acupuncture alleviates cancer pain or hot flushes in breast and prostate cancer patients, although further randomised controlled trials (RCTs) were recommended. In contrast, a
Cochrane meta-analytic review of 11 RCTs concluded that acupuncture-point stimulation (manual acupuncture, electroacupuncture, self-/practitioner-administered acupressure) in combination with antiemetics demonstrated benefits for acute chemotherapy-induced nausea and/or vomiting and complemented the positive evidence for postoperative nausea and vomiting.\textsuperscript{196} Additionally, an exploratory meta-analysis of 11 Chinese non-randomised clinical trials of poor quality found that acupuncture was associated with an increase in leukocytes during chemotherapy and chemoradiation, suggesting that acupuncture may be effective in reducing leukopenia in patients undertaking such treatments.\textsuperscript{197} Finally, several pilot studies suggest that acupuncture may improve radiation-induced xerostomia in head and neck cancer patients (e.g. [Cho et al, Garcia et al]),\textsuperscript{198,199} although RCTs are needed to further confirm these promising results.

\textbf{1.4.3 Exercise interventions}

There are two broad categories of exercise. Aerobic or cardiorespiratory exercise involves large muscle groups performing continuous or intermittent physical activity over an extended period of time, while anabolic or resistance exercise involves performing sets of repetitive movements against a resistance during which neuromuscular fatigue occurs within 6-12 repetitions.\textsuperscript{200} Exercise may be home-based or take the form of highly structured, supervised interventions. Cancer survivors and patients undergoing treatment are generally prescribed aerobic and/or resistance exercise of low to moderate intensity and regular frequency (3-5 times per week) for at least 20 minutes per session.\textsuperscript{201}

Aerobic and resistance exercise appear to be relatively safe in cancer patients during treatment or survivorship, even in home-based programmes and older or advanced cancer patients.\textsuperscript{202,203} Recent meta-analytic and systematic reviews have found that serious adverse events (e.g. back injury; falls; development or exacerbation of lymphoedema, anaemia or cachexia) are rare, and that the most common minor adverse effects (e.g. hip/calf pain, pulled hamstring, shoulder tendonitis) of exercise interventions were no more frequent compared to control interventions in RCTs.\textsuperscript{203-205}

A meta-analysis and systematic review of exercise-based and psychological interventions revealed in a subgroup analysis of 17 RCTs that there were no significant decreases in cancer-related fatigue (CRF) during treatment or survivorship for predominantly non-
metastatic cancer patients who completed various exercise-based interventions.\textsuperscript{206} In contrast, a Cochrane meta-analytic review of 28 RCTs found a small beneficial effect of exercise in reducing symptoms of CRF during treatment or survivorship in patients (predominantly diagnosed with breast cancer) who completed various exercise-based interventions compared to control interventions.\textsuperscript{207} A more recent meta-analysis of 18 RCTs examined the effects of different exercise parameters on CRF symptoms experienced during cancer treatment.\textsuperscript{208} Overall, exercise produced small significant reductions in CRF for breast cancer patients and moderate significant reductions in prostate cancer patients. Supervised aerobic exercise interventions proved more effective in reducing CRF during breast cancer treatment than home-based programmes, which did not significantly decrease CRF. Clearly, further large RCTs comparing different forms of exercise interventions across settings and patient populations with CRF are needed.

Looking beyond CRF, a meta-analysis of 16 randomised and 14 non-randomised trials found that exercise interventions resulted in small positive effects on clinical and QoL outcomes (physical functioning, symptoms other than fatigue, body composition, fatigue, mood, overall QoL) during cancer treatment, although larger effects were generally contributed by poorer quality studies.\textsuperscript{209} Similarly, a systematic review of 3 RCTs and 5 non-randomised trials found positive effects on QoL and physical outcomes in metastatic cancer patients, although heterogeneity was problematic and limited the generalisability of results.\textsuperscript{210} Also, a Cochrane meta-analytic review of 9 RCTs revealed a moderate positive effect of exercise interventions on physical functioning during adjuvant breast cancer treatment (and insufficient evidence for other outcomes, such as fatigue, mood disturbance, immune function and weight gain), although heterogeneity again was problematic.\textsuperscript{211} A more recent meta-analysis of exercise and behavioural interventions revealed in a subgroup analysis of 17 RCTs that physical exercise produced small positive effects on fatigue, depression, body image and QoL in breast cancer survivors or patients receiving treatment.\textsuperscript{212}

Finally, in the most comprehensive evaluation to date, a meta-analysis and systematic review of 74 RCTs and 8 non-randomised trials (including 66 judged to be of high quality) showed a large beneficial effect of exercise interventions for cancer survivors on lower and upper body strength and moderate effects on fatigue and breast cancer-specific concerns.\textsuperscript{205}
Small to moderate positive effects in cancer patients undergoing treatment were observed for physical activity level, aerobic fitness, muscular strength, functional QoL, anxiety and self-esteem. More large RCTs, as prescribed for CRF, are recommended in evaluating exercise interventions targeting other clinical and QoL outcomes.

1.5  **Energy therapies**

Energy therapies involve the use of two types of energy fields. Veritable energy fields, which can be measured, employ mechanical vibrations (e.g. sound) and electromagnetic forces including visible light, magnetism, monochromatic radiation (e.g. laser beams), and rays from other parts of the electromagnetic spectrum. Specific, measurable wavelengths and frequencies are used to treat individuals.\(^{213}\) In contrast, putative energy fields or biofields are theorised to surround the body and have yet to be scientifically measured. Biofield therapies are based on the concept that humans are infused with a subtle form of energy or life force (termed differently in different cultures; for example, qi in TCM, ki in the Japanese Kampo system, doshas in Ayurvedic medicine, and elsewhere as prana, etheric energy and other names) that can be manipulated to effect changes in the physical body and influence health.\(^{214,215}\)

1.5.1  **Biofield therapies**

Biofield therapies refer to techniques which use energy fields that purportedly surround the human body to stimulate one’s own healing (internal practices; e.g. internal Qigong) or healing in others (external practices; e.g. external Qigong, therapeutic touch, healing touch, Reiki, Johrei, polarity therapy). Energy fields are sometimes manoeuvred by manipulating the body using light touch or placing the hands above the body. The broad goal of biofield therapies is to heal mental or physical disorders by rebalancing the energy fields in the body or by drawing upon spiritual energies for such healing. Cancer patients may use them to improve general well-being and QoL (e.g. pain relief), particularly in palliative and supportive care settings. Biofield therapies are generally safe when administered by trained practitioners. Although few (if any) adverse events have been reported for touch therapies (healing touch, therapeutic touch, Reiki),\(^{216}\) use of Reiki is not advised for individuals with (a history of) psychosis, personality disorders or bipolar disorder.
1.5.1.1 Qigong

Qigong is the most studied biofield therapy among cancer patients and refers to a whole host of different meditative exercises (sometimes combined with breathing techniques, imagery and/or vocalisation of sounds) from traditional Chinese medicine used to prevent or slow disease and maintain health. Medical Qigong, however, has been specifically developed for the treatment and cure of disease (e.g. hypertension, arthritis, cancer, HIV), and may be used as an adjunct to conventional medical treatments. Given its utilisation of meditation, imagery and breathing techniques and dependence on regular practice, Qigong has many parallels to Western behavioural medicine.

Qigong is generally safe for most individuals when instructed by qualified practitioners and practiced correctly according to standard moderate principles. Abnormal psychosomatic responses and culture-bound psychiatric disorders (specific to individuals of Chinese or other Asian ethnicities, even when living in Western countries) may be induced, however, when Qigong is practiced inappropriately, excessively and/or unguided, particularly by psychologically vulnerable individuals. Serious adverse events are rare, but Qigong-induced psychiatric disorders are becoming more prevalent in China. Adverse effects may include sensory or somatic disturbances (e.g. headache, dizziness, chest tightness, tachycardia, breathlessness); motor disturbances (e.g. muscle twitching, tremors, odd limb movements, uncontrolled motor activity); cognitive impairment (e.g. memory, attention); psychological symptoms (e.g. anxiety, irritability, hypochondriasis, obsessive thoughts or images, delusions, visual/auditory hallucinations, disorganised speech, dissociation, altered consciousness, disorientation, mania, depression, suicidal or bizarre behaviour); and allergic skin reactions.

An exploratory review of 21 Chinese studies (mostly controlled) revealed that cancer patients predominantly treated with internal Qigong and conventional medical treatment exhibited a consistent tendency for greater improvement on biological indicators and/or longer survival time than those who received conventional treatment alone, but concluded that there was much need for replication and improved methodological quality in future studies. A more recent systematic review of 9 controlled studies involving palliative/supportive care cancer patients, however, was less positive and concluded that the efficacy of internal Qigong (alone or combined with conventional medical treatment) in
cancer care is not yet supported due to the poor methodological quality of existing studies, and recommended that large-scale RCTs be performed along with studies investigating possible scientific mechanisms. Finally, a systematic review of 66 RCTs and observational studies examining a variety of practitioner-administered biofield therapies (external Qigong, therapeutic touch, Reiki, spiritual healing, healing touch and others) in different medical populations found moderate (level 2) evidence for their efficacy in reducing acute pain in cancer patients and postoperative and hospitalised patients, but mixed (level 4) evidence for chronic pain, fatigue, physiological arousal (heart/respiratory rate, blood pressure) and QoL in cancer patients. Again, larger high-quality studies were advised.

1.5.2 *Bioelectromagnetic-based therapies*

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as magnetic, pulsed or alternating-/direct-current fields. Examples include magnetic, millimetre wave, sound energy (vibrational or frequency), and light therapy.

1.5.2.1 *Microwave (UHF radiowave)/Tronado therapy*

Microwave or ultra high frequency (UHF) therapy is designed to treat cancer via exposure of tumorous tissue to electromagnetic radiation delivered using frequencies ranging 300MHz-3GHz (although super high and extra high frequencies ranging up to 300GHz have reportedly been utilised also). UHF frequencies commonly used include 200-300MHz, 434MHz, 915MHz and 2450MHz. Microwave therapy is generally thought to exert therapeutic effects via direct or indirect heating of cancer cells, thus thermometry is typically undertaken at the time of treatment to measure intra-tumour temperature. Microwave therapy is usually combined with conventional radiotherapy or uncommonly with infusions of glucose-blocking agents (e.g. cyclophosphamide, cystine disulphide or penicillamine disulphide), and is often administered 5 days per week over a period of weeks.

A systematic review of 58 controlled and uncontrolled studies (mostly poor quality due to the absence of single or double-blind RCTs and inadequate patient follow-up, and exhibiting significant clinical heterogeneity), largely comparing microwave therapy and radiotherapy combined to microwave therapy alone in relation to tumour response and
overall survival, found minimal evidence to support the routine use of microwave therapy for cancer treatment.\textsuperscript{228} Additionally, in the same review, a limited clinical audit of the medical records of 179 cancer patients treated in Western Australia suggested that microwave therapy with radiotherapy resulted in greater toxicity than radiotherapy alone or microwave therapy with glucose-blocking agents for patients with bladder or other invasive cancers. Some of the more common adverse effects associated with microwave therapy appear to be pain, erythema, fibrosis, necrosis, ulcerations, blisters and thermal burns. Third degree burns, arterial rupture and development of fistulae have been reported on occasions, as have deaths (often related to inadvertent heating of blood vessels or infections following invasive thermometry).\textsuperscript{228,229}

2. **Summary Conclusions**

The complementary and alternative therapies used by cancer patients are diverse in their origin, premise (including proposed or actual mechanisms of action), practice, efficacy and safety. Cancer patients and other members of the public are mostly unaware of distinctions between conventional drugs registered by the Therapeutic Goods Administration (TGA) and may believe that a CAM listed by the TGA has been assessed as both effective and safe and approved for such use by the Federal Government. Additionally, many complementary and alternative therapies have long histories as components of ancient traditional medical practices, but have only been subjected to rigorous scientific investigation in the last 10-20 years. More research is required to evaluate or confirm the efficacy and safety of many of these therapies.

Currently, however, there is evidence from high quality clinical trials that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving QoL and psychological functioning (e.g. relaxation). There is evidence of potential harm also. Nutritional supplements, herbal preparations, and other natural therapies among the biologically-based practices may pose direct safety risks because of their potential adverse effects or interactions with conventional anticancer treatments (chemotherapy, radiotherapy, surgery, hormonal therapies) and other medications. Some should not be used under any circumstances in cancer patients, irrespective of potential benefit (e.g. St. John’s wort), while others may be beneficial when patients are not undergoing these treatments.

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and have no other contraindications (e.g. valerian for short-term amelioration of sleep problems in non-surgical cancer patients). Alternative therapies promoted as “cures” in place of conventional treatments (e.g. shark cartilage) have the potential to cause patients (and their loved ones) the most harm, however, when they forego evidence-based cancer treatments that are likely to be more effective.

In conclusion, whether termed complementary medicine or integrative oncology, cancer physicians in Australia should strongly consider offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services. Conceivably, this may influence patients to continue with mainstream care and help them avoid any potential harm that may occur with autonomous CAM use. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment and care.

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3.2 Post-Publication Update to the Systematic Review in Study 2

This literature update of the systematic review of CAMs used by cancer patients that comprised study 2 will follow the same structure observed in the preceding manuscript.

3.3 Whole Medical Systems

3.3.1 Homeopathy

Two subsequent reviews evaluating the efficacy and/or safety of homeopathy in cancer patients have been published. Consistent with the systematic review in study 2, Frenkel (2010) concluded in a narrative review of randomised controlled trials (RCTs) and observational studies that while homeopathic medicines appear to be safe and may offer symptom relief and concomitant improvement in QoL for cancer patients, the outcomes were equivocal and further clinical trials were required. Additionally, the author noted that no controlled trials to date had demonstrated anticancer effects. Furthermore, in a recent systematic review of 57 meta-analytic/systematic reviews (including 11 relating to cancer) involving homeopathic controlled clinical trials, the Australian National Health and Medical Research Council (2013) found insufficient evidence that homeopathy is an effective treatment for any of the 68 health conditions considered. Endemic of the great majority of studies evaluated, there was a paucity of large, good-quality studies amongst the 7 RCTs of homeopathic management of cancer treatment-related symptoms (adverse effects of venous cannulation, chemotherapy-induced nausea/vomiting and stomatitis, hot flushes in women with a history of breast cancer, radiodermatitis in breast cancer patients undergoing radiotherapy); all of which were assigned a very low or low level of confidence rating for the weight of evidence provided.

3.3.2 Naturopathy

Given the overlap of naturopathic remedies with other categories of CAM, updates will be reviewed in their respective sections below.

3.3.3 Traditional Chinese Medicine

Three subsequent reviews evaluating the efficacy and/or safety in cancer care of traditional Chinese medicine (TCM) in general have been published. In a systematic review of 2385 Chinese RCTs and 579 non-randomised controlled trials / observational studies evaluating the efficacy of TCM (predominantly herbal medicine and acupuncture-point
stimulation) ± conventional treatment (72% combined), 756 (26%) studies recommended TCM be incorporated into standard treatment based on efficacy and safety (Li et al., 2013). However, the review authors assessed only 5 of those studies as well-designed RCTs exhibiting significantly improved survival, and recommended further studies and improved reporting of randomisation and blinding procedures in future Chinese controlled trials to meet international standards. Similar conclusions were also drawn in systematic reviews of Chinese retrospective case series reports (Yang et al., 2012) and case studies (Liu et al., 2011) evaluating TCM in cancer care. These outcomes are consistent with the systematic review in study 2.

### 3.4 Mind-Body Techniques

#### 3.4.1 Relaxation

Two subsequent reviews evaluating the efficacy of relaxation techniques in cancer care have been published. Consistent with the systematic review in study 2, a large meta-analytic/systematic review of psychological-based interventions revealed that relaxation training (± imagery techniques) demonstrated significant small-medium effect sizes for emotional distress, anxiety, depression and QoL in cancer patients at post-treatment (based on 46 RCTs; Faller et al., 2013). The authors concluded that beneficial effects of relaxation training were evident in the short-term, although the effects on emotional distress and anxiety outcomes may have been more pronounced due to possible publication bias (i.e. the disproportionate contribution of larger effect sizes by small studies). Additionally, in a review of pharmacological/non-pharmacological interventions for hot flushes, Morrow and colleagues (2011) concluded that relaxation techniques (two trials of post-menopausal women, a systematic review of psychoeducational interventions including 9 RCTs involving breast cancer survivors) appeared to alleviate hot flushes and should be considered as an alternative or as a complement to non-hormonal medications in individuals with cancer. However, further studies were recommended given the poor methodological quality of the evidence.

#### 3.4.2 Meditation

Two subsequent reviews evaluating the safety of meditation practices have been published or newly-located. Consistent with the systematic review in study 2, serious adverse events were found to be rare in two meta-analytic/systematic reviews of RCTs
involving medical patients and trait anxiety-prone populations, respectively (Arias, Steinberg, Banga, & Trestman, 2006; Orme-Johnson & Barnes, 2014). Furthermore, Arias and colleagues (2006) concluded that the outcomes supported the safety of meditation practices for treating medical patients (including emotional disturbance in cancer patients), particularly those with non-psychotic mood and anxiety disorders. This further reinforces the recommendation of study 2 that, first and foremost, meditation practices (transcendental or Vipassana meditation, in particular) should be used with caution or are best avoided in cancer patients with (a history of) psychosis or related symptomatology.

Eight subsequent reviews (and one RCT of transcendental meditation) evaluating the efficacy of meditation practices in cancer care have been published or newly-located. Consistent with study 2, meta-analytic/systematic reviews of mindfulness-based stress reduction (MBSR) involving 3 RCTs and 3 controlled trials plus 6 observational studies, respectively, suggested that MBSR compared to standard care may decrease anxiety, stress and depressed mood in breast cancer patients and survivors (Cramer, Lauche, Paul, & Dobos, 2012; Zainal, Booth, & Huppert, 2012). Similar outcomes were reported in other systematic reviews of breast cancer patients and survivors (Casellas-Grau, Font, & Vives, 2014; Matchim, Armer, & Stewart, 2011), as well as recent meta-analytic/systematic reviews of MSBR ± other mindfulness-based therapies involving mixed cancer patients and survivors (Piet, Würtzen, & Zachariae, 2012; Musial, Büssing, Heusser, Choi, & Ostermann, 2011; Shennan, Payne, & Fenlon, 2011; Hofmann, Sawyer, Witt, & Oh, 2010). The general consensus among the review authors, however, was that the methodology employed was poor and more large, high-quality RCTs were required involving male and other non-breast cancer populations (preferably diagnosed with psychological disorders to be targeted), active treatment control groups (e.g. relaxation training), standardised treatment protocols and measures of mindfulness and longer follow-up periods.

Finally, in the only controlled trial of transcendental meditation (TM) in the cancer literature to the author’s knowledge, a single-blind RCT involving 130 older, predominantly early-stage breast cancer patients revealed significant improvements in overall QoL and emotional and social well-being after a median 18 months of TM when compared with standard care (Nidich et al., 2009). Improvements in functional and spiritual well-being were not exhibited by TM patients, however. As with mindfulness, further RCTs are required involving larger samples of different cancer patients and survivors (preferably diagnosed with psychological disorders to be targeted), active treatment control
groups, standardised treatment protocols and longer follow-up periods. Adverse effects should also be monitored given previous concerns raised about the safety of intensive TM (refer to study 2).

### 3.4.3 Hypnotherapy

One subsequent review evaluating the efficacy of hypnotherapy in cancer prevention and care has been published (Montgomery, Schnur, & Kravits, 2013). In a comprehensive narrative review, Montgomery and colleagues (2013) found mixed evidence for the efficacy of hypnotherapy in cancer prevention based on previous meta-analytic/systematic reviews. While overweight/obesity is a risk factor for cancer and hypnotherapy has the capacity to double weight loss when combined with cognitive-behavioural therapy in weight loss programmes, the authors overlooked the necessity of presenting meta-analytic findings of such programmes that actually show significant reduction of cancer risk or mortality. Additionally, they found insufficient evidence from several meta-analytic/systematic reviews to support the use of hypnotherapy for smoking cessation, and recommended more rigorous RCTs examining the additive effect of hypnotherapy combined with other treatments and potential moderators of any beneficial treatment effects (e.g. social support).

In relation to cancer diagnosis, based on 4 RCTs and a cost-benefit study, the review authors found that hypnotherapy may be effective in controlling acute pain and distress in breast and other cancer patients undergoing diagnostic procedures (as per study 2), with significant overall cost savings being delivered for breast biopsies alone. Identical outcomes were revealed for surgical procedures and percutaneous cancer treatment also, with clinical benefits extending to reduced recovery and treatment time in the former and less pain medication in the latter compared to standard care or empathic attention control groups. Large-scale RCTs of hypnotherapy involving non-breast cancer patients (curative and palliative) undergoing chemotherapy or radiotherapy as well as cancer survivors, and including longer follow-up periods and cost-benefit analyses were recommended.

### 3.4.4 Yoga

Twelve subsequent reviews evaluating the efficacy and/or safety of yoga in cancer care have been published. Several systematic/meta-analytic and narrative reviews provide preliminary support for the efficacy of yoga interventions in breast cancer patients and
survivors. Positive short-term benefits were demonstrated for a range of outcomes including (overall) QoL, general, physical/functional, emotional and social well-being, anxiety, depression, mood and stress (Shneerson, Taskila, Gale, Greenfield, & Chen, 2013; Sadja & Mills, 2013; Zhang, Yang, Tian, & Wang, 2012; Cramer, Lange, Klose, Paul, & Dobos, 2012a; Buffart et al., 2012; Harder, Parlour, & Jenkins, 2012; Culos-Reed, Mackenzie, Sohl, Jesse, Zahavich, & Danhauer, 2012; Levine & Balk, 2012; Lin, Hu, Chang, Lin, & Tsauo, 2011). Mixed preliminary evidence was reported for fatigue (Sadja & Mills, 2013; Zhang et al., 2012; Cramer et al., 2012b; Harder et al., 2012; Buffart et al., 2012; Culos-Reed et al., 2012; Boehm, Ostermann, Milazzo, & Büsing, 2012), while no significant benefits were detected for sleep quality (Zhang et al., 2012; Buffart et al., 2012). Long-term benefits of yoga in breast cancer patients and survivors, however, were difficult to ascertain as few studies included long-term follow-up.

Overall, the great majority of studies included in these reviews suffered from a number of limitations, including small sample sizes, biased sampling (e.g. mostly Caucasian women), poor screening (e.g. few fatigue studies, if any, purposely recruited patients or survivors suffering cancer-related fatigue), poor blinding practices (e.g. few studies reported blinding of outcome assessors), heterogeneity of yoga intervention type, components and duration/length, no use of objective measures where appropriate (e.g. physiological measures for fatigue, such as haemoglobin levels), no inclusion of active treatment control groups (e.g. physical activity intervention group), and no long-term follow-up or assessment of adverse effects. Larger, high-quality RCTs addressing these limitations are required.

Finally, a recent Cochrane meta-analytic review found inconclusive evidence to support the use of yoga interventions in haematological cancer patients, and advised that large, high-quality RCTs were needed (Felbel, Monsef, Engert, & Skoetz, 2014). Only one small RCT met criteria for inclusion, which revealed no benefit of Tibetan yoga over and above standard care for distress, depression, anxiety and fatigue and only low quality evidence supporting improved sleep quality. Adverse effects were not addressed either.

3.4.5 Tai Chi

Two subsequent reviews evaluating the efficacy of tai chi in breast cancer care have been published. Consistent with study 2, two small meta-analytic/systematic reviews of RCTs provided insufficient support for the positive impact of tai chi on physical and
psychological outcomes in breast cancer patients and survivors (Zeng, Luo, Xie, Huang, & Cheng, 2014; Yan, Zhang, Sun, & Cui, 2013). Non-significant effect sizes were reported for several outcomes (physical, social/family and functional well-being, other QoL concerns, body mass index, body fat mass, bone mineral density, muscle strength), while only a small effect size was identified for emotional well-being in the latter study. Again, large high-quality RCTs examining the efficacy and safety of tai chi in breast and other cancer populations are required to address the same limitations observed in the yoga literature reported above.

3.4.6 Music-Related Therapies

Since study 2, a distinction in nomenclature has been made more apparent in the cancer literature between “music therapy” and “music medicine”. Music medicine involves passive listening, usually prerecorded music selected by medical staff (with or without a background in music therapy) that may or may not consider patient preferences (Trondalen & Bonde, as cited in MacDonald, Kreutz, & Mitchell, 2012; Bradt, Dileo, & Shim, 2013). In contrast, music therapy comprises prerecorded, live and/or interactive music that is individually tailored by a music therapist that engages in a therapeutic process with patients (Bradt et al., 2013). Either may be used alone or in combination with relaxation/imagery techniques. Fifteen subsequent reviews evaluating the efficacy and/or safety of music-related interventions (music therapy, music medicine) in cancer care have been published or newly-located.

In relation to cancer diagnosis and surgical procedures, two meta-analytic studies examining RCTs involving colonoscopy (a screening method for colon cancer) found that music medicine was a safe, effective technique for reducing procedure time, anxiety and sedative medication (Bechtold et al., 2009; Tam, Wong, & Twinn, 2008), but not procedural pain (Bechtold et al., 2009) Similarly, a small systematic review of RCTs involving colposcopy (a diagnostic test for cervical cancer following an abnormal pap smear) suggested that anxiety and pain levels may be reduced by listening to music during the procedure (Galaal, Bryant, Deane, Al-Khaduri, & Lopes, 2011). Additionally, a large Cochrane meta-analytic review and two systematic/narrative reviews of controlled trials (Bradt et al., 2013; Gooding, Swezey, & Zwischenberger, 2012; Nilsson, 2008), albeit of poor methodological quality overall, suggested that self-reported pre-operative anxiety may be reduced by music-related interventions (predominantly passive listening compared to
standard care), but this may not translate to physiological indicators (heart/respiratory rate, systolic/diastolic blood pressure, skin temperature; Bradt et al., 2013). No adverse effects were identified either (Bradt et al., 2013). Similarly, a Cochrane meta-analytic review and three systematic/narrative reviews of controlled trials (Cepeda, Carr, Lau, & Alvarez, 2006; Cole & LoBiondo-Wood, 2014; Gooding et al., 2012; Engwall & Duppils, 2009), albeit of poor methodological quality overall, suggested that music-related interventions could be used as an adjuvant to pain medication to reduce postoperative pain and analgesic use. Further high-quality RCTs are required examining the impact on procedural and pre-/postoperative outcomes of specific music-related interventions, alone and in comparison to or combination with other active treatments (e.g. relaxation/imagery, psychoeducation, pharmacotherapy). Ideally, they would incorporate both homogeneous and heterogeneous samples of cancer patients, more music therapy interventions, standardised types and durations of music intervention, a combination of standardised self-report measures and physiological measures, baseline measures of medication intake and cost-benefit analyses of any reduced medication use.

In cancer care per se, a Cochrane meta-analytic review of 30 controlled trials (including two paediatric studies) and a meta-analytic/systematic review of 32 RCTs provided preliminary support for the efficacy of music-related interventions relative to standard care or other active treatment control groups (Bradt et al., 2011; Zhang et al., 2012). Benefits were demonstrated for a range of psychological and physiological outcomes, including self-reported (coping) anxiety, mood, pain, heart/respiratory rate and blood pressure. Mixed evidence was found for depression and none for the amelioration of fatigue, physical status or QoL. These two reviews have since been criticised for unnecessarily including heterogeneous and ambiguous data from studies not only of poor methodological quality, but also from several studies predating guidelines for reporting clinical trials established in the mid-1990s (Tsai et al., 2014; Nightingale, Rodriguez, & Carnaby, 2013). Furthermore, a limited re-analysis of the aforementioned Cochrane review indicated that music-related interventions did, indeed, have a significant impact on QoL following the removal of one problematic study (Archie, Bruera, & Cohen, 2013).

In a more contemporary meta-analytic review of 21 higher-quality controlled trials and a large comprehensive narrative review of controlled/observational studies, evidence suggested that music-related interventions may have positive effects on self-reported anxiety, depression, mood, pain, fatigue and QoL in cancer patients (Tsai et al., 2014;
Subgroup analyses in the meta-analytic review also revealed that music-related interventions were more effective when patients rather than medical staff or researchers selected the music. In contrast, a meta-analytic/systematic review of 13 high-quality RCTs suggested a positive impact on self-reported anxiety in cancer patients in the systematic review, but then revealed a non-significant effect size when 4 amenable RCTs were subjected to meta-analysis and subsequent subgroup analysis (Nightingale et al., 2013). The authors argued that the high quality study selection combined with study heterogeneity (variable samples and music intervention approaches) accounted for the disparity of their results from previous meta-analytic reviews. Nevertheless, despite the merits of these two most recent meta-analytic reviews, both were still limited by the omission of studies that contained active treatment control groups and analyses examining physiological measures of anxiety. Consequently, the conclusions of study 2 still hold—that is, only preliminary evidence for efficacy exists and larger, high-quality RCTs are required (as specified for procedural and pre-/postoperative outcomes above), but use of music-related interventions in cancer patients could be supported in the interim given its very good safety profile and economy in terms of time and expense.

3.4.7 Support Groups

Since study 2, the concept of internet cancer support groups (ICSGs) has gained in popularity, so much so that it has been the subject of two published or newly-located reviews. Briefly defined, ICSGs enable cancer patients and survivors to share experiences and opinions and to seek, receive and provide information (diagnosis, treatment, other cancer-related resources), advice or emotional support online (Griffiths, Calear, & Banfield, 2009). The online resources utilised include chat rooms, bulletin boards, mailing lists/newsgroups/online web forums, instant messaging and blogs (Griffiths et al., 2009; Im & Chee, 2008).

Two subsequent reviews evaluating the efficacy of ICSGs in cancer care have been published. Griffiths and colleagues (2009) in their systematic review of 28 studies examined the effects on depression of internet support groups (ISGs) in a range of populations (e.g. patients, caregivers, adolescents) including breast cancer patients (6 studies, 2 RCTs). While the poor methodological quality and heterogeneity of the studies precluded meta-analysis, they found that breast cancer ISGs were more likely to report reduced depression than studies of other populations (Griffiths et al., 2009). Nevertheless,
these results were rendered inconclusive by the low quality of the studies and the majority being performed by one research group. In a more comprehensive systematic review of 24 studies evaluating ICSGs and related online resources in cancer patients and survivors (mostly small studies of Caucasian breast cancer survivors, 4 RCTs), Hong and colleagues (2012) found that most studies reported psychosocial benefits. However, evidence was deemed inconclusive as none of the RCTs reported significant benefits (Hong, Peña-Purcell NC, & Ory, 2012). Large, high-quality RCTs involving homogeneous and heterogeneous cancer populations (e.g. treated patients vs survivors, non-breast cancer and ethnically diverse samples) are required, comparing ICSGs to active treatment control groups (e.g. more traditional support groups) across both psychosocial and physical/QoL outcomes and including long-term follow-up.

3.4.8 Spirituality, Religion and Prayer

Three subsequent reviews evaluating the role of spirituality and religion in cancer prevention and care have been published. In a large, comprehensive systematic review examining the relationship between religion/spirituality and health, 123 of 137 studies (and 90% of the 83 methodologically most rigorous of these studies) demonstrated a significant inverse relationship between religion/spirituality and cigarette smoking, while none reported significant positive associations (Koenig, 2012). Given the causative relationship between cigarette smoking and lung cancer, the author concluded that decreased cigarette smoking associated with religion/spirituality will lead to a reduction in lung cancer and concomitant chronic obstructive pulmonary disease, not to mention reduced risk for cancer in general. More equivocally, 16 of 29 studies (and 60% of the 20 methodologically most rigorous of these studies) also revealed a significant inverse relationship between religion/spirituality and cancer risk or poor prognosis, while none reported elevated cancer risk or poorer prognosis among the methodologically most rigorous studies. Nevertheless, consistent with study 2, the systematic review was unfortunately compromised by associations observed in the (predominantly cross-sectional, observational) studies being confounded by individuals being more likely to become religious/spiritual following significant life events (e.g. bereavement), no adjustment being made for relevant demographic and lifestyle factors, and poor conceptualisation and/or measurement of religiosity/spirituality (Stefanek, McDonald, & Hess, 2005; de Jager et al., 2010; Masters & Hooker, 2013).
In relation to adjustment to and coping with cancer, two detailed systematic and narrative reviews found limited evidence for a positive relationship between adaptive religious or spiritual coping and psychological, spiritual and general well-being in cancer patients and breast cancer survivors/patients, and poorer well-being for negative religious or spiritual coping (Masters & Hooker, 2013; Schreiber & Brockopp, 2012). As recommended in study 2, more large longitudinal studies are required that compare spirituality and/or religion (across faiths) as primary endpoints to other coping strategies (e.g. social support) in specific cancer populations, and adequately control for potential confounding variables (e.g. the aforementioned variables above, stage of illness, prognosis).

3.5 Biologically-Based Practices

3.5.1 Nutritional Supplements (Dietary/Food Supplements)

3.5.1.1 Antioxidants

Twenty-five subsequent reviews evaluating the efficacy and/or safety of antioxidants in cancer prevention and care have been published. With respect to chemoprevention, a meta-analysis of 20 RCTs indicated that antioxidant supplements (vitamins A, C, E; selenium; beta-carotene) alone or in combination did not significantly reduce colorectal cancer incidence, colorectal adenoma recurrence or cancer-related/overall mortality (Pais & Dumitrascu, 2013). Vitamin C combinations were the only exception and significantly reduced colorectal cancer incidence, but not mortality. Similar outcomes were revealed in a Cochrane meta-analytic review of 8 controlled and cohort studies evaluating the effects of dietary flavonoid intake on colorectal cancer and adenoma incidence (Jin, Leng, & Li, 2012). A meta-analysis of 13 observational studies examining antioxidant intake (vitamins A, C, E; beta-carotene), however, found limited evidence that dietary intake of vitamin C and beta-carotene, but not vitamins A and E, reduced the risk of colorectal adenoma (precursor of colorectal cancer), although more large, high-quality studies were recommended (Xu et al., 2013). Similarly, results were mixed when both antioxidant intake and supplementation were examined in reviews of breast cancer and prostate cancer risk. A meta-analysis of 51 RCTs, cohort studies and case-control studies indicated that total vitamin A and total retinol intake significantly reduced breast cancer risk across different study designs, but not total vitamin E or dietary vitamin A or E intake (Fulan et al., 2011). Additionally, a meta-analysis of 33 cohort and case-control studies
revealed that dietary intake of alpha- or beta-carotene, but not dietary or total intake of other carotenoids (including lycopene), significantly reduced breast cancer risk (Hu et al., 2012). Finally, a systematic review of RCTs, cohort and observational studies found inconclusive evidence for the use of dietary intake or supplementation of antioxidants (vitamins C and E; selenium; carotenoids) in reducing prostate cancer risk (Ilic, Forbes, & Hassed, 2011; Chen, Song, & Zhang, 2013). Similar outcomes were also observed in a meta-analysis of 17 cohort and case-control studies for gastric cancer (Yang, Yang, Wang, Wang, & Song, 2013), and a Cochrane meta-analytic review found lower cancer incidence and cancer mortality associated with selenium exposure in 55 observational studies, but no such mortality associated with selenium supplementation (Vinceti et al., 2014). Nevertheless, the evidence for selenium supplementation in 8 RCTs (Yi, Yang, et al., 2014) indicated that supplementation of selenium may reduce cancer risk, but that outcomes of the observational studies should be interpreted with caution given several methodological limitations (e.g., assessment issues with selenium exposure). Several reviews have also focused exclusively on specific antioxidants in relation to cancer prevention. A meta-analysis of 6 RCTs found that selenium supplementation was associated with a lower risk of liver cancer, and that preventative effects were exerted for lung cancer and in populations with high baseline selenium levels. Nevertheless, the authors advised that outcomes of the observational studies should be interpreted with caution for selenium supplementation in 8 RCTs (Yi, Yang, et al., 2014). Nevertheless, the evidence for selenium supplementation in 55 observational studies, but no such mortality associated with selenium exposure in 55 observational studies, but no such mortality associated with selenium exposure.
et al., 2011b). However, given its association with elevated risk of diabetes at higher baseline selenium levels, the authors suggested that use of selenium supplementation be limited until further studies are performed.

Turning to adjuvant cancer treatment, two meta-analyses (21 RCTs and 8 RCTs, respectively) have demonstrated a range of positive treatment outcomes in solid tumour patients of using melatonin as an adjunct to chemotherapy ± radiotherapy or supportive/palliative care (Seely et al., 2012; Wang et al., 2012). They included significant improvements in 1-year survival, complete/partial tumour response, stable disease and various toxicities due to chemotherapy ± radiotherapy (thrombocytopenia, leukopenia, fatigue, asthenia, neurotoxicity, nausea and vomiting, hypotension). Additionally, no adverse effects were reported. Furthermore, a meta-analysis of 10 prospective observational studies involving breast cancer patients and survivors suggested that vitamin C supplementation and dietary intake may be associated with significantly increased breast cancer survival and reduced overall mortality, although several limitations of the included studies (e.g. non-adjustment of confounding demographic and/or lifestyle factors including pre-diagnosis vitamin C use; self-reporting of dietary intake) and the review itself (e.g. safety was not considered) require more large high-quality studies be performed (Harris, Orsini, & Wolk, 2014).

More equivocally, a systematic review examining intravenous vitamin C in 37 studies (2 RCTs, 15 uncontrolled trials, 6 observational studies, 14 case studies) found very limited evidence suggesting that high-dose intravenous vitamin C (≥ 5g) combined with chemotherapy may enhance survival, tumour response, time to relapse, QoL, physical functioning and and various chemotherapy- or cancer-related symptoms (fatigue, nausea, insomnia, constipation, depression); however, no evidence exists for its efficacy as a standalone anticancer treatment (Fritz et al., 2014). Additionally, limited evidence was demonstrated for the safety of intravenous vitamin C when adequate precautions are taken (e.g. use of graduated dosing schedules; concomitant administration with calcium/potassium/magnesium chloride to offset electrolyte imbalances, and reduce kidney stone risk in patients with such a history; Fritz et al., 2014; Stephenson, Levin, Spector, & Lis, 2013; Riordan et al., 2005). The most commonly reported adverse effects of intravenous vitamin C include transient nausea (due to osmotic load during infusion), headaches, lightheadedness and dry mouth, while high-dose administration has also been associated with more serious, dose-limiting adverse events in electrolyte imbalances [e.g.
grade 3/4 hypokalaemia (low blood potassium) and hypernatraemia (high sodium blood concentration); Stephenson et al., 2013; Welsh et al., 2013; Monti et al., 2012; Riordan et al., 2005]. Contraindications of high-dose intravenous vitamin C include cancer patients with (a history of) acute/chronic renal dysfunction, glucose-6-phosphate (G6PD) deficiency due to risk of haemolysis (red blood cell breakdown) or haemochromatosis (iron overload; Riordan et al., 2003, 2004), or those at increased risk of tumour necrosis (e.g. brain metastasis, aggressive malignancies; Campbell & Jack, 1979). Finally, trials of low-dose intravenous vitamin C combined with various chemotherapy/symptom control regimens (paclitaxel/carboplatin, gemcitabine, arsenic trioxide, melphalan, bortezomib, dexamethasone) also suggested few concerns with drug interactions (Fritz et al., 2014), with the exception of bortezomib used to treat multiple myeloma or mantle cell lymphoma (Perrone et al., 2009). Nevertheless, the review authors acknowledged that the outcomes are far from conclusive due to the poor quality of the studies (e.g. lack of control groups, small sample sizes, use of heterogenous trial methodologies and populations), which precluded meta-analysis and limitations of the review itself (e.g. no assessment of publication bias). Further well-designed RCTs evaluating the efficacy and safety of intravenous vitamin C (including optimal dosing schedules) as an adjunct to cancer therapy, and involving active treatment control groups and long follow-up periods are advised.

In contrast, a subgroup meta-analysis of 6 RCTs found that the use of amifostine (synthetic antioxidant) as an adjunct to radiotherapy ± chemotherapy had no significant effect on complete/partial response in head and neck cancer patients compared to placebo or clinical observation (Gu et al., 2014). Furthermore, a meta-analysis of 12 high-quality RCTs, predominantly involving lung and head and neck cancer patients with locally advanced disease, revealed that the use of amifostine as an adjunct to radiotherapy ± chemotherapy conferred no significant benefit for overall survival or progression-free survival in studies with a median follow-up of 5.2 years (Bourhis et al., 2011). The most common adverse effects of intravenous amifostine reported were nausea/vomiting, transient hypotension and allergic reactions (grade 3/4: 4-6% average incidence; Gu et al., 2014; cf. subcutaneous amifostine: nausea/vomiting; Jensen et al., 2010), which can lead to cessation in up to 25% of patients (Rades et al., 2004). Concerns regarding the cytoprotective effects of amifostine extending beyond normal tissue to tumours and therefore compromising survival appear unfounded, although the authors of the latter review recommended further RCTs designating survival as a primary endpoint rather than a secondary one to provide a
more definitive answer.

Finally, in regard to treatment toxicity *per se*, the American Society of Clinical Oncology has recommended in clinical practice guidelines that amifostine’s cytoprotective properties may lend its possible use to the prevention of cisplatin-induced nephrotoxicity and the reduction of acute/late xerostomia among head and neck cancer patients receiving fractionated radiotherapy, as well as grade 3/4 neutropenia in general (Hensley et al., 2009). A recent meta-analytic/systematic review of 17 RCTs involving head and neck cancer patients treated with radiotherapy ± chemotherapy provided qualified support for this position (Gu et al., 2014). Subgroup analyses revealed that the use of amifostine significantly reduced grade 2-4 acute or late xerostomia and grade 3-4 mucositis in head and neck cancer patients receiving radiotherapy alone (and not concurrent chemoradiotherapy), but not grade 3/4 leukopenia, anaemia and thrombocytopenia across treatments. Significant improvement was also observed for grade 3/4 dysphagia, but extreme heterogeneity observed in the 5 RCTs examined rendered these results inconclusive. In contrast, the Multinational Association of Supportive Care in Cancer (MASCC) found insufficient evidence to support the use of amifostine to reduce acute/late xerostomia among (chemo)radiotherapy patients (Jensen et al., 2010). In their systematic review of 16 studies (9 RCTs, 6 cohort studies, 1 cross-sectional study; predominantly head and neck cancer patients), whilst most studies exhibited beneficial effects on xerostomia, amifostine failed to demonstrate in most studies that it also mitigated reductions in salivary flow rate secondary to radiotherapy. The authors also held that most studies were of questionable methodological quality (e.g. no placebo use in control arms), thus further high-quality RCTs are recommended.

The MASCC has also determined that there is insufficient support for the use of amifostine in the prevention/management of oral mucositis in cancer patients (Nicolatou-Galitis et al., 2013). In their systematic review of 30 studies (organised by type of cancer treatment and amifostine administration), the authors observed that all studies suffered from major flaws (e.g. no double-blinding or use of placebo in control arms, use of historical controls) and clinical heterogeneity (e.g. variable time/dose schedules of amifostine administration and type/intensity of cancer treatments). Similarly, a Cochrane meta-analytic review, based on 11 RCTs involving predominantly head and neck cancer patients receiving radiotherapy ± chemotherapy, found weak unreliable evidence that amifostine may prevent oral mucositis in cancer patients (Worthington et al., 2011). Large, well-
designed RCTs, involving homogeneous cancer populations, standardised time/dose administration schedules and placebo or active control treatments, are required to clarify the role of amifostine (alone and in combination with other preventative strategies) as an intervention for oral mucositis.

Amifostine has also been evaluated in the prevention/management of chemotherapy toxicities related to platinum-based agents. A Cochrane meta-analytic review, based on 7 small controlled trials involving cancer patients treated with platinum-based chemotherapy (cisplatin, carboplatin, oxaliplatin), revealed that amifostine received as an adjunct modestly reduced or prevented neurotoxicity assessed post-treatment (0-6 months) compared to placebo, but that the evidence was inconclusive given the trials lacked methodological rigour (i.e. omission of primary measures, such as the proportion of patients who received increased dosing of platinum-based chemotherapy due to reduced neurotoxicity; no objective measures of neurotoxicity; Albers, Chaudhry, Cavaletti, & Donehower, 2014). The most commonly reported adverse effects were transient hypotension (8-62% incidence) and hypocalcaemia (11%). Similarly, a meta-analysis of 4 RCTs found insufficient support for the use of amifostine as an adjunct to cisplatin in reducing or preventing ototoxicity (symptoms include sensorineural hearing loss, tinnitus, dizziness; Duval & Daniel, 2012). Reported adverse effects included hypocalcaemia, hypotension, vomiting and sneezing. Further large RCTs are needed to clarify the role (if any) of amifostine in the prevention and/or management of chemotherapy toxicities secondary to platinum-based chemotherapy.

3.5.1.2 Omega-3 Fatty Acids (n-3 Polyunsaturated Fatty Acids)

Eight subsequent reviews evaluating the efficacy and/or safety of omega-3 fatty acids in cancer prevention and care have been published. With respect to chemoprevention (and consistent with study 2), a meta-analysis of 19 RCTs revealed that omega-3 fatty acid supplementation had no significant effect on cancer incidence or overall mortality compared to placebo (Zhang, Gao, Hou, & Zhou, 2014). Several recent meta-analytic/systematic reviews have examined the association of dietary intake of omega-3 fatty acids or fish and cancer risk in epidemiological studies (prospective cohort/case-control studies), with few positive outcomes. No significant associations were observed for risk of breast, prostate, colorectal or gastric cancer (Zheng, Hu, Zhao, Yang, & Li, 2013; Chua, Sio, Sorongon, & Dy, 2012; Shen, Zhou, Dong, Ding, & Wu, 2012; Qin, Xun, & He,
2012; Wu et al., 2011). Partly consistent with study 2, however, weak protective associations were found between high alpha-linolenic acid (ALA) dietary intake and prostate cancer risk (Chua et al., 2012), as well as breast cancer risk (Zheng et al., 2013). Nevertheless, further large epidemiological studies are warranted given the many challenges involved in evaluating the association between dietary fat and cancer risk (e.g. adjusting for confounding dietary, lifestyle and/or reproductive/genetic factors across populations, quantifying ALA and other different fats classified as omega-3 fatty acids, the effect of potential contaminants contained in fish and other dietary sources of omega-3 fatty acids; Khaw, 2013).

In relation to supportive care (and broadly consistent with study 2), a systematic review of 38 studies (including 10 controlled trials) involving omega-3 fatty acids, fish oil and/or eicosapentaenoic acid (EPA) indicated that omega-3 fatty acid treatment is unlikely to be effective in ameliorating refractory cachexia in advanced cancer patients (Ries et al., 2012). In fact, the authors suggested that the 8 week treatment duration recommended in several studies may render omega-3 fatty acid treatment burdensome for advanced cancer patients with poor prognosis, particularly if any of the reported mild adverse effects (e.g. abdominal discomfort, nausea, diarrhoea, belching) that may occur prove dose-limiting over time. More positively, however, the authors observed promising outcomes (faster wound healing, fewer postoperative complications) in the use of parenteral/enteral omega-3 fatty acid supplementation following cancer surgery. Similarly, another systematic review based on 5 RCTs suggested that postoperative parenteral supplementation may reduce the length of hospital stay of surgical oncology patients (van der Meij, van Bokhorst-de van der Schueren, Langius, Brouwer, & van Leeuwen, 2011). Further large RCTs are required to confirm the efficacy of omega-3 fatty acid supplementation in the surgical oncology setting.

3.5.1.3 Shark Cartilage and AE-941 (Neovastat®)

No subsequent reviews or controlled trials evaluating the efficacy and/or safety of shark cartilage products that are of relevance to the cancer field were located.

3.5.1.4 Laetrile and Amygdalin (Vitamin B17)

One subsequent review evaluating the efficacy and safety of laetrile or amygdalin in cancer treatment has been published. Consistent with study 2, the authors of a Cochrane
meta-analytic review were unable to locate any RCTs or quasi-RCTs meeting the inclusion
criteria, and concluded that there was no reliable evidence for the alleged curative effects of
laetrile or amygdalin in cancer patients (Milazzo, Ernst, Lejeune, Boehm, & Horneber,
2011). Moreover, laetrile/amygdalin were associated with a high risk of developing serious
adverse effects due to cyanide poisoning (especially after oral ingestion), which may be
further compounded by concomitant high vitamin C intake, a genetically predisposed,
diminished capacity to detoxify cyanide or vegetarianism coupled with vitamin B12
deficiency (Chan, 2006).

3.5.2 Chinese Herbal Medicine

3.5.2.1 Astragalus [Astragalus Membranaceus, Astragalus Propinquus, Radix Astragali,
Huang Qi, Astragalus Mong(h)olicus, Milk Vetch]

Four subsequent reviews evaluating the efficacy and/or safety of astragalus or
astragalus-based Chinese herbal medicines in cancer treatment and care have been
published or newly-located. A meta-analysis of 65 RCTs (mostly small Chinese studies)
suggested that astragalus-based herbal medicines used as an adjunct to platinum-based
chemotherapy significantly improved survival (1-, 2-, 3-year), complete/partial tumour
response and performance status in advanced non-small lung cancer patients (Duguoa, Wu,
Seely, Eyawo, & Mills, 2010). A more recent meta-analysis of 26 Chinese RCTs revealed
identical outcomes for astragalus-based herbal medicines used as an adjunct to radiotherapy
in non-small-lung cancer patients, but also found significantly reduced radiotherapy
toxicity (radiation pneumonia, white blood cell toxicity; He, Zhou, Wang, & Zhao, 2013).
Positive outcomes were also observed for survival, complete/partial response and risk of
progressive disease in a meta-analysis of RCTs involving liver cancer patients receiving
adjuvant transcatheter arterial chemoemolization / astragalus-based herbal medicines (Wu,
Dugoua, Eyawo, & Mills, 2009), and for complete response, chemo toxicity
(nausea/vomiting, grade 3/4 leukopenia) and QoL in a meta-analysis of RCTs involving
gastric cancer patients treated with adjuvant chemotherapy (5-fluorouracil +
leucovorin/oxaliplatin) / astragalus polysaccharides (Wang, Tian, Ge, Gan, & Yang, 2014).
The major drawback acknowledged by the authors of each of these reviews, however, is
that most RCTs were not only small, but performed in China and therefore highly prone to
suspect randomisation procedures (amongst other methodological limitations) and
publication bias. Consequently, as per study 2, larger and more rigorous RCTs are needed
to confirm the efficacy and safety of astragalus-based herbal medicines, and preferably involving comparisons to adjunctive astragalus monopreparations in addition to standard anticancer therapy.

3.5.2.2 Ginseng (*Panax Ginseng, Radix Ginseng, Asian Ginseng, Red Ginseng, Ren Shen, Panax Quinquefolium, American Ginseng, White Ginseng, Eleutherococcus Senticosus, Siberian Ginseng, Angelica Sinensis, Female Ginseng, Dong Quai*)

Ginseng products are available in many forms including fresh slices (raw form), extracts (tincture or boiled), powder, tea, juices, and tablets/capsules. In Asian countries, ginseng is widely used as an adjunct to conventional anticancer treatments (Qi et al., 2010). The traditional Chinese herbal preparation widely used for such clinical purposes is Shengmai, which is a mixture extracted from ginseng, ophiopogon and schisandra (Zhou et al., 2014). Mass production is based on a standardised formula and it is available in different forms including capsules (Shenyi), powder, oral liquids and injection (Shenmai). Recent *in vitro* and *in vivo* studies of ginseng polysaccharides, ginsenosides and active metabolites (e.g. compound K) have demonstrated anticancer, anti-proliferative, anti-angiogenic, apoptotic and radioprotective properties (Nag et al., 2012; Zong, Cao, & Wang, 2012; He et al., 2011; Ming et al., 2011; Jeong et al., 2010; Lee, Johnke, Allison, O'Brien, & Dobbs, 2005).

Five subsequent reviews (and two RCTs) evaluating the efficacy and/or safety of ginseng and ginseng-based Chinese herbal medicines in cancer prevention and care have been published or newly-located. Regarding chemoprevention, a systematic review of 65 randomised trials involving healthy and medical populations (including 2 cancer studies) revealed insufficient evidence for ginseng preventing gastric cancer incidence or recurrence (Shergis, Zhang, Zhou, & Xue, 2013). Despite positive outcomes, the authors observed several methodological (e.g. suspect randomisation/blinding procedures, small samples) and heterogeneity issues (e.g. the type, method of preparation, dose and standardised active ingredients of ginseng used). Large RCTs addressing these limitations are advised.

In relation to cancer treatment, a comprehensive narrative review based on 6 Chinese controlled trials found insufficient evidence for enhanced clinical outcomes (complete response, survival, disease progression, immune response, haematological toxicity, QoL) when Shengmai or ginsenoside Rg3 (Shenyi capsules) was used as an adjunct to chemotherapy in cancer patients (Chen et al., 2014). Similar conclusions were
also drawn in a systematic review based on 4 Korean RCTs that evaluated the effects of red ginseng versus standard care/treatment on immune response and nutritional status in gastric and colon cancer patients (J. Choi, Kim, T. Y. Choi, & Lee, 2013). Further large high-quality RCTs are required.

Turning to symptom management, two recent RCTs investigating the effect of ginseng on cancer-related fatigue have produced encouraging results. In a good quality, dosing-finding, double-blind pilot RCT of 290 patients with cancer-related fatigue, no significant differences were found between three collective American ginseng arms (750-, 1000- and 2000-mg/day) and placebo (matching capsules) with respect to activity interference and self-reported fatigue (or toxicity) at 4- and 8-weeks post-baseline (Barton et al., 2010). However, subset analyses revealed a trend for higher doses (1000- and 2000-mg/day) exerting greater effects on fatigue, QoL and satisfaction with fatigue management. In a follow-up double-blind RCT of 364 patients and survivors with cancer-related fatigue, no significant differences were observed on any measure (including toxicity) between the ginseng (2 x 1000mg doses per day) and placebo arms at 4 weeks post-baseline; however, significant improvements were observed in self-reported fatigue and physical functioning with ginseng after 8 weeks of treatment (Barton et al., 2013). Furthermore, subgroup analysis revealed that patients receiving active cancer treatment reported significant improvements in fatigue at both 4 and 8 weeks compared to placebo, but cancer survivors did not. Nevertheless, further large RCTs are recommended involving not only both homogeneous and heterogeneous cancer populations, but also objective as well as subjective measures of fatigue, physical functioning and activity levels in comparing ginseng to active control treatments (e.g. physical exercise). Special attention should also be paid to the methodological challenges of ginseng studies in cancer (e.g. difficulties in double-blinding due to the potent odour of ginseng capsules or aftertaste following ingestion; conditions that are possible contraindications of ginseng use or are fatigue-inducing but unrelated to cancer; Elam, Carpenter, Shu, Boyapati, & Friedmann-Gilchrist, 2006).

Finally, consistent with study 2, ginseng has not been associated with any serious adverse events in recent systematic reviews of studies involving healthy, cancer and other medical populations (Choi et al., 2013; Shergis et al., 2013; Qi et al., 2011). The most commonly reported adverse effects included gastrointestinal upset, constipation and insomnia. Divergently, however, studies observed no herb-drug interactions between Asian
ginseng and warfarin (S. H. Lee, Y. M. Ahn, S. Y. Ahn, Doo, & B. C. Lee, 2008; Y. H. Lee et al., 2010), and variable inhibition on platelet aggregation of ginsenosides isolated from processed ginseng (J. G. Lee et al., 2009, 2010). Nevertheless, given the potential irreversibility of such effects, patients should discontinue ginseng use at least one week prior to surgery (Ang-Lee, Moss, & Yuan, 2001). Furthermore, recent case reports suggest that Asian ginseng may interact with imatinib (used to treat chronic myeloid leukaemia, gastrointestinal stromal tumors and other malignancies) and raltegravir (antiretroviral) to produce hepatotoxicity via inhibition of the cytochrome P450 C3A4 enzyme (Bilgi, Bell, Ananthakrishnan, & Atallah, 2010; Mateo-Carrasco, Gálvez-Contreras, Fernández-Ginés, & Nguyen, 2012). Consequently, Asian ginseng should be avoided or used with caution with these and other drugs metabolised by the cytochrome P450 C3A4 enzyme, and in patients with (a history of) liver dysfunction.

3.5.2.3 Ginger (*Zingiber Officinale*)

Three subsequent reviews evaluating the efficacy and safety of ginger in the prevention/management of chemotherapy-induced nausea and vomiting (CINV) have been published. A meta-analytic/systematic review of 5 double-blind RCTs comparing ginger to placebo or conventional antiemetics (predominantly metoclopramide or ondansetron) revealed insufficient support for the use of ginger in CINV control (Lee & Oh, 2013). Subgroup meta-analysis of 4 RCTs indicated that the incidence of acute nausea and acute vomiting, and the severity of acute nausea did not differ significantly between the ginger and control groups. Mixed supportive evidence was also observed in a systematic and narrative review of 7 RCTs (including 3 crossover trials; Marx et al., 2013; Haniadka, Rajeev, Palatty, Arora, & Baliga, 2012). In each case, the conflicting study outcomes were attributed to various methodological limitations (double-blinding difficulties due to the potent odour of ginger capsules and aftertaste following ingestion; variations in the active compounds, dosages and treatment initiation periods of the ginger used; inadequate control over potentially confounding variables including pre-existing anticipatory nausea/vomiting, gender, chemotherapy emetogenicity and antiemetic/ginger use and compliance, as well as order effects in crossover trials; use of different study endpoints for ginger effects; subjective nature of nausea combined with the diverse standardised measures used; small samples). Consequently, more large rigorous studies of CINV control were recommended comparing ginger to current standard antiemetics (e.g. aprepitant) and placebo.
Finally, consistent with study 2, few adverse effects of ginger were observed in the CINV studies. Reported side-effects included mild gastrointestinal symptoms (heartburn, stomach upset, diarrhoea), bruising or flushing, rash, dizziness, drowsiness/sleepiness, dry mouth, thirst and restlessness, but generally incidence was not significantly greater compared to the control groups in these studies (Ryan et al., 2012; Manusirivithaya et al., 2004; Pace, 1986). Interestingly, however, and consistent with trends in previous cancer-unrelated ginger research (e.g. Arfeen et al., 1995), two studies reported a significant decline in CINV control at higher doses of ginger (1.5-2g per day) compared to lower doses of ginger (0.5-1g per day) or the placebo (Ryan et al., 2012; Zick et al., 2009) when combined with conventional antiemetics. Ryan and colleagues (2012) suggested that ginger may compete with antiemetics for the same receptors when used in tandem, thus reducing the uptake of such medications and lowering antiemetic coverage.

3.5.2.4 Lingzhi / Reishi Mushroom (*Ganoderma Lucidum, Ganoderma Tsugae*)

One subsequent review (and a case series study) evaluating the efficacy and/or safety of Lingzhi in cancer treatment have been published. A Cochrane meta-analytic review of 5 Chinese RCTs found insufficient evidence for the use of commercially prepared Lingzhi as a standalone cancer treatment, and inconclusive evidence for enhanced tumour response when combined with chemotherapy or radiotherapy in lung cancer patients (Jin, Ruiz Beguerie, Sze, & Chan, 2012). Additionally, there was inconclusive evidence for enhanced immune response (leukocyte count, natural killer cell activity) with the exception of increased T-cell counts (CD3, CD4 and CD8, but not CD4/CD8 ratio), and very limited evidence that it enhanced performance status at post-treatment compared to placebo or conventional treatment. Overall, given the poor methodological quality of the studies (i.e. mostly small studies, all performed in China and prone to suspect randomisation/blinding procedures), the authors suitably recommended that large, high-quality double-blind RCTs be performed to evaluate the long-term survival benefit (among others, as well as safety) of Lingzhi when combined with conventional anticancer treatment and preferably in non-Asian populations.

Turning to safety, consistent with study 2, few adverse effects (nausea and insomnia in one study only) of commercially prepared Lingzhi were experienced by cancer patients in the above review, with no study reporting haematological or liver toxicity (Jin et al., 2012). Curiously, however, a recent case series of 5 Chinese gastric cancer patients
observed that *Ganoderma lucidum* spore (Lingzhi spore) herbal supplementation (generally 1.8g/day over 1-2 months) was associated with elevated CA 72-4 serum tumour marker levels (sans clinical symptoms or objective evidence of disease progression) when combined with chemotherapy or different Chinese herbal medicines (Yan et al., 2014). Given CA 72-4 levels may be used as an indicator of disease progression in gastric cancer (e.g. Ucar et al., 2008) and trigger clinicians to modify cancer treatment, *Ganoderma lucidum* spore supplementation should be used with caution or perhaps best avoided in such patients.

3.5.2.5 Green Tea (*Camellia Sinensis, Thea Sinensis, Polyphenon E*)

Twenty subsequent reviews evaluating the efficacy and/or safety of green tea in cancer prevention have been published or newly-located. A Cochrane meta-analytic review of 51 studies (21 case-control, 23 cohort, 1 RCT), predominantly involving Asian populations (*n* = 47), found insufficient and conflicting evidence to make any firm recommendations regarding green tea consumption for cancer prevention (Boehm et al., 2009). Recent meta-analytic reviews of case-control and cohort studies produced mixed results regarding the protective effects of green tea for oesophageal cancer in Asian populations, but consistently suggested that green tea consumption may reduce oesophageal cancer risk in Asian women (Zheng et al., 2013; Sang, Chang, Li, & Jiang, 2013; P. Zheng, H. M. Zheng, Deng, & Zhang, 2012). Similar mixed outcomes were observed in meta-analyses of green tea consumption for bladder cancer (Wu et al., 2013; Wang et al., 2013) and prostate cancer risk in Asian populations (Lin et al., 2014; Zheng et al., 2011), as were gender effects on gastric cancer risk in Japan in a meta-analytic/systematic review of 6 cohort studies (Sasazuki et al., 2012). However, the observed gender effects may be due to higher smoking rates in Asian men modifying the effect of green tea (e.g. Kuriyama et al., 2006), and/or phytoestrogens in green tea having a greater protective effect in women than men (e.g. Cheng, 2007). Nevertheless, a potential oestrogen-related protective mechanism against oesophageal and gastric cancer (or any other cancer) warrants further investigation in Asian and other populations.

Various meta-analytic/systematic reviews of case-control and cohort studies suggest that green tea consumption in Asian populations may protect against the development of gastric (Kang, Rha, Oh, & Nam, 2010), oral (Wang, Yang, Zhang, & Wu, 2014) and liver cancer (Fon Sing, Yang, S. Gao, J. Gao, & Xiang, 2011). Similarly, three meta-
analytic/systematic reviews suggest protective effects of green tea for ovarian and other gynaecological malignancies across both Asian and Caucasian populations (Gao et al., 2013; Trudel et al., 2012; Butler & Wu, 2011). In contrast, meta-analytic reviews of cohort and/or case-control studies have found insufficient evidence to conclude that green tea consumption may protect against breast (Wu, Zhang, & Kang, 2013) and colorectal cancer in Asian populations (Wang et al., 2012; Wang, Gao, & Fang, 2012). Clearly, further large, long-term epidemiological studies (especially cohort studies involving non-Asian populations) are needed to provide more definitive and generalisable conclusions about the chemopreventive effects of regular green tea intake (beverage or extract). Furthermore, they must exert control over several confounding variables or limitations that have likely compromised the outcomes of individual studies (e.g. adjustment for demographic and lifestyle factors, such as sex, smoking, alcohol intake and body mass index; dose and temperature of green tea beverage) and the ensuing meta-analytic/systematic reviews (e.g. publication bias, study heterogeneity) performed thus far.

Finally, consistent with study 2, few adverse effects have been reported when green tea has been used in moderate amounts orally (3-9 cups/day, ≤ 1200ml/day, minimum of 250mg/day catechins) or topically as appropriate (green tea extract containing 7% caffeine; Ahn, 2003; Pisters et al., 2001; Katiyar, 2000; Boehm et al., 2009). Chronic excessive oral consumption (5-6 litres/day or >250-300mg/day) has been associated with tachyarrhythmia and sleep disturbance due to the caffeine content (IOM Institute of Medicine, 2001). Additionally, in phase I trials involving cancer patients green tea extract has generally been well-tolerated (Laurie, Miller, Grant, Chris, & Ng, 2005; Pisters et al., 2001). Mild side-effects, partly due to caffeine content, included fatigue, pain and central nervous system disturbances (nausea, insomnia, headaches, anxiety, restlessness) at lower doses (0.5-1.0g/m² per day), and gastrointestinal disturbances (dyspepsia, diarrhoea, polyuria) and polydipsia (excessive thirst) at higher doses (1.0-3.0g/m² per day). Grade 3/4 dose-limiting toxicities attributed to caffeine content at high doses (> 3.0g/m² per day) included hypertension and gastrointestinal/central nervous system disturbances (diarrhoea, nausea, insomnia, agitation), but improved with dose reduction of green tea extract (Laurie et al., 2005; Pisters et al., 2001; Fritz et al., 2013).
3.5.2.6 Ginkgo (*Ginkgo Biloba*, EGB 761)

Three subsequent reviews (and two RCTs plus a crossover study) evaluating the efficacy and/or safety of ginkgo in cancer prevention and care have been published. In the largest double-blind RCT of ginkgo supplementation (EGB 761, 120mg twice daily) conducted, involving dementia risk in 3069 elderly Americans (≥75 years, median follow-up = 6.1 years), a secondary analysis revealed no support that regular use prevents cancer (Biggs, Sorkin, Nahin, Kuller, & Fitzpatrick, 2010). Clearly, further large prospective studies that are more representative of the general population and having longer follow-up periods are required, given several limitations of the study (e.g. cancer cases not requiring hospitalisation could not be identified, ginkgo dose may not have been optimal for cancer prevention). In another double-blind RCT of ginkgo supplementation (EGB 761, 60mg twice daily) involving 160 chemotherapy-naïve breast cancer patients, regular use during adjuvant chemotherapy (and one month beyond) provided no subjective or objective evidence for the prevention of chemotherapy-related cognitive dysfunction compared to placebo at any time point up to 2 years post-treatment (Barton et al., 2013). Further large RCTs are required to provide further confirmation of these outcomes.

Turning to safety, a prospective crossover trial involving 60 early-stage breast cancer survivors receiving hormonal therapy (tamoxifen, anastrozole, letrozole; n = 20 each) reported that the majority of women experienced either no side-effects or mild symptoms (most commonly, headache, flatulence, hot flushes, nausea and diarrhoea, some of which would have been due to the hormonal treatment *per se*; Vardy et al., 2013). Furthermore, recent systematic reviews (Shi & Klotz, 2012; Hermann & von Richter, 2012; Li, Zeng, Yu, & Zhou, 2013) have indicated that recommended doses of ginkgo (up to 240mg/day) do not have significant or clinically-relevant effects on cytochrome P450 enzyme activity (CYP3A4, CYP1A2, CYP2C9, CYP2D6, CYP2B6, CYP2E1), with one exception (CYP2C19). Modest induction of cytochrome P450 C219 enzyme activity has been observed with higher doses of ginkgo (≥240mg/day) and may be CYP2C19 genotype-dependent (i.e. induction is greater in poor metabolisers than extensive metabolisers; Lei et al., 2009; Yin, Tomlinson, Waye, Chow, & Chow, 2004). While further studies are required, ginkgo intake in the interim is either best avoided or should be monitored in patients taking omeprazole (proton pump inhibitor for gastrointestinal disorders), voriconazole (triazole antifungal for invasive fungal infections, such as candidiasis) or other medications metabolised by the cytochrome P450 C219 enzyme.
3.5.3 Western Herbal Medicine

3.5.3.1 St. John’s Wort (Hypericum Perforatum, LI 160, Kira®, WS 5570/5572/5573, Perika®, Hyperiplant®, Ze 117, Remotiv®)

Despite the large volume of clinical studies since the 1980s that have examined the efficacy of St. John’s wort (SJW), very few clinical studies have investigated its potential use in cancer treatment and care (Ernst, 2013). In fact, as far as can be ascertained, no RCT examining the efficacy (and safety) of SJW among cancer patients exists in the scientific literature, even in regard to depression which is its most popular therapeutic use. Consequently, 13 subsequent published or newly-located reviews (and 13 other studies) that have evaluated the safety and efficacy of SJW and are of relevance to cancer care will be discussed.

A narrative review of 16 post-marketing surveillance studies of SJW extract (standardised by hypericin and/or hyperforin content) as an antidepressant suggest that use in recommended doses is associated with a low rate of adverse events (≤ 6%; Schulz, 2006). Adverse effects are generally mild-moderate or transient, with gastrointestinal symptoms (e.g. constipation, nausea), allergic reactions (e.g. skin reddening/itching), dizziness/confusion, restlessness, fatigue, tiredness, anxiety and dryness of mouth being most common and largely attributed to hypericin/pseudohypericin content (Russo et al., 2014; Schulz, 2006; International Journal of Toxicology, 2001; Greeson, Sanford, & Monti, 2001; Barnes, Anderson, & Phillipson, 2001). However, the safety of self-administered SJW products without medical supervision is of concern and has been under-researched. A small number of studies to that end have reported adverse effects including psychological symptoms, allergic reactions and visual disturbances, which study participants attributed to self-administered use of SJW products (International Journal of Toxicology, 2001; Ernst, 2013). Furthermore, SJW extracts or oil containing high hypericin content (0.5mg/kg of body weight) may result in photodermatitis, based on reports of excessive cutaneous phototoxicity observed in HIV patients with regular use (Gulick et al., 1999). Indeed, clinical studies have shown that single oral doses of SJW (300-1800mg, 0.3% hypericin) resulted in hypericin registering in blood plasma, with repeated doses leading to a steady-state plasma concentration being achieved after only 14 days despite hypericin having an elimination half-life of 24-27 hours (Staffeldt, 1994; International Journal of Toxicology, 2001; Ernst, 2013). Possible contraindications of SJW products therefore include photosensitivity, known skin allergies, atopy or allergic hypersensitivity, pregnancy and
lactation.

Human studies have further suggested that SJW can have serious herb-drug interactions with medicines (including anticancer agents), particularly those with narrow therapeutic indices, by affecting drug metabolism (via induction of cytochrome P450 enzymes, particularly cytochrome P450 3A4 / 2C19, and P-glycoprotein) or levels of neurotransmitters (primarily serotonin; Goey, Mooiman, Beijnen, Schellens, & Meijerman, 2013; Li et al., 2013; Posadski, Watson, & Ernst, 2012; Shi & Klotz, 2012). In addition to imatinib and irinotecan, a recent probe study amongst cancer patients revealed that SJW extract (300mg Hyperiplant®, three times daily over 14 days) significantly increased the clearance of docetaxel (CYP 3A4 substrate) and thus is best avoided by metastatic breast and other cancer patients to prevent potential undertreatment (Goey et al., 2014). In contrast, probe studies have found no clinically-relevant effects of low-hyperforin-content SJW preparations [e.g. Ze 117, 0.2% hypericin (1mg in the daily dose) and ≤0.2% hyperforin (≤1mg in the daily dose), 250mg twice daily] when combined with various drugs metabolised by cytochrome P450 or P-glycoprotein enzymes (midazolam, alprazolam, caffeine, tolbutamide, digoxin, cyclosporine, oral contraceptives; Mueller et al., 2006, 2009; Arold et al., 2005; Mai et al., 2004; Will-Shahab, Bauer, Kunter, Roots, & Brattström, 2009). This evidence suggests that the potential for many herb-drug interactions is associated with the hyperforin content of SJW and may be mitigated by using low-hyperforin-content SJW extracts. The main problem therein, however, lies with the fact that clinical trials suggest that the therapeutic effect exerted by SJW extracts on mild-moderate depression is dependent on the hyperforin content (e.g. Laakmann, Schule, Baghai, & Keiser, 1998). Recent narrative reviews evaluating the antidepressive effects of SJW extracts of varying hyperforin content provide little evidence to the contrary (Kasper, Caraci, Forti, Drago, & Aguglia, 2010; Russo et al., 2014), with only a few RCTs purportedly examining low-hyperforin-content SJW extract (Ze 117, 0.2% hypericin, unknown hyperforin content, 250mg twice daily) for mild-moderate depression in the short-term (albeit with equivalent efficacy and compared to placebo/standard antidepressants, but involving gender disproportionate samples, ≥2:1 females to males; Woelk, 2000; Schrader, 2000; Schrader, Meier, & Brattström, 1998). Clearly, further large high-quality RCTs with longer follow-up periods extending beyond post-treatment are required to examine the efficacy and safety of low-hyperforin-content SJW extracts for the treatment of both mild-moderate and major depression (as well as other clinical problems, such as anxiety).
Ideally, these would be performed under close medical supervision amongst patients screened for depressive symptoms (or other targeted symptoms) from homogeneous/heterogeneous cancer populations and involve comparison to both placebo and active control treatments (e.g. prescription antidepressants and/or psychological therapy).

Finally, SJW may have interactions when used concomitantly with other herbal supplements or foods. Specifically, reports suggest that it may potentiate the sedative effects (and any adverse effects) when combined with herbs or foods possessing such properties (e.g. valerian, lemon balm, kava, hops, catnip, Siberian ginseng, goldenseal, California poppy, German chamomile, wild carrot/lettuce, celery, sage; Jellin, Gregory, Batz, & Hitchen, 2004). Moreover, given the wide variety of SJW preparations that are marketed, only some are of high quality (Ernst, 2013) and many online manufacturers, pharmacies and health food stores fail to provide sufficient information concerning known drug interactions, contraindications and adverse effects of SJW treatment (Thakor, Leach, Gillham, & Esterman, 2011).

3.5.3.2 Garlic (*Allium Sativum*)

Eight subsequent reviews (and one large cohort study) evaluating the efficacy and/or safety of garlic in cancer prevention and care have been published. A recent meta-analysis based on 7 observational studies (3 cohort, 4 case-control; retrospective/prospective) suggested that high garlic intake may reduce colorectal cancer risk, although no association was found in cohort studies or for garlic supplementation *per se* (Turati, Guercio, Pelucchi, La Vecchia, & Galeone, 2014). In contrast, the large American Cancer Society CPS-II Nutrition Cohort study involving older American adults (42,824 men, 56,876 women, 1,130 colorectal cancer diagnoses over 7 year follow-up) found no significant association between current daily garlic consumption or supplementation and colorectal cancer risk, but a possible increased risk in men who formerly used garlic supplements (compared to those who have never used; McCullough, Jacobs, Shah, Campbell, & Gapstur, 2012). Similarly, a more recent meta-analysis based on 5 prospective observational studies revealed that garlic supplementation possibly increased the risk of colorectal cancer (Zhu, Zou, Qi, Zhong, & Miao, 2014). Clearly, further large prospective cohort studies are required, preferably involving populations with higher garlic intake and early lifetime exposure and focusing on the quantities and modality of intake.
(i.e. preparation/cooking methods and supplemental garlic formulation) effective for cancer prevention.

Consistent with study 2, a meta-analysis based on 12 observational studies (1 cohort, 11 case-control; Zhou et al., 2011) and a narrative review based on 14 case-control studies (Guercio, Galeone, Turati, & La Vecchia, 2014) suggested that high garlic consumption may reduce gastric cancer risk, but recommended further studies given potential confounding factors (including garlic exposure misclassification of self-report measures) and ambiguity in the dose-risk relationship. Finally, a meta-analysis based on 7 observational studies (2 prospective cohort, 5 case-control) suggested that garlic consumption conferred protective effects for prostate cancer, but recommended further well-designed prospective cohort or intervention studies given the relatively small number of studies and study heterogeneity observed (Zhou, Ding & Liu, 2013).

Finally, subsequent reviews of herb-drug interactions have confirmed that garlic appears to be generally safe, with two minor exceptions (Izzo, 2012; Shi & Klotz, 2012; Hermann & von Richter, 2012). Human clinical trials have demonstrated that the efficacy of chlorzoxazone (muscle relaxant) may be reduced by garlic oil or garlic oil extract due to its atypical reliance on the cytochrome P450 C2E1 enzyme as a sole/predominant clearance pathway (Gurley, Gardner, & Hubbard, 2005; Gurley et al., 2002; Loizou & Cocker, 2001). Additionally, while garlic powder (600mg twice daily) modestly decreased the systemic clearance of docetaxel in metastatic breast cancer patients, significantly reduced clearance could not be ruled out in chemotherapy patients carrying a cytochrome P450 3A5*1A allele (Cox et al., 2006).

3.5.3.3 Kava (*Piper Methysticum*, Kava-Kava, Kavain, WS1490)

Three subsequent reviews evaluating the efficacy and/or safety of kava that are of relevance to cancer care have been published or newly-located. In contrast to study 2, a more recent meta-analysis of 6 placebo-controlled RCTs performed in Germany suggested that WS1490 acetone extracts (standardised kava extract; 150-300mg/day over 4-24 weeks) had positive effects on self-reported anxiety in individuals diagnosed with non-psychotic anxiety disorders, but statistical significance was not achieved for all outcomes (even when one gender-biased study was excluded in sub-analysis; Witte, Loew, & Gaus, 2005). Larger RCTs examining the anxiolytic effects of WS1490 (and other forms of kava) outside Germany are required, preferably involving homogeneous/heterogeneous cancer
populations and active control treatments (e.g. benzodiazepines) with consideration given to preparation methods (e.g. aqueous vs acetone/ethanol extracts), dose-response, treatment duration (short- vs long-term) and safety.

Turning to safety, recent systematic/narrative reviews (Sarris, LaPorte, & Schweitzer, 2011; Rychetnik & Madronio, 2011) have reinforced safety concerns about the hepatotoxicity of kava, but suggest that the genetic polymorphism of the cytochrome P450 enzymes (e.g. CYP2D6 activity is deficient in approximately 79% of Caucasian populations, but is negligible in Pacific/Asian/Aboriginal populations who have not exhibited kava hepatotoxicity) and/or use of acetone/ethanol kava extracts (cf. aqueous kava extracts) have been primarily responsible for serious occurrences (Poolsup, Li Wan Po, & Knight, 2000; Wanwimolruk, Bhawan, Coville, & Chalcroft, 1998; Singh, 2005; Russmann et al., 2003; Clough, Bailie, & Currie, 2003; Coulter, 2007). Similarly, chronic use of aqueous kava extracts (average quantity of 118g/week over 1-18 years) have been associated with dry scaly skin (dermatopathy), elevated liver enzyme levels (gamma-glutamyl transferase, alkaline phosphotase) and lower lymphocyte counts in Australian Aboriginal populations (Clough et al., 2003). Furthermore, in a comprehensive systematic review of predominantly controlled observational studies among Australian Aboriginal populations, chronic and/or heavy ingestion of water-infused kava beverages for recreational purposes (50 times more potent than the recommended therapeutic dosage of 140-250mg/day of kavalactones; LaPorte, Sarris, Stough, & Scholey, 2011) was found to cause scaly skin rashes (dermatopathy), weight loss, elevated gamma-glutamyl transferase liver enzyme levels, nausea, appetite loss or indigestion (Rychetnik & Madronio, 2011). Other associated adverse effects included conjunctivitis, impotence or loss of libido, elevated cholesterol, low motivation and slowed/lazy activity, poor psychosocial outcomes (financial, work/family) and self-reported poor overall health. Finally, a meta-analytic/systematic review of 10 RCTs suggested that traditional- or commercially-prepared kava does not produce cognitive impairment when acutely administered (single doses), but that there was very limited evidence that chronic use (large doses) may reduce visual attention accuracy on tasks during heavy cognitive demand (e.g. driving, operating heavy machinery) and hence caution was advised (LaPorte et al., 2011). Clearly, large high-quality RCTs examining the safety of kava are required as specified above.
3.5.3.4 Valerian (*Valeriana Officinalis*)

Two subsequent reviews (and one RCT) evaluating the efficacy and/or safety of valerian in cancer care have been published. In the only controlled trial of valerian in the cancer literature to the author’s knowledge, a double-blind placebo-controlled RCT involving 202 cancer patients receiving treatment revealed no significant improvement in self-reported sleep quality after 8 weeks of oral valerian (450mg capsules an hour before bedtime each night; Barton et al., 2011). However, significant improvements were observed in secondary sleep outcomes including sleep latency, amount of sleep per night, sleep difficulties and drowsiness, as well as self-reported fatigue outcomes. Further RCTs are recommended to examine the role valerian may play in the management of both sleep disturbance and fatigue in cancer patients, and should include both objective and subjective measures of primary and secondary endpoints. Finally, in terms of toxicity, no significant differences in side-effects (nausea, headaches, trouble waking) between treatment arms were reported by cancer patients in the RCT above (Barton et al., 2011). Additionally, recent systematic and narrative reviews (Kelber, Nieber, & Kraft, 2014; Izzo, 2012) of valerian found no plausible evidence for herb-drug interactions in case studies or probe studies involving healthy individuals, nor any clinically-relevant effects on cytochrome P450 3A4, 2D6, 2E1 and 1A2 pathways that could diminish the efficacy of associated medications (Gurley et al., 2005).

3.5.3.5 Evening Primrose Oil (*Oenothera Biennis*)

No subsequent reviews or controlled trials evaluating the efficacy and/or safety of evening primrose oil that are of relevance to the cancer field were located.

3.5.3.6 Black Cohosh (*Actaea Racemosa, Cimicifuga Racemosa, Isopropanolic Black Cohosh Extract, iCR, Remifemin®, Ethanolic Black Cohosh Extract, CR BNO 1055, Ze 450, Cr 99*)

Seven subsequent reviews (and one prospective observational study) evaluating the efficacy and/or safety of black cohosh in breast cancer care and risk have been published or newly-located. Consistent with study 2, recent meta-analytic/systematic reviews (including a Cochrane review) of RCTs, cohort and/or prospective observational studies have found insufficient evidence to support the use of black cohosh for hot flushes and other menopausal symptoms (e.g. night sweats, vaginal dryness) in peri-/post-menopausal
women and breast cancer patients or survivors (Leach & Moore, 2012; Burbos & Morris, 2011; Fritz et al., 2014). Given significant limitations and heterogeneity in existing studies, however, more rigorous RCTs of longer duration (> 6 months) are required, preferably involving homogeneous/heterogeneous cancer populations (breast, prostate and other gynaecological malignancies) and should include standardised doses/schedules, active control treatments (e.g. fluoxetine), objective and subjective measures, and important secondary outcomes (e.g. QoL, sexuality, sleep problems, musculoskeletal health, anxiety, safety).

Black cohosh still appears to be generally safe, with no herb-drug interactions reported and few (if any) serious adverse events concerning hepatotoxicity assigned probable or certain causality (Beer & Neff, 2013; Teschke, Schwarzenboeck, Schmidt-Taenzer, Wolff, & Hennermann, 2011; Mahady et al., 2008). Minor adverse effects include nausea, vomiting, headaches, dizziness, mastalgia and weight gain (Rostock et al., 2011; Wu, 2011; Huang, 2011; Zava, Dollbaum, & Blen, 1998). Regarding hepatotoxicity, a meta-analysis of 5 double-blind, placebo-controlled RCTs involving healthy peri-/post-menopausal women (40-60 years) revealed no evidence that isopropanolic black cohosh extract (Remifenin®, 40-128mg daily for 3-6 months) adversely affects liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltranspeptidase; Naser et al., 2011). Similar outcomes were also reported in a more recent systematic review of isopropanolic or ethanolic black cohosh extract use among peri-/post-menopausal women with or without breast cancer, even at doses or treatment durations exceeding European guidelines for use (based on 14 clinical studies including 9 RCTs; Beer & Neff, 2013).

In relation to other potential adverse effects, a systematic review suggested that black cohosh does not exert significant oestrogenic effects on breast, endometrial or vaginal tissues, or influence circulating hormone levels in breast cancer survivors and non-breast cancer populations (based on 12 RCTs and 5 uncontrolled trials; Fritz et al., 2014). Similar outcomes were also reported in another systematic review of isopropanolic or ethanolic black cohosh extract use among peri-/post-menopausal women with or without breast cancer (based on 19 clinical studies including 10 RCTs; Beer & Neff, 2013). Additionally, preliminary evidence suggested black cohosh is not associated with increased breast cancer risk or recurrence (based on 4 observational studies); however, as large prospective studies of longer duration (> 6 months) are required for confirmation, thus women with oestrogen-
dependent tumours should avoid or use black cohosh with caution in the interim. Finally, no serious adverse events or herb-drug interactions were observed in a systematic review evaluating breast cancer survivors’ use of black cohosh while receiving hormonal therapy (tamoxifen and/or raloxifene; based on 5 clinical trials and one cohort study; Fritz et al., 2014; Rostock et al., 2011).

3.5.3.7 Echinacea (Echinacea Purpurea, Echinacin®, Echinacea Angustifolia, Echinacea Pallida, Radix Echinaceae, Esberitox N®, Samital®)

Two subsequent reviews (and 5 clinical trials plus 1 case report) evaluating the efficacy and/or safety of echinacea or echinacea-based botanical preparations in cancer treatment and care have been published or newly-located. Preliminary data from a few small case series/studies has revealed insufficient evidence that echinacea extract (Echinacin®) confers increased survival or other benefits when used as an adjunct to palliative chemotherapy in advanced cancer patients (Pilkington, 2012; Basch et al., 2005). Similarly, preliminary evidence from a number of small randomised trials and case series/observational studies is inconclusive for the use of echinacea-based herbal extracts [Esberitox N®, ethanolic-aqueous extract comprising Radix echinaceae, thuja (Thujae occidentalis) and wild indigo root (Radix baptisiae tinctoriae)] in the management of radiation-induced leukopenia (Pilkington, 2012; Basch et al., 2005). Clearly, large RCTs are required. Finally, preliminary evidence from two small clinical trials (single-blind, placebo-controlled RCT involving head and neck cancer patients; observational study involving haematology patients) suggest that a standardised echinacea-containing botanical extract [Samital®, Vaccinium myrtillus (bilberry), Macleaya cordata fruits and Echinacea angustifolia roots] may ameliorate oral and/or gastrointestinal mucositis (and related outcomes, such as pain, eating difficulties and QoL) induced by chemotherapy ± radiotherapy (Pawar et al., 2013; Bertoglio et al., 2013). Studies, however, are still very much in their infancy. Clearly, large double-blind RCTs comparing Samital® to active control treatments (e.g. antiemetics, analgesics, proton pump inhibitors) in different cancer populations are needed.

Short-term use of echinacea is still generally safe. Echinacea and echinacea-based or –containing extracts have been well-tolerated in preliminary cancer clinical trials (Pawar et al., 2013; Bertoglio et al., 2013). Furthermore, no serious adverse events or clinically-relevant herb-drug interactions have been reported in probe studies involving chemotherapy
patients receiving docetaxel (Goey et al., 2013) or HIV patients receiving antiretroviral therapy (Moltó et al., 2011, 2012). However, caution or avoidance may be advised in chemotherapy patients receiving etoposide ± cisplatin, given a recent case report of a non-small cell lung cancer patient exhibiting profound thrombocytopenia that was attributed to cytochrome P450 3A4 inhibition of etoposide (Bossaer & Odle, 2012).

3.5.3.8 Milk Thistle (*Silybum Marianum, Carduus Marianum*)

One subsequent review (and two clinical trials) evaluating the safety of milk thistle in cancer care have been published or newly-located. Milk thistle still appears to be generally safe. No adverse events or drug interactions were reported in a small crossover trial of chemotherapy patients receiving irinotecan who were administered milk thistle extract (80% silymarin; 200mg daily, three times daily over 12 days; van Erp et al., 2005), thus indicating safety of concurrent use for many classes of chemotherapy agents (Frenkel et al., 2013). Additionally, two clinical trials found that large to very large doses of milk thistle (silybin-phytosome; 2.5-20g/day) were relatively safe in localised prostate cancer patients preparing for surgery and advanced cancer patients also (Flaig et al., 2007, 2010). All toxicities were mild (e.g. diarrhoea, hyperbilirubinaemia), with two exceptions ($n=2$; grade 4 postoperative thromboembolic event; grade 3 elevated liver toxicity, alanine aminotransferase). Nevertheless, further studies of milk thistle at higher doses in different cancer populations are needed.

3.5.3.9 European Mistletoe (*Viscum Album L.*, *Viscum Fraxini-2, Iscador®, Eurixor®, Helixor®, abnobaVISCUM, Isorel, Cephalektin, Lektin, PS76A, Lectin ML-1, INN: Aviscumine, PS76A2, Lektino™)

Eight subsequent reviews evaluating the efficacy and/or safety of mistletoe in cancer treatment and care have been published or newly-located. A large systematic review of anthroposophic medicine in Europe including 133 clinical trials of mistletoe product use in cancer therapy (RCTs, prospective-retrospective non-RCTs and uncontrolled trials) found predominantly favourable clinical outcomes, uncommon side-effects or other harmful risks (usually mild/moderate), and high patient satisfaction regarding outcomes and safety (Kienle, Glockmann, Grugel, Hamre, & Kiene, 2011). However, further high-quality studies were advised given substantial heterogeneity in the methodological quality of the clinical trials. Additionally, a meta-analysis of 4 retrolective, matched-pairs controlled
cohort studies (i.e. treatment consistent with patient preferences had already started prior to study initiation) found a moderate effect size for survival advantage of mistletoe extract used as an adjunct to conventional anticancer treatment, but observed several limitations to retropective study designs (e.g. possible inaccuracies in cancer diagnosis or screening history, different starting points, inequalities in documentation and monitoring) in addition to study heterogeneity (Ostermann & Büsing, 2012). Similarly, a comprehensive narrative review of mistletoe extract use in breast cancer suggested that adjuvant mistletoe therapy may enhance survival and QoL and reduce adverse effects of conventional treatments (based on 20 clinical studies, including 10 randomised and/or controlled trials), but recommended further high-quality clinical trials given study heterogeneity (Marvibaigi, Supriyanto, Amini, Abdul Majid, & Jaganatha, 2014). Moreover, another 15 clinical studies demonstrated that subcutaneous mistletoe extract was able to boost immune response in breast and other cancer patients. This is consistent with an earlier review that found that many clinical trials showed positive effects of mistletoe extract (Iscador®) on natural killer cell activity, although the author in that instance recommended dedicated studies with optimised treatment schedules and comparable doses be performed to confirm the immunomodulatory effects of mistletoe (Braedel-Ruoff, 2010).

Several mistletoe extracts and products have been studied in cancer clinical trials, most commonly Iscador® amongst others [e.g. Eurixor®, Helixor®, Lektin (PS76A), Lektinol™ (PS76A2), Isorel, abnobaVISCUM and recombinant lectin ML-1 (INN: Aviscumine)]. A meta-analysis of 22 controlled studies (41 data sets; 12 prospective; 5 RCTs, 10 matched-pairs design; all moderate/poor quality) indicated that Iscador® was associated with significantly improved cancer survival when compared to no active treatment (standard cancer care), but observed several limitations to these findings (significance was observed in matched-pairs design studies, but not RCTs; all studies were of moderate/poor methodological quality, including loose matched pairings in matched-control design studies; publication bias; Ostermann, Raak, & Büsing, 2009). A more recent systematic review suggested that Iscador® may enhance survival and reduce adverse effects of conventional anticancer therapy as an adjuvant rather than as a standalone treatment (based on 11 clinical studies, including 3 RCTs and 6 prospective/retrospective cohort studies; National Cancer Institute, 2014). However, it was observed that some studies had major methodological weaknesses (e.g. use of mean as opposed to the standard less-biased median survival, unblinded treatment, historical controls and retrospective
Similar positive outcomes and methodological weaknesses were also witnessed in the same review based on 11 clinical studies (8 RCTs, 3 non-RCTs) examining other mistletoe preparations [Eurixor®, Helixor®, PS76A (Lektin), Isorel, abnobaVIScUM, Viscum fraxini-2], and were mirrored for QoL-related outcomes in a meta-analysis of 13 prospective clinical trials (9 RCTs, 4 non-RCTs, all unblinded and poor quality) comparing Iscador® to standard care in cancer patients (Büssing, Raak, & Ostermann, 2012).

Despite the wide range of mistletoe products used in human studies, serious adverse events are still rare and reported side-effects have generally been minimal. A recent systematic review based on 69 clinical studies (22 RCTs, 3 non-RCTs, 44 single-arm studies, medical/healthy populations) revealed that higher doses of mistletoe extract (up to 1500mg) or isolated mistletoe lectins (up to 0.0064mg/kg or 6.4μg/kg body weight) exerted no immunosuppressive effects (Kienle, Grugel, & Kiene, 2011). Reported adverse effects were dose-dependent and mainly consisted of influenza-like symptoms, local reactions at the injection site (e.g. erythema, induration, swelling, pain), fever and chills, headaches, fatigue/dizziness and mild gastrointestinal symptoms. Adverse events (n = 7; anaphylaxis, reversible grade 3 hepatotoxicity, hive-like angioedema/urticaria) were rare and occurred at very high doses of recombinant lectin ML (0.0048-0.0064mg/kg body weight) and mistletoe extract. Nevertheless, clinicians should monitor cancer patients using high-dose mistletoe.

3.6 Manipulative and Body-Based Practices

3.6.1 Massage Therapy

Nine subsequent reviews (and 3 case studies) evaluating the efficacy and/or safety of massage therapy in cancer treatment and care have been published or newly-located. Consistent with study 2, a systematic review of 6 studies (3 RCTs, 1 quasi-experimental, 2 observational) suggested that partial/full-body massage provided acute relief of perceived cancer pain and reduced dosage fluctuations of analgesic use in palliative care patients (prognosis < 6 months), although no significant reduction in the frequency of analgesics was observed (Falkensteiner, Mantovan, Müller, & Them, 2011). However, evidence of benefit for pain (and concomitant anxiety and depression) should be considered preliminary, at best, given the heterogeneity exhibited by the small number of studies involved. More large high-quality RCTs evaluating different types of massage among palliative cancer patients are required, and should involve standardised interventions (e.g.
Several massage therapy studies have been performed in breast cancer patients and survivors. A meta-analytic/systematic review of 6 predominantly small RCTs revealed insufficient evidence for the use of massage as supportive care for breast cancer patients (pain, fatigue, general breast cancer symptoms, depression, anxiety, anger/hostility, QoL; M. S. Lee, E. N. Lee, & Ernst, 2011). A more recent meta-analytic/systematic review of 18 RCTs, however, revealed limited evidence for the beneficial effect of massage therapy on anger, fatigue and QoL among breast cancer patients/survivors (compared to standard care or active control treatments, such as self-initiated social support), but no significant improvements in depression, anxiety, pain, cortisol levels (stress) or upper limb lymphoedema (Pan, Yang, Wang, Zhang, & Liang, 2013). Again, more large high-quality RCTs as detailed above are recommended, involving assessment of both short- and long-term effects of massage therapy among (breast) cancer patients or survivors.

Several aromatherapy studies, predominantly small, have been conducted amongst cancer patients. A systematic review of 18 aromatherapy studies (± massage therapy; 9 RCTs, 2 non-RCTs, 7 uncontrolled) suggested limited evidence for short-term benefits on anxiety (subjective/objective), depression and pain in cancer patients, but insufficient/inconclusive evidence for other indices (sleep, cortisol levels, psychological/overall well-being, subjective symptom relief, QoL; Boehm, Büssing, & Ostermann, 2012).

Turning to surgical patients, a Cochrane meta-analytic/systematic review of 6 RCTs and 3 case-controlled trials (mostly adult females, 1 paediatric study) revealed insufficient evidence for the use of isopropyl alcohol or peppermint oil vapour inhalation aromatherapy to reduce acute postoperative nausea (and vomiting; ≤ 1 hour) when compared to conventional antiemetic treatment (ondanestrone, promethazine; Hines, Steels, Chang, & Gibbons, 2012). Isopropyl alcohol vapour inhalation was more effective than saline placebo but not conventional antiemetics in reducing the proportion of patients requiring rescue antiemetics, and patient satisfaction was no greater either compared to antiemetics. Nevertheless, large high-quality RCTs are needed, preferably involving surgical cancer patients and aromatherapy other than isopropyl alcohol, to investigate the acute and delayed effects on postoperative nausea and vomiting, respectively, relative to standard antiemetics and other active control treatments. Interestingly, a more recent narrative review examining
the effects of various aromatherapy essential oils in surgical patients suggested that peppermint oil had positive effects on acute postoperative nausea, but appears overstated as the only study that assessed nausea as an endpoint out of the three identified since the Cochrane review did not achieve significance (Stea, Beraudi, & De Pasquale, 2014). Similar conclusions based on 3 controlled trials were drawn regarding the inhalation effects of lavender or orange essential oils on self-reported pre-surgical/procedural anxiety, but arguably were more valid. Inconclusive/insufficient evidence, however, was indicated for peri-operative pain, infection prophylaxis after oral surgery and post-surgical wound healing, although topical tea tree oil warrants further investigation for wound healing given recent favourable preliminary results (Chin & Cordell, 2013; Blackwood et al., 2013; Edmondson et al., 2011; Stea et al., 2014).

Despite the wide variety of massage therapies, even within individual modalities such as aromatherapy, serious adverse events are still uncommon; and more so when the massage is of the less exotic variety, and administered and tailored to patients by trained professionals (see Collinge, MacDonald, & Walton, 2012). The chief modifications for oncology massage are in regard to use of pressure (reduced pressure and/or avoidance of direct or deep tissue massage as appropriate; e.g. lymphoedema), joint movement (e.g. bone metastases, osteoporosis), patient position for comfort, and extent/duration of massage (e.g. palliative patients may require shorter partial- rather than full-body massages if they are in poor general health; Collinge et al., 2012; Falkensteiner et al., 2011).

Massage lubricants and use of essential oils in aromatherapy may hold the most potential for adverse effects due to allergic reactions. A safe dilution generally accepted by practitioners for most non-toxic, unadulterated aromatherapy/essential oils used on the skin is a maximum of 2.5% for adults, which equates to 2 drops of essential oil per 100 drops of carrier oil (2% dilution: 10-12 drops of essential oil per ounce of carrier oil; Boehm et al., 2012; Lis-Balchin, 1999). Alternatively, 5-10 drops of essential oil per bath is the usual dosage for full-body baths. A recent systematic review yielded 71 cases of adverse effects resulting from aromatherapy, most frequently involving the commonly-used essential oils lavender, peppermint, tea tree oil and ylang-ylang (Posadzki, Alotaibi, & Ernst, 2012). Adverse effects ranged from mild to severe (including one death), with contact dermatitis most implicated with prolonged topical exposure. Oral ingestion of essential oils, commonly practiced in Australia and France, holds much greater risk in large amounts and is generally not advised (e.g. life-threatening phototoxic skin reactions after ingestion of
psoralen and exposure to artificial UV radiation; Kaddu, Kerl, & Wolf, 2001; coma induced by chronic ingestion of cough drops containing menthol; Baibars, Eng, Shaheen, Alraiyes, & Alraies, 2012). Additionally, repeated topical exposure to lavender and tea tree oils has been associated with reversible prepubescent gynaecomastia due to oestrogenic and anti-androgenic effects (Henley, Lipson, Korach, & Bloch, 2007), and may be best avoided by cancer patients with oestrogen-dependent tumours. Finally, use of novel essential oils by aromatherapists generally holds greater risk, given they are commonly derived from wild plants with many cultivations of differing chemical compositions and sourced from unregulated markets with unknown toxicity (Lis-Balchin, 1999).

3.6.2 Acupuncture

Twenty subsequent reviews evaluating the efficacy and/or safety of acupuncture in cancer treatment and care have been published or newly-located. A systematic review of 7 systematic reviews (mostly good-quality reviews predominantly based on a small number of poor-quality studies, often Chinese, with high risk of bias) suggested that acupuncture-point stimulation (manual acupuncture, electroacupuncture, self-/practitioner-administered acupressure) combined with antiemetics was effective in the treatment of acute chemotherapy-induced nausea and vomiting, but there was insufficient evidence for other symptoms encountered in supportive and palliative cancer care (general treatment-related toxicities, hot flushes, pain, leukopenia, xerostomia; Ernst & Lee, 2010). Further large rigorous RCTs are required, however, comparing acupuncture-point stimulation (or any of its individual modalities) to sham variants (if suitable), standard antiemetics and other treatments for chemotherapy-induced nausea and vomiting. Similarly, a more recent systematic review of 17 systematic/non-systematic reviews found a consensus for the use of acupuncture-point stimulation for chemotherapy-induced nausea and vomiting based on 9 of the reviews; however, significant heterogeneity witnessed by the authors in quality, interventions, control groups and outcome measures rendered studies unviable for meta-analysis and needed to be addressed in future RCTs (Towler, Molassiotis, & Brearley, 2013). Positive effects were also indicated for hot flushes, xerostomia, cancer-related fatigue, cancer pain (including arthralgia and neuropathic pain), dyspnoea and anxiety, but were predominantly from lower-quality non-systematic reviews. Finally, in one of the most recent systematic reviews of acupuncture RCTs in cancer care (n = 41), acupuncture-point stimulation was deemed an appropriate adjunctive treatment for uncontrolled
chemotherapy-induced nausea and vomiting based on 11 RCTs, but additional studies were advised to further consolidate this finding (Garcia et al., 2013). Yet again, the efficacy of acupuncture was inconclusive/insufficient for other symptoms (pain, hot flushes, xerostomia, anxiety, fatigue) due to a high risk of bias among studies (e.g. inadequate blinding of patients and outcome assessors; use of single unblinded acupuncturists across all patients in sham-controlled trials; small samples).

Despite the outcomes of these systematic review overviews in cancer care, the effects of acupuncture on symptoms other than chemotherapy-induced nausea and vomiting bears closer examination, especially where meta-analytic reviews have been performed or more recent systematic reviews have been published. In relation to cancer pain, a meta-analytic/systematic review of 15 RCTs suggested that acupuncture is not more effective than pharmacotherapy \((n = 8)\), but may enhance the effects of conventional pharmacotherapy in reducing pain compared to pharmacotherapy alone \((n = 7;\) Choi, Lee, Kim, Zaslawski, & Ernst, 2012). Nevertheless, poor methodological quality of the trials precluded any firm conclusions and large rigorous RCTs examining both efficacy and safety of acupuncture in cancer pain were recommended, using validated outcome measures and controlling for potential confounding variables (e.g. use of over-the-counter pain analgesics or other treatments, comorbid pain conditions, physiological effects of sham acupuncture, non-specific placebo effects related to patient expectations or patient-practitioner interactions). Additionally, a systematic review of 7 clinical trials (3 RCTs, 1 retrospective non-RCT, 3 case series/reports) suggested that acupuncture may be effective in ameliorating chemotherapy-induced neuropathic pain (common toxicity of the vinca alkaloids, platinum derivatives and taxanes, as well as newer agents such as bortezomib and thalidomide), but the current evidence is quite limited due to the poor methodological quality and heterogeneity of the studies (Franconi, Manni, Schröder, Marchetti, Robinson, 2013). Large high-quality RCTs as detailed above are required.

Turning to menopausal hot flushes, a Cochrane meta-analytic review of 16 RCTs (including 7 cancer studies) suggested that acupuncture compared to sham treatment had beneficial effects for severity but not frequency of hot flushes in peri-/post-menopausal women. Subgroup analysis rendered both effects negligible, however, when breast cancer studies were removed, indicating that the effect of acupuncture on hot flushes may differ for peri-/post-menopausal breast cancer survivors (Dodin et al., 2013). Indeed, a more recent systematic review of 6 acceptable-quality (RCTs: 5 breast, 1 prostate cancer) and 10
low-quality studies (9 uncontrolled; 6 breast, 4 prostate) found a significant reduction in hot flushes at the end of acupuncture treatment (up to 43% in higher-quality RCTs compared to pretreatment) in breast/prostate cancer patients and survivors, which was maintained at post-treatment follow-up (range: 3-12 months; Frisk, Hammar, Ingvar, & Spetz Holm, 2014). Nonetheless, the evidence is limited by the general small nature, heterogeneity (e.g. acupuncture types included traditional, auricular and electroacupuncture; hormonal vs non-hormonal therapy status of participants) and poor methodological quality of the studies. Consequently, larger high-quality RCTs with longer follow-up periods (particularly among prostate cancer patients/survivors) are required to confirm these encouraging outcomes, and should compare traditional acupuncture to sham acupuncture and other types of acupuncture and interventions for hot flushes (e.g. venlafaxine).

In relation to cancer-related fatigue, a meta-analysis of 7 RCTs suggested that acupuncture was no more effective than sham acupuncture \( (n = 3) \), no treatment / wait-list control \( (n = 2) \) or active control treatments \( (n = 2; \) acupressure or self-acupuncture) in cancer patients/survivors (Zeng, Luo, Finnegan-John, & Cheng, 2013). General QoL and functioning status was not significantly impacted upon either \( (n = 3) \). The authors, however, found that acupuncture combined with passive and/or active education interventions was significantly better in managing cancer-related fatigue in the short-term than usual care \( (n = 2; \) up to 10 weeks post-treatment), but rendered this finding invalid by statistically pooling studies that were not sufficiently similar in their definition of usual care (i.e. one study combined passive education and physician usual care for enhanced usual care, while the other simply employed physician usual care). More equivocally, a systematic review of 7 RCTs demonstrated inconclusive evidence for the use of acupuncture/electroacupuncture in cancer-related fatigue management for cancer patients/survivors (Posadzki et al., 2013). Notably, the authors observed significant methodological, statistical and clinical heterogeneity across studies, which precluded meta-analysis. Clearly, large rigorous RCTs with longer follow-up periods are required to determine whether acupuncture has any specific beneficial effect on cancer-related fatigue beyond non-specific placebo effects.

In regard to immune system function, a meta-analytic/systematic review of 31 controlled trials (predominantly Chinese with at least moderate heterogeneity; Chen, Li, Cho, & Zhang, 2013) among lung cancer patients evaluated the use of acupuncture-point stimulation [acupuncture needle insertion, acupuncture injection with herbs, acupoint
plaster application, moxibustion (thermal skin stimulation by burning dried mugwort and/or other herbs compressed into a moxa stick at acupuncture/moxibustion points)]. Consistent with study 2, limited evidence suggested that acupuncture-point stimulation as an adjunct to conventional anticancer treatment or as a standalone intervention may be associated with enhanced immunomodulatory effects (by increasing interleukin-2, various T-cell/T-helper cell and natural killer cell activity), haemoglobin and platelet levels, as well as reduced bone marrow suppression secondary to conventional treatment in lung cancer patients. Positive effects were also shown for grade 2-4 chemotherapy-induced nausea and vomiting, performance status and QoL. Nevertheless, the authors advised large well-designed RCTs among lung cancer patients to confirm these results, given heterogeneity (e.g. frequency/duration of acupoint stimulation, diverse control interventions), high risk of study bias (e.g. inadequate blinding and randomisation procedures) and the unknown effects exerted by herbs used in some acupuncture-point stimulation procedures (acupoint injection, plaster application, moxibustion). Unsurprisingly, similar outcomes and conclusions were also observed in a Cochrane systematic review of non-pharmacological interventions for dyspnoea regarding the use of acupuncture/acupressure amongst lung cancer and chronic obstructive pulmonary disease patients (n = 5; Bausewein, Booth, Gysels, & Higginson, 2008).

Finally, additional RCTs evaluating the efficacy and safety of acupuncture in ameliorating radiation-induced xerostomia have been performed since study 2. Two systematic reviews of 3-4 small RCTs demonstrated that acupuncture provided subjective symptom relief of radiation-induced xerostomia among head and neck cancer patients, but no objective symptom relief compared to sham acupuncture or usual care (Zhuang et al., 2013; O'Sullivan & Higginson, 2010). Consequently, insufficient evidence was demonstrated to support acupuncture as an effective and safe treatment or prophylaxis for radiation-induced xerostomia, but there was sufficient merit to warrant large well-designed RCTs with long follow-up periods. Specifically, the design of these trials must employ standardised treatments (e.g. number and type of included acupoints, intervention type/frequency/intensity/duration, non-specific placebo effects), appropriate placebo (i.e. inert sham acupuncture that induces neither activation nor deactivation) and active treatment control groups (e.g. saliva-inducing mouthwashes), and standardised outcome measures (e.g. subjective: saliva quality, appetite, nausea, daily fluid intake and sleep diaries; objective: magnetic resonance sialography of salivary gland function; Zhuang et al.,
Interestingly, comparable insufficient evidence (albeit promising) and conclusions for rigorous RCTs were offered regarding manual acupuncture/electroacupuncture when compared to pharmacotherapy (oral or intramuscular injections) for hiccup relief in cancer patients, in a meta-analytic/systematic review of 5 RCTs (all small Chinese RCTs with high risk of bias, but no significant heterogeneity; Choi, Lee, & Ernst, 2012).

Despite the wide variety of acupuncture techniques, serious adverse effects are still rare; particularly when administered by trained licensed professionals and sterile procedures are observed (He, Zhao, Li, Xi, & Guo, 2012; Zhang, Shang, Gao, & Ernst, 2010; Ernst, 2010). The most frequent adverse events are fainting, pneumothorax, subarachnoid haemorrhage and infection (due to insufficient knowledge and inadequate sterile practices by acupuncturists), while the most serious ones are cardiovascular injuries, subarachnoid haemorrhage, pneumothorax, recurrent cerebral haemorrhage and death related to these (He et al., 2012; Zhang et al., 2010; Ernst, 2010). Possible contraindications include bleeding abnormalities (e.g. severe clotting disorders, such as haemophilia), needle phobia, cardiac conditions necessitating pacemakers or defibrillators (electroacupuncture only), seizure disorders, infection or immunosuppression, cachexia, oedema, cancer-induced bone pain, hyperalgesia or allodynia and pregnancy (Fønnebø, 2013; Paley, Johnson, & Bennett, 2011; Filshie & Hester, 2006).

### 3.6.3 Exercise Interventions

Seventeen subsequent reviews evaluating the efficacy and/or safety of exercise interventions in cancer treatment and care have been published. In an update to a Cochrane meta-analytic/systematic review reported in study 2, evaluation of 56 RCTs (including 28 breast cancer studies) indicated once again that various exercise-based interventions collectively had a small beneficial short-term effect in reducing cancer-related fatigue during treatment or survivorship at post-intervention relative to control group comparisons (predominantly no intervention, wait-list control or usual care; Cramp & Byron-Daniel, 2012). Subgroup analyses revealed small beneficial short-term effects for breast and moderate effects for prostate cancer patients/survivors (i.e. solid tumours), but none for those with haematological malignancies. Similar outcomes were also observed for aerobic exercise, but not resistance exercise in comparison to control group arms. Furthermore, improvements in cancer-related fatigue were not maintained at follow-up in the few studies.
available ($n = 5$; range: 1-12 months) and results were mixed as to whether exercise-based interventions had a positive impact on QoL ($n = 33$). Similarly, a more recent meta-analytic/systematic review of 72 RCTs found a moderate beneficial short-term effect for exercise interventions reducing cancer-related fatigue during treatment or survivorship at post-intervention compared to control group arms (usual care or non-exercise interventions), with more recent RCTs contributing larger effects (Tomlinson, Diorio, Beyene, & Sung, 2014). Stronger effects were exhibited for solid tumours than haematological or mixed malignancies, but did not differ by type of exercise intervention. Furthermore, medium and small short-term improvements in depression ($n = 20$) and sleep disturbance ($n = 17$), respectively, were demonstrated also. Nevertheless, as recommended previously, further large RCTs comparing different forms of exercise interventions (aerobic, resistance, combined) across settings in homogeneous/heterogeneous cancer populations with cancer-related fatigue are required. Specifically, they should involve cancer patients/survivors screened for cancer-related fatigue (via self-report and clinical measures), standalone exercise interventions (i.e. not exercise-based interventions including components such as relaxation/meditation or nutritional counselling), standardised interventions tailored to target populations (e.g. exercise type, frequency/intensity and duration/length), comparison of different exercise settings (e.g. unsupervised home-based vs supervised institution-based, individual vs group programmes), active non-exercise control interventions (e.g. nutritional counselling), subjective/objective outcome measures (including related secondary outcomes, such as sleep disturbance) and longer follow-up periods post-intervention. Adjustment for potential confounding factors should also be performed (e.g. baseline characteristics such as sex, age, and disease/treatment status; dietary changes or use of other fatigue relief strategies while on-study).

Looking beyond cancer-related fatigue, a Cochrane meta-analytic/systematic review of 56 controlled trials (54 RCTs, 30 breast cancer studies) found that exercise interventions had small/medium short-term positive effects on overall QoL (and fatigue; up to 12 weeks post-intervention compared to usual care or non-exercise interventions), but negligible longer-term effects (up to 6 months post-intervention) in planned or actively treated patients and cancer survivors (Mishra et al., 2012). Small/medium improvements in the short- and longer-term were also demonstrated for physical, role and social functioning, but benefits were negligible or inconsistent for a number of other QoL/psychosocial outcomes (anxiety, depression, emotional well-being, body image, pain, sleep disturbance, cognitive
functioning). Subgroup analyses further revealed that exercise had more positive effects on several QoL outcomes in non-breast cancer survivors (overall QoL, physical and role functioning, depression, fatigue, sleep disturbance and emotional well-being), or when it was of moderate/vigorous intensity (overall QoL, physical functioning, anxiety, fatigue, sleep disturbance). Breast cancer survivors fared better than other cancer survivors, however, with respect to anxiety. Nonetheless, the authors advised caution in interpreting these results given heterogeneity (interventions, outcome measures) and high risk of bias among studies. Additionally, they recommended further rigorous RCTs (as prescribed above for cancer-related fatigue) examining whether any beneficial effects of exercise interventions can be maintained much beyond the end of active programmes and, to this end, the collection of qualitative data in such trials to gain insight into how to sustain changes in exercise behaviours among cancer patients/survivors. Interestingly, in another meta-analytic/systematic review of 15 controlled studies focusing on resistance exercise among actively treated patients and cancer survivors, similar short-term improvements (physical functioning, muscular strength/endurance, body composition, QoL) and observations regarding sustained benefit were also offered (Focht et al., 2013).

Judging from the recent proliferation of reviews, there is growing interest in the prescription of exercise interventions to improve clinical outcomes for cancer patients pre- and post-surgically. A systematic review of 18 clinical trials (mostly small and involving aerobic exercise and lung cancer patients; 10 RCTs, 3 non-RCTs, 6 pilot studies) showed preliminary evidence suggesting that exercise undertaken pre-surgically by cancer patients may improve physical and functional recovery outcomes (cardiorespiratory fitness, functional walking capacity, rate of incontinence), but insufficient evidence for other outcomes (QoL, post-surgical length of hospital stay; Singh, Newton, Galvão, Spry, & Baker, 2013). Additionally, a systematic review of 20 clinical trials (mostly small involving supervised aerobic exercise; 8 RCTs; 9 pre-surgical, 9 post-surgical, 2 pre/post-surgical) also suggested that exercise-based interventions undertaken by non-small cell lung cancer patients was associated with improvement in some clinical outcomes (cardiopulmonary exercise capacity, muscle strength, fatigue, postoperative complications, post-surgical length of hospital stay), but that there was insufficient/inconclusive evidence for other outcomes (patient acceptability, QoL, pulmonary function, blood gas indicators; Crandall, Maguire, Campbell, & Kearney, 2014). Clearly, large high-quality studies (not unlike those prescribed above) are required to confirm these encouraging outcomes among surgical
cancer patients, with special focus on intervention design and feasibility perceptions of surgeons and other health professionals, patient acceptability and intervention adherence and adverse effects.

In the same manner as pre/post-surgical cancer patients, there has been a recent proliferation of reviews examining the effects of exercise interventions on symptom management in prostate cancer patients. In a systematic review of 8 RCTs and 4 non RCTs, various exercise-based interventions (≥2 sessions weekly for 4-26 weeks) were associated with improvements in muscle mass/thickness/strength/endurance, proportion of body fat, functional capacity, fatigue, physical/social functioning and overall QoL (group-based interventions only, mostly resistance exercise) and aerobic endurance (group-based interventions, home-based interventions, mostly aerobic exercise plus group counselling) in older prostate cancer patients receiving active or inactive treatment (generally 66-72 years old and 2-4 years post-diagnosis on average, with at least one other comorbid condition; Keogh & MacLeod, 2012). Similarly, a systematic review of 25 RCTs suggested that varied exercise interventions were associated with benefits for physical fitness, body composition, incontinence (home-based pelvic floor/sphincter exercise only), fatigue and QoL in prostate cancer patients receiving active medical treatment (radiotherapy, androgen-deprivation therapy, pre/post-surgical care) or subsequent aftercare (Baumann, Zopf, & Bloch, 2012). Other systematic reviews (Gardner, Livingston, & Fraser, 2014; Chipperfield, Brooker, Fletcher, & Burney, 2013) have focused on varied exercise interventions among prostate cancer patients undergoing androgen-deprivation therapy per se. Based on a limited number of small RCTs and uncontrolled or pre/post-intervention studies, the reviews suggested preliminary evidence for beneficial effects on muscle strength/endurance and lean body mass (resistance exercise more than aerobic), cardiorespiratory fitness, functional capacity and prostate-specific antigen or testosterone levels, but insufficient/inconclusive evidence for other outcomes (QoL, depression, anxiety, fatigue, body fat content, cardiometabolic risk markers, bone health). Again, large high-quality RCTs are clearly needed as detailed previously to identify optimal dose-response effects of exercise interventions and the minimum dose required for benefit in prostate cancer patients.

The greatest proliferation of reviews evaluating exercise interventions in cancer care recently has focused on cancer survivors. Two meta-analytic/systematic reviews of high-quality RCTs (n₁ = 37, n₂ = 15) demonstrated that varied exercise interventions (3 sessions
for several weeks on average) compared to usual care ± written/telephone educational support had a small overall positive effect on depressive symptoms experienced by cancer survivors and patients starting/receiving adjuvant treatment (generally white American women, average age 51 years and diagnosed with curable breast cancer; Brown et al., 2012; Craft, Vaniterson, Helenowski, Rademaker, Courneya, 2012). Subgroup and moderator analyses revealed the greatest improvement in depressive symptoms were observed in cancer patients/survivors aged 47-62 years or breast cancer patients/survivors per se, fully/partially-supervised group-based interventions, higher intensity/frequency aerobic exercise interventions and exercise interventions with longer sessions (>30 minutes). Similarly, a meta-analysis of 78 RCTs and pre/post-intervention studies found that exercise interventions (23 sessions, 50 minutes long over 13 weeks on average) enhanced QoL outcomes in both the short- and longer-term (up to months post-intervention) amongst cancer survivors (mostly breast cancer patients), although they were more effective when they involved women or moderate intensity aerobic exercise interventions (Ferrer, Huedo-Medina, Johnson, Ryan, & Pescatello, 2011). Number of intervention sessions, higher intensity resistance exercise interventions and training of intervention facilitators did not significantly influence QoL outcomes.

Turning to clinical outcomes, a systematic review of 21 small clinical trials (10 RCTs, 6 non-RCTs, 5 pre/post-intervention studies; 18 adult studies) found preliminary evidence suggesting that varied exercise interventions (chronic and/or acute; acute = 1 session) were associated with increased natural killer cell activity, lymphocyte proliferation and granulocyte levels, as well as maintenance of other immune function indicators (leukocyte, lymphocyte, natural killer cell, T-cell/T-helper cell, C-reactive protein and pro/anti-inflammatory mediator levels) in cancer survivors and patients starting/receiving treatment (Kruijsen-Jaarsma, Révész, Bierings, Buffart, & Takken, 2013). Additionally, a meta-analytic/systematic review of 11 RCTs focusing on resistance exercise interventions (generally 2-3 sessions for 12-52 weeks, average intensity: 50-80% one-repetition maximum, 6 sets for each muscle group per week) showed large positive effects on lower/upper-limb muscle strength, moderate effects on lean body mass and proportion of body fat and small effects on fatigue and QoL, in cancer survivors and patients undergoing treatment (mostly women diagnosed with breast cancer) compared to control conditions (no exercise, usual care or alternative intervention or exercise type; Strasser, Steindorf, Wiskemann, & Ulrich, 2013). Clearly, further large high-quality RCTs are needed as
detailed previously to identify optimal dose-response effects of exercise interventions and the minimum dose required for benefit in cancer survivors, particularly in non-breast cancer populations.

Finally, aerobic and resistance exercise interventions still appear to be relatively safe in cancer survivors and patients. Controversy, however, still surrounds whether lymphoedema in breast cancer patients is a necessary contraindication of exercise interventions, particularly those involving resistance exercise. Two recent meta-analytic/systematic reviews of clinical studies published after 2001 ($n_1 = 11$ RCTs; $n_2 = 19$, 7 RCTs, 4 narrative/systematic reviews) have suggested that varied resistance and/or aerobic exercise interventions or weight training regimes are not associated with the development or exacerbation of breast cancer-related lymphoedema in women with or at-risk of it post-surgery during adjuvant treatment or survivorship, and may have beneficial effects on limb strength and physical QOL outcomes (Paramanandam & Roberts, 2014; Kwan, Cohn, Armer, Stewart, & Cormier, 2011). Nevertheless, the moderating effects of pressure garment use during exercise, as well as the supervision and intensity of such interventions require clarification in further research.

3.7 Energy Therapies

3.7.1 Biofield Therapies

3.7.1.1 Qigong

Three subsequent reviews evaluating the efficacy and safety of Qigong in cancer treatment and care have been published. A narrative review examining the effects of varied medical Qigong interventions among cancer patients receiving treatment (5 RCTs, 5 pre/post-intervention studies; mostly small, poor-quality studies with high risk of bias) found inconclusive evidence for benefit on QoL outcomes (e.g. overall QoL, cancer-related fatigue) and psychological distress, but limited preliminary evidence for positive effects on clinical outcomes such as immune function, leukopenia and long-term survival (Oh et al., 2012). In contrast, a systematic review of 23 controlled trials (8 RCTs, 15 non-RCTs; predominantly small, poor-quality studies with high risk of bias) found that poor-quality non-RCTs showed favourable effects of varied Qigong interventions on QoL and clinical outcomes (notably, overall QoL, cancer-related fatigue and immune function) among cancer patients receiving treatment, while moderately better-quality RCTs produced mixed results at best (Chan et al., 2012). Consequently, the authors concluded that the poor quality
and high risk of bias of the studies precluded any firm conclusions about whether Qigong interventions should be adopted in supportive cancer care. More equivocally, a recent meta-analytic/systematic review of Qigong and tai chi interventions revealed limited benefit of Guolin/medical Qigong on overall QoL in the short-term among cancer patients receiving treatment compared to usual care (based on 5 small RCTs), but insufficient/inconclusive evidence for other health outcomes (depression, anxiety, cancer-related fatigue, inflammation and immune function; Zeng et al., 2014). Consistent with study 2, larger high-quality RCTs are recommended (particularly given the very good safety profile demonstrated in recent cancer studies; Zeng et al., 2014; Oh et al., 2012), and they should examine the short- and long-term efficacy of different forms of Qigong interventions in homogeneous/heterogeneous cancer populations. Specifically, they should involve both cancer patients and survivors, standardised interventions tailored to target populations (e.g. form of Qigong, frequency/intensity and duration/length), comparison of different formats (e.g. individual vs group), active control interventions (e.g. aerobic and/or resistance exercise, acupuncture), subjective/objective outcome measures as appropriate (e.g. cancer-related fatigue) and use of a suitable placebo control group to account for non-specific effects of Qigong practitioner-patient interactions (e.g. usual cancer care + telephone support).

3.7.2 Bioelectromagnetic-Based Therapies
3.7.2.1 Microwave (UHF Radiowave)/Tronado Therapy

No subsequent reviews or controlled trials evaluating the efficacy and/or safety of microwave or ultra high frequency (UHF) therapy that are of relevance to the cancer field were located.
References


Qin, B., Xun, P., & He, K. (2012). Fish or long-chain (n-3) PUFA intake is not associated with pancreatic cancer risk in a meta-analysis and systematic review. Journal of Nutrition, 142(6), 1067-1073.


Stephenson, C. M., Levin, R. D., Spector, T., & Lis, C. G. (2013). Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. *Cancer Chemotherapy and Pharmacology, 72*(1), 139-146.


3.8 Preface to Commentary Article Based on Study 2 – “Embracing Complementary and Alternative Medicine (CAM) for All the Right Reasons”

The manuscript describing a general discussion of the present PhD thesis (with special focus on study 2) in the form of an expert comment article, written for a wider medical audience including general practitioners and allied healthcare professionals, underwent peer review and was published by the Medical Journal of Australia (MJA) InSight. The manuscript in the raw format form in which it was published is presented overleaf. Appendix E also contains the published work, as it appears in publication online.

To provide further background, the commentary article was an invited publication extended by Kath Ryan, editor of MJA Insight, following presentation of the systematic review findings of study 2 at an international/domestic cancer conference held in Brisbane, Australia (see page overleaf), which attracted a media release from the conference organisers and precipitated several media reports/interviews. The invited commentary contributes to the present thesis by illustrating an endeavour toward achieving the challenging, lofty heights of translational research in medicine and health, whereby the aim was to "translate" basic research findings into medical and clinical practice in oncology and enhance meaningful health outcomes and the overall well-being of current and future cancer patients.

Original Publications


 REGARDLESS of whether doctors like it or believe in it, complementary and alternative medicine is used by more than half of all Australians [http://www.ncbi.nlm.nih.gov/pubmed/17718647](http://www.ncbi.nlm.nih.gov/pubmed/17718647) each year.


There are many stumbling blocks for patients in talking about CAM with doctors. They range from the very real prospect of receiving a negative or indifferent response, to doctors simply not asking about CAM, through to the worrying belief of many patients that CAM is entirely “natural” and safe alongside conventional treatment.

Doctors need to nurture an environment where patients can talk about their use of CAM without fear of disapproval, if for no reason other than the prospect that their use may cause serious drug interactions with conventional treatments (cancer or otherwise) or adverse side-effects on their own.

The safety and efficacy of over 50 individual complementary and alternative therapies were evaluated across more than 300 meta-analytic and systematic reviews. Weighing up risk vs benefit, the top 10 therapies that cancer patients should be discouraged from using are St. John’s wort, laetrile/amygdalin/vitamin B17, kava, ginkgo biloba (EGb 761), lingzhi/reishi mushroom, green tea, ginseng, black cohosh, shark cartilage and garlic.

Generally, botanical agents pose the greatest risk of harm to cancer patients. In particular, their use as unproven alternative therapies (e.g., laetrile/amygdalin) in place of conventional medicine should be strongly discouraged.

Some herbal medicines, dietary supplements and other “natural” therapies have toxic and potentially life-threatening effects (e.g., laetrile/amygdalin can cause cyanide poisoning and death; kava and black cohosh may cause liver problems). Others interact with chemotherapy and prescription drugs (e.g., St. John’s wort potentially interacts with 70%-80% of all prescription medicines, and reduces the efficacy of some chemotherapy drugs). Some cause complications during radiotherapy and surgery (e.g., garlic, ginkgo biloba and ginseng may increase bleeding).

That said, we shouldn’t tar all CAM interventions with the same brush as there is substantial evidence to support the safe and effective use of some interventions. Clinical trials have shown that some therapies, when used in support of conventional treatments, are beneficial in reducing symptoms or emotional distress and improving the quality of life of cancer patients.

Weighing up risk vs benefit once again, the top 10 most effective and safe therapies from my review for people with cancer are relaxation techniques, support groups led by health professionals, physical activity programs, music therapy, meditation (including mindfulness), acupuncture, massage, omega-3 fatty acids, yoga and ginger (combined with prescription antiemetics).

Generally, mind-body and manipulative/body-based therapies have the greatest potential for benefit among cancer patients. Relaxation techniques, for example, are the most effective non-
pharmacological approach for the relief and prevention of depression and anxiety in patients undergoing cancer treatment.

Relaxation can also reduce nausea/vomiting, cancer-related pain and fatigue and, in respiratory cancer patients, breathing difficulties. Physical activity programs involving aerobic or resistance exercise can also be particularly beneficial for physical/emotional wellbeing and fatigue, even in metastatic cancer patients.

Patients may seek guidance about CAM therapies and medical practitioners are in the prime position to provide this. Therefore, doctors ought to be educated about CAM. Medical schools and hospitals should integrate teaching about CAM into medical training. Doctors need to become familiar with websites and online databases that provide information about the wide range of therapies available. The Cancer Council Australia [http://www.cancer.org.au/about-cancer/treatment/complementary-therapies-and-cancer.html](http://www.cancer.org.au/about-cancer/treatment/complementary-therapies-and-cancer.html) and Australasian Integrative Medicine Association [https://www.aima.net.au/resources/databases/](https://www.aima.net.au/resources/databases/) are good starting points.

Cancer specialists should consider offering access to safe and effective complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services.

As long as complementary therapies used by cancer patients are safe and under medical supervision, where is the harm? Hippocrates once said: “As to diseases, make a habit of two things — to help, or at least, to do no harm.”

When patients don’t feel that they can talk about CAM with their doctors for fear of disapproval and doctors don’t routinely take the time to ask, is that likely to help or harm the patient with cancer? It’s certainly a question every doctor should ponder.

 Carlo Pirri is a research psychologist/consultant and PhD candidate based at Murdoch University, Perth. He is a working party member of the Complementary and Integrated Therapies Interest Group established by the Clinical Oncological Society of Australia.
Chapter 4: Integrating Complementary and Conventional Medicine

4.1 Preface to General Discussion and Summary Conclusions

The manuscript describing a general discussion of the current status of complementary and alternative medicine in cancer, in Australia and elsewhere, underwent peer review and was published in a special issue of Cancer Forum dedicated to complementary and alternative medicine. The invited publication included a broad summary of the two studies reported in the present PhD thesis and several others, their clinical implications and recommendations for future research and clinical practice, and thus serves as the concluding chapter of this thesis. The manuscript in the form in which it was published is presented overleaf.

Original Publication

INTEGRATING COMPLEMENTARY AND CONVENTIONAL MEDICINES

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Abstract

Complementary and alternative medicine (CAM) continues to evoke fierce debate and divergent views within the medical community. It remains an attractive and commonly used treatment option for many cancer patients regardless of whether their doctors like it or believe in it. Consequently, it divides health professionals providing conventional cancer care and CAM practitioners offering unconventional care. CAM, for reasons varying from a desire to control symptoms and prevent and treat cancer to accessibility, has assumed significant importance in cancer treatment for many patients. An estimated 14% to 65% of Australian adults diagnosed with cancer use CAMs (with estimates as high as 80% to 91% in Europe and the US). Cancer patients who use CAM are typically female, younger, more educated, and of higher socioeconomic status. Moreover, 33% to 77% of patients do not disclose CAM use to their physicians. Given the increasing desire of cancer patients to use CAM, it is important that clinicians have a good understanding of the evidence available for the efficacy and safety of specific complementary and alternative therapies.

Current evidence from high quality cancer clinical trials indicates that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving quality of life (QoL) and psychological functioning. Problematically, however, CAMs are often perceived by cancer patients as being more “natural” and, by association, safer than conventional treatments. CAMs can
directly harm patients via toxic or allergic reactions to their use alone, interactions with chemotherapy agents and prescribed medications, or contaminants in their manufacturing or from the environment. Some herbal medicines, nutritional supplements and other natural therapies have toxic and potentially life-threatening effects (e.g. kava, comfrey and black cohosh may cause hepatotoxicity); interact with chemotherapy and prescription drugs (e.g. St. John’s wort may result in serotonin syndrome when taken with antidepressants, and reduce the efficacy of chemotherapy involving irinotecan and imatinib); or cause complications during surgery (e.g. garlic, ginkgo biloba and ginseng may increase bleeding), radiotherapy and other anticancer treatments. Consequently, some complementary therapies should not be used under any circumstances irrespective of potential benefit (e.g. St. John’s wort), while others may be beneficial when cancer patients are not undergoing these treatments and have no other contraindications. CAMs may also cause indirect harm to patients. Resultant delays in conventional treatment potentially compromise treatment outcomes, QoL and survival.

It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies, in order to receive benefit while avoiding harm. Additionally, as a consequence of the safety risks associated with CAM use, clinicians are strongly encouraged to routinely ask patients about complementary and alternative therapy use. Several recommended approaches (including a preliminary set of communication guidelines) for discussing CAM with cancer patients have been published.

In conclusion, whether termed integrative cancer care or complementary medicine, cancer physicians in Australia should strongly consider offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services. Conceivably, this will influence patients to continue with mainstream care and help them avoid any potential harm that may occur with autonomous CAM use. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment and care.
Introduction
Complementary and alternative medicine (CAM) continues to evoke fierce debate and divergent views within the medical community. It remains an attractive and commonly used treatment option for many cancer patients regardless of whether their clinicians like it or believe in it. Consequently, it divides health professionals providing conventional cancer care and CAM practitioners offering unconventional care.

Background
Definitions
The US National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as ‘a group of diverse medical and health care systems, practices and products that are not presently considered part of conventional medicine’.\(^1\) Complementary and alternative therapies must be distinguished, however. “Complementary therapies” are adjuncts to conventional medical treatment that are increasingly perceived as an important part of supportive care;\(^2,3\) they are often used for symptom management and to enhance quality of life (QoL) and overall patient care.\(^4\) “Alternative therapies”, in contrast, are clinically unproven and are used instead of conventional treatments.\(^2\) They can be particularly damaging to cancer patients as delay or outright refusal of conventional treatment often compromises their likelihood of cure or remission.\(^5\) More recently, the term “integrative oncology” has emerged and involves a standard of care for cancer patients that utilises safe, evidence-based complementary therapies in conjunction with conventional anticancer treatments via a multidisciplinary approach designed to evaluate and treat the whole person rather than the disease per se.\(^6\)

Prevalence and Cost of Complementary and Alternative Medicine (CAM) Use
In the most recent population surveys in 2005/06 an estimated 67% of Australians used CAM,\(^7\) which was at least equivalent to prescription drug use\(^7,8\) and represented out-of-pocket spending of AUD$4.13 billion, with as many visits being made to CAM practitioners as medical practitioners (approximately 68 million each).\(^9\) In adult cancer patients, a systematic review of 21 studies worldwide reported an average prevalence of CAM use of 31.4% (range: 7-64%).\(^10\) Other studies report even higher prevalence depending on CAM definitions used and cancer populations studied (e.g. up to 91% of US
patients reported CAM use including prayer and exercise). In Australia, CAM use by cancer patients has varied widely from 14.5% to 65%.

Profile of CAM Users, Reasons Cancer Patients Use CAM, and Disclosure of CAM Use by Patients

Cancer patients may make the decision to use CAM upon diagnosis, during conventional treatment, in response to disease progression or recurrence, or during remission/survivorship. Cancer patients who use CAM are typically female, younger, more educated, and of higher socioeconomic status. There are many reasons why cancer patients use CAM (Table 1), including cancer cure or prolongation of life; relief from cancer symptoms and conventional treatment side-effects; to assist conventional treatments; boosting immunological function or energy; enhancing physical, emotional and spiritual well-being; and maintaining a sense of control or hope. Finally, research indicates that 33% to 77% of patients do not disclose CAM use to their physicians, including 40% of cancer patients in one Australian study.

Cancer Physicians’ Concerns and Attitudes Regarding CAM

Collectively, there is a lack of scientific evidence for the efficacy of CAMs in oncology. Certainly, no CAM has proven effective in reliably curing or suppressing any form of cancer. A useful distinction, however, is that between cancer cure and cancer care. Some CAMs (e.g. mind-body techniques such as relaxation, acupuncture, massage) have proven relatively effective and safe in relieving disease/treatment symptoms and enhancing QoL/psychosocial functioning and, thus, are important in caring for patients throughout the cancer experience. Other CAMs (e.g. herbs, nutritional supplements, antioxidants), however, have drawn steadfast opposition from oncologists, primarily because they remain unproven in clinical trials; possess greater health risks due to adverse interactions with prescribed cancer treatments or medications (e.g. CAM-drug interactions,
**Table 1.** Reasons why cancer patients use complementary and alternative medicine (CAM)

<table>
<thead>
<tr>
<th>Common Reasons</th>
<th>Other Reasons</th>
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<tbody>
<tr>
<td>Cure or prolongation of life&lt;sup&gt;20-29&lt;/sup&gt;</td>
<td>Perceptions that CAMs are natural, beneficial and will cause no harm&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptom relief from cancer and its treatment&lt;sup&gt;19,27,30,32&lt;/sup&gt;</td>
<td>Encouragement from family, friends and other cancer patients/survivors&lt;sup&gt;19,28,35-37&lt;/sup&gt;</td>
</tr>
<tr>
<td>Assist conventional anticancer treatments (e.g. surgery, chemotherapy, radiotherapy)&lt;sup&gt;21,25&lt;/sup&gt;</td>
<td>Media influence&lt;sup&gt;38,39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Boost immunological function&lt;sup&gt;16,19,27,30&lt;/sup&gt;</td>
<td>Cultural values and beliefs&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Boost energy levels&lt;sup&gt;16,19,27,30&lt;/sup&gt;</td>
<td>Poor cancer prognosis&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enhance physical, emotional and/or spiritual well-being&lt;sup&gt;15,16,32,33&lt;/sup&gt;</td>
<td>Strengthen the body to cope with conventional anticancer treatments&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maintain a sense of control over their cancer and its treatment&lt;sup&gt;16,19,20,22,24,25,32,34&lt;/sup&gt;</td>
<td>Reduce the need for invasive, painful or expensive anticancer treatments&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maintain hope of successfully overcoming cancer&lt;sup&gt;16,19,20,22,24,25,32,34&lt;/sup&gt;</td>
<td>Enhance quality of life&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Prevent recurrence following conventional anticancer treatment&lt;sup&gt;41,42&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>High accessibility of CAMs (e.g. due to non-prescription or self-referral)&lt;sup&gt;43&lt;/sup&gt;</td>
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<td></td>
<td>Greater one-on-one attention from CAM practitioners</td>
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<tr>
<td></td>
<td>Dissatisfaction with conventional medical care&lt;sup&gt;43&lt;/sup&gt;</td>
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<td></td>
<td>Poor doctor-patient relationship&lt;sup&gt;43&lt;/sup&gt;</td>
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</tbody>
</table>

**Table 2.** Concerns held by physicians for cancer patients using complementary and alternative medicine (CAM)<sup>53,96</sup>

<table>
<thead>
<tr>
<th>Primary Concerns</th>
<th>Other Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific CAMs are unproven in clinical trials</td>
<td>Financial harm due to the excessive cost associated with CAMs</td>
</tr>
<tr>
<td>Adverse interactions with conventional treatments or medications (e.g. CAM-drug interactions, surgical complications such as bleeding)</td>
<td>Psychological harm caused by CAM use (e.g. by creating false hope in medically hopeless situations)</td>
</tr>
<tr>
<td>Reduced chance of cure or remission (due to CAM use delaying or reducing the efficacy of conventional treatments)</td>
<td>Abandonment of conventional treatment</td>
</tr>
<tr>
<td>Shorter survival time (due to CAM use delaying or reducing the efficacy of conventional treatments)</td>
<td>Patients confusing physicians’ willingness to discuss and support their choice to use CAMs with actual medical support for them</td>
</tr>
<tr>
<td></td>
<td>Litigation against physicians if they (appear to) advocate use of CAMs that prove to be a failure</td>
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</table>
surgical complications such as bleeding); and may delay or reduce the efficacy of conventional treatments and, subsequently, compromise the likelihood of cure/remission and shorten survival time (Table 2).53

**Efficacy and Safety of CAM**

In one population survey, 75% of people agreed that combining conventional medical treatment and CAM was preferable to using either alone.54 Problematically, however, CAMs are often perceived by cancer patients as being more “natural” and, by association, safer than conventional treatments.82 CAMs can directly harm patients via toxic or allergic reactions to their use alone, interactions with chemotherapy agents and prescribed medications, or contaminants in their manufacturing or from the environment (e.g. heavy metals, pesticides, bacteria, fungi).51,53 Some herbs, nutritional supplements and other botanical agents have toxic and potentially life-threatening effects (e.g. kava, comfrey and black cohosh may cause hepatotoxicity);55,56 interact with chemotherapy and prescription drugs (e.g. St. John’s wort may result in serotonin syndrome when taken with antidepressants, and reduce the efficacy of chemotherapy involving irinotecan and imatinib);53,56 or cause complications during surgery (e.g. garlic, ginkgo biloba and ginseng may increase bleeding) and radiotherapy (see Table 3 for a summary of direct harm that may result from CAM use).53,57,58

CAMs may also cause indirect harm to patients (Table 4). Resultant delays in conventional treatment potentially compromise treatment outcomes, QoL and survival.59,60 Financial or emotional burden (e.g. prolonged denial), or the squandering of precious, limited time that some patients have left also constitute indirect harm. Finally, patients may fall victim to harm as a result of the unsafe practices of CAM practitioners with inadequate training or competence, often owing to the absence of self-regulatory bodies and unsatisfactory government legislation protecting health consumers. Moreover, harm may be exacerbated by regulatory deficiencies in monitoring the biological potency of herbal crops or use of the correct plant species (causing wide variation in therapeutic efficacy); product standardisation in terms of purity and dosage (resulting in possible substitution/adulteration and incorrect dosing or preparation); and product labelling or advertising.61
### Table 3. Safety of complementary and alternative medicine: direct harm resulting from CAM use by cancer patients

<table>
<thead>
<tr>
<th>Direct Harm</th>
</tr>
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<tbody>
<tr>
<td>Toxic reactions to specific CAMs per se</td>
</tr>
<tr>
<td>e.g. laetrile/amygdalin causes cyanide poisoning, which may result in death</td>
</tr>
<tr>
<td>e.g. high-dose beta-carotene increases lung cancer incidence and cancer mortality in smokers</td>
</tr>
<tr>
<td>e.g. ephedrine alkaloids, such as ephedra/ma huang, may cause cardiovascular events including hypertension, tachycardia, heart attack and stroke</td>
</tr>
<tr>
<td>e.g. chronic use of valerian (≥ 2-4 months) may result in insomnia, as well as withdrawal effects (e.g. delirium, tachycardia) if also used heavily</td>
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</tbody>
</table>

| Adverse CAM-drug interactions with chemotherapy agents |
| e.g. kava, black cohosh, laetrile/amygdalin and echinacea, among other herbal medicines and nutritional supplements, may increase the risk of acute or chronic liver failure (and resultant death or liver transplant) when receiving hepatotoxic chemotherapy drugs, including cyclophosphamide, methotrexate, camptothecins (for instance, irinotecan), taxanes (for instance, paclitaxel), vinca alkaloids (for instance, vinorelbine) and EGFR-TK inhibitors (for instance, erlotinib and cetuximab) |

| Adverse CAM-drug interactions with other prescribed medications |
| e.g. ginseng, garlic, ginkgo biloba, ginger, Lingzhi and St. John’s wort, among others, may increase bleeding when used concurrently with anticoagulant/antiplatelet medications (e.g. warfarin, aspirin) |
| e.g. St. John’s wort may cause serotonin syndrome (e.g. hypervigilance, agitation, muscle twitching, mental status changes, sweating, fever, shivering, rigidity, tachycardia/hypertension resulting in possible shock and death) when combined with prescription antidepressants |
| e.g. valerian may increase the effects of sedatives (benzodiazepines and barbiturates), hypnotics and anxiolytics when used concurrently |

| Adverse interactions with other CAMs |
| e.g. laetrile/amygdalin combined with dietary intake of fruit seeds (for instance, apricot, bitter almond, peach, apple), raw almonds or megadoses of vitamin C increases the risk of cyanide poisoning and resultant death |
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Direct Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse interactions with comorbid medical or psychiatric illnesses</strong></td>
</tr>
<tr>
<td>e.g. ginseng, garlic, ginkgo biloba, ginger, Lingzhi, St. John’s wort and massage therapy, among other CAMs, may increase bleeding and risk of resultant death in cancer patients with coagulation disorders</td>
</tr>
<tr>
<td>e.g. kava, black cohosh, laetrile/amygdalin and echinacea, among others, are potentially hepatotoxic and increase the risk of irreversible liver damage (and resultant death or liver transplant) in cancer patients with liver disorders</td>
</tr>
<tr>
<td>e.g. ephedrine alkaloids (for instance, ephedra/ma huang) and Siberian ginseng/eleuthero (Eleutherococcus senticosus) possess immunostimulatory properties, thus use increases the risk of cardiovascular events (e.g. heart attack) and resultant death in cancer patients with cardiovascular disease</td>
</tr>
<tr>
<td>e.g. meditation, hypnotherapy and Reiki may exacerbate psychological problems in cancer patients with psychosis, personality disorders and/or other psychiatric illnesses (for instance, schizophrenia, borderline personality disorder and bipolar disorder, respectively)</td>
</tr>
<tr>
<td><strong>Adverse effects during or following (cancer) surgery due to CAM-drug interactions (for instance, anaesthetics), inhibition of platelet function, excessive sedation, hypertensive effects, or slow wound healing</strong></td>
</tr>
<tr>
<td>e.g. ginseng, garlic, ginkgo biloba, ginger, Lingzhi and St. John’s wort, among others, may increase bleeding during or following surgery if not ceased at least 4-7 days prior to surgery</td>
</tr>
<tr>
<td>e.g. St. John’s wort, valerian, garlic and kava, among others, may increase/decrease the effects of anaesthetics administered prior to surgery if not ceased at least 4-7 days beforehand</td>
</tr>
<tr>
<td>e.g. shark cartilage is best avoided prior to surgery as it may slow wound healing postoperatively</td>
</tr>
<tr>
<td><strong>Adverse interactions with radiotherapy</strong></td>
</tr>
<tr>
<td>e.g. Microwave/UHF therapy + radiotherapy may result in greater adverse effects than radiotherapy alone for bladder or other invasive cancers</td>
</tr>
<tr>
<td><strong>Adverse interactions with hormonal therapy or other conventional anticancer treatments</strong></td>
</tr>
<tr>
<td>e.g. ephedrine alkaloids such as ephedra/ma huang increase the risk of cardiovascular disease in prostate/testicular cancer patients receiving hormone therapy</td>
</tr>
<tr>
<td><strong>Adverse interactions with genetic predispositions or tendencies</strong></td>
</tr>
<tr>
<td>e.g. laetrile/amygdalin increases the risk of cyanide poisoning and resultant death in genetically predisposed patients with a diminished capacity to detoxify cyanide</td>
</tr>
<tr>
<td>e.g. atopic patients with a genetic tendency towards hypersensitivity may be more prone to allergic reactions (rashes, increased asthma, anaphylaxis resulting in possible death) when using echinacea</td>
</tr>
</tbody>
</table>
### Table 3. (Continued)

<table>
<thead>
<tr>
<th><strong>Direct Harm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased efficacy of prescription medications</strong></td>
</tr>
<tr>
<td>e.g. St. John’s wort may reduce the efficacy of opioids (for instance, morphine, fentanyl, oxycodone, buprenorphine) for cancer pain in (palliative) patients when used concurrently</td>
</tr>
<tr>
<td>e.g. St. John’s wort may reduce the efficacy of antidepressants (for instance, SSRIs such as sertraline; SNRIs such as venlafaxine; tricyclics such as amitryptiline, MAOIs such as phenelazine) when used concurrently</td>
</tr>
<tr>
<td><strong>Decreased efficacy of chemotherapy</strong></td>
</tr>
<tr>
<td>e.g. St. John’s wort can reduce the efficacy of irinotecan and increase myelosuppression in advanced colorectal and lung cancer patients; and may reduce the efficacy of imatinib for gastrointestinal stromal tumours, chronic myeloid leukaemia and other malignancies</td>
</tr>
<tr>
<td>e.g. green tea may reduce the efficacy of bortezomib in multiple myeloma and mantle cell lymphoma patients</td>
</tr>
<tr>
<td><strong>Decreased efficacy of radiotherapy</strong></td>
</tr>
<tr>
<td>e.g. limited evidence suggests that use of antioxidants may protect tumour cells and reduce the efficacy of radiotherapy</td>
</tr>
<tr>
<td><strong>Decreased efficacy of hormonal therapy or other conventional anticancer treatments</strong></td>
</tr>
<tr>
<td>e.g. female ginseng (<em>Angelica sinensis</em>)/dong quai, red clover and soy exert oestrogenic effects, and may reduce the efficacy of hormonal (anti-oestrogen) therapy for breast and other hormone-sensitive cancers</td>
</tr>
<tr>
<td><strong>Adverse effects due to contamination of CAM products in manufacturing or from the environment (e.g. by heavy metals, pesticides, bacteria, fungi or other impurities)</strong></td>
</tr>
<tr>
<td>e.g. excessive consumption of shark cartilage or fish may result in adverse effects due to toxic levels of mercury and other contaminants</td>
</tr>
<tr>
<td>e.g. contamination of laetrile/amylgdalin manufactured in Mexico (the world’s largest supplier) and Chinese herbal medicines by bacteria and other impurities may lead to infection or disease (e.g. hepatitis B or C, herpes simplex, varicella zoster, tuberculosis)</td>
</tr>
<tr>
<td><em>Adverse effects due to substitution or adulteration of CAM products with prescription or non-prescription drugs (e.g. corticosteroids, hormones, salicylates, antihistamines, caffeine)</em></td>
</tr>
<tr>
<td>e.g. adulteration/substitution of Chinese herbal medicines and nutritional supplements such as laetrile/amylgdalin are not uncommon (for instance, unspecified adulteration with corticosteroids may lead to the hormonal disorder Cushing’s syndrome and adverse interactions with diabetic and heart medications among others)</td>
</tr>
</tbody>
</table>
### Table 3. (Continued)

**Direct Harm**

Adverse effects or negligible/decreased efficacy of CAM products as a result of not being standardised (i.e. in terms of purity and dosage)

- e.g. excessive doses of shark cartilage supplements may produce common side-effects (for instance, gastrointestinal symptoms such as nausea, vomiting, stomach upset, constipation/diarrhoea and taste alteration) and more serious adverse effects due to toxic levels of mercury, cadmium and other contaminants, given there is no generally accepted recommended dosage or duration for administration.

- e.g. shark cartilage products typically contain varying amounts of active ingredients, and therefore may not have any biological activity (for instance, liquid shark cartilage preparations reportedly contain over 99% water and less than 1% protein; powdered shark cartilage may contain excessive binding agents and fillers, including collagen, gelatin, talc, magnesium stearate and silica).

**Adverse effects or negligible/decreased efficacy of CAMs due to product mislabelling or misleading advertising**

- e.g. mislabelling of Chinese herbal medicines and nutritional supplements such as laetrile/amylgdalin are not uncommon in regard to unlisted adulterants and may cause adverse effects (for instance, unspecified adulteration with corticosteroids may lead to the hormonal disorder Cushing’s syndrome and adverse interactions with diabetic and heart medications amongst others).

- e.g. BeneFin (powdered shark cartilage), SkinAnswer (glycoalkaloid skin cream) and MGN-3 (rice-bran extract) were falsely promoted and marketed by Lane Labs-USA from 1997 to 2004 as effective and safe treatments for cancer and other diseases through books, articles, brochures, websites and employee statements. In 2004, Lane Labs were fined $1 million and ordered to refund customers and destroy all inventory of these products, except for a quantity of BeneFin needed for research purposes. Subsequently, two RCTs involving advanced cancer patients demonstrated that BeneFin was ineffective in improving survival or quality of life compared to standard conventional care.

**Adverse effects or negligible/decreased efficacy of CAMs as a result of CAM practitioners with inadequate training or competence**

- e.g. acupuncturists lacking experience or competence are more likely to cause minor adverse effects (for instance, local bleeding and needling pain), as well as major adverse events (for instance, pneumothorax).

- e.g. the skill of instructors in meditation or relaxation techniques may be important in determining whether the occurrence of paradoxical anxiety symptoms become valuable learning opportunities for teaching management of stress/anxiety or, alternatively, adverse events.

- e.g. massage therapists should avoid applying direct pressure over known tumours to prevent adverse effects in cancer patients; no massage or reduced pressure is also advisable for cancer patients with coagulation disorders, bone metastases, open wounds or radiation dermatitis, and prosthetic devices (for instance, infusaport, colostomy bag, stents).

- e.g. homeopaths lacking experience or competence may prescribe homeopathic medicines in such ultra-low concentrations that they possess no clinical therapeutic efficacy whatsoever.

CAM = complementary and alternative medicine; MAOIs = monoamine oxidase inhibitors; RCTs = randomised controlled trials; SNRIs = serotonin and noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.
Table 4. Safety of complementary and alternative medicine (CAM): indirect harm resulting from CAM use by cancer patients

<table>
<thead>
<tr>
<th>Indirect Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially compromised treatment efficacy, quality of life and survival of cancer patients</td>
</tr>
<tr>
<td>if CAM use results in the delay, abandonment or complete refusal of conventional anticancer treatment$^{59,60}$</td>
</tr>
<tr>
<td>Decreased likelihood of comprehensive multidisciplinary input in conventional treatment plans and important evidence-based follow-up plans for cancer patients</td>
</tr>
<tr>
<td>Financial burden due to the excessive costs associated with CAMs</td>
</tr>
<tr>
<td>Psychological distress (e.g. due to prolonged denial, by creating false hope in medically hopeless situations)</td>
</tr>
<tr>
<td>Precious, limited time of some cancer patients (e.g. advanced disease patients with poor prognosis, patients with disease progression or recurrence) may be squandered</td>
</tr>
<tr>
<td>Indirect harm stemming from CAM practitioners lacking experience or competence (e.g. misdiagnosis resulting in the delay of appropriate cancer treatment)$^{61}$</td>
</tr>
<tr>
<td>Compromised clinical trial outcomes if the effects of unknown CAM use by trial patients are misattributed to new conventional anticancer treatments being investigated$^{62,63}$</td>
</tr>
</tbody>
</table>

Despite the long history of most CAMs, rigorous scientific research evaluating their efficacy and safety is a recent phenomenon. A diverse range of CAMs are utilised by cancer patients in Australia and elsewhere, and the heterogeneity of these techniques appear to be reflected in their reported efficacy also.$^{6,51,58,64-66}$ Some show considerable promise and in years to come may be integrated into everyday clinical practice, while others are ineffective and, worse still, directly harmful. Subsequently, there is a sizable gap between the use of some popular CAMs and the evidence to support that use.

**Future Research in CAM and Establishing Research Priorities**

Relatively little CAM research has been performed in Australia. Unfortunately, research gaps are the rule rather than the exception in the CAM area. Disincentives to CAM research are not purely financial, but also involve a lack of qualified investigators among CAM practitioners and methodological and ethical difficulties unique to conducting CAM clinical trials. Furthermore, until recently Australia had no national research body to encourage and
prioritise CAM research, or co-ordinate collaborative research between CAM and conventional medical practitioners (cf. US NCCAM, UK National Cancer Research Institute, European Commission). A formal collaborative approach to establish common research goals was initiated in 2007 by the creation of the Australian National Institute of Complementary Medicine (NICM) and the inclusion of complementary medicine in the overall health and medical research strategic plan of the National Health and Medical Research Council. The mission of the NICM is to increase complementary medicine research and investment across Australia, effectively linking complementary medicine researchers and practitioners with the broader research community, industry and other stakeholders to provide strategic focus and foster excellence in research.

Ultimately, the NICM’s primary objective is to translate complementary medicine research evidence (safety, quality, efficacy, cost effectiveness) into clinical practice and relevant policy. To this end, the NICM has established three collaborative research centres: (1) Traditional Chinese Medicine, (2) Natural Medicines and (3) Neurocognition, and Nutraceuticals and Herbal Medicine, which have secured approximately $8M in research funding from government, universities and other collaborative partners. Emphasis is currently focused on areas of high disease burden, where preliminary evidence is strong and demonstrates likelihood of positive impact. Cancer is one of those areas and integrative oncology research has been initiated as a result of a partnership between the NICM and the National Breast Cancer Foundation. Importantly, this research falls in two high priority areas for cancer patients: (1) complementary therapies in the management of disease symptoms and side-effects of conventional anticancer treatments; and (2) adverse effects of CAM-drug interactions during conventional treatments (i.e. drug toxicity, therapeutic failure). Other high priority areas that need to be addressed, however, include: (3) quality control and labelling of herbal medicines, nutritional supplements and other natural products, and quality control of practitioner-administered CAMs; (4) the role of nutrition and other forms of CAM in cancer prevention, as well as the potential role they serve in cancer survivorship and prevention of recurrence; and (5) the mechanisms of action underpinning beneficial complementary therapies.
Integrative Cancer Care in Australia Today

Most medical schools offer CAM-based courses and/or training in the US and Europe (91% of US medical schools for the graduating class of 2009, up from 26% in 2001), and many hospitals there offer integrative therapies for patients. However, relatively little has been accomplished to make evidence-based complementary therapies available to (cancer) patients in Australian hospitals, despite growing demand. A few notable exceptions exist, though.

The SolarisCare Foundation Cancer Support Centre was established in 2001 at Sir Charles Gairdner Hospital (SCGH), the second largest teaching hospital in Perth, Western Australia. Complementary therapy and supportive care services offered by SolarisCare include psychological and group support, relaxation/meditation, several types of massage therapy and other manipulative and body-based practices, touch therapies and education/information, but purposely exclude therapies that involve ingesting substances (e.g. nutritional supplements). Initially met with considerable opposition from some medical practitioners, more than 25,000 free sessions have been provided to over 1800 cancer patients and their carers statewide by a team of over 100 qualified/trained volunteers. SolarisCare has recently expanded its free and paid services to the privately-run St. John of God Hospital, Subiaco and to rural cancer patients and their carers in Bunbury and other regional centres in Western Australia. Of interest, however, is that 85% of individuals using their services have been women, and 55% have reported a diagnosis of breast cancer.

The Peter MacCallum Cancer Centre, Australia’s only dedicated cancer hospital, in Melbourne, Victoria provides complementary therapy and supportive care services to patients and their families in the form of psychological support, different types of massage therapy, relaxation/meditation, stress management and education/information, with some emphasis on music therapy. Also under construction is the Olivia Newton-John Cancer and Wellness Centre, which is based at Austin Hospital in Heidelberg, Victoria. The centre’s “wellness” therapies and support services will complement the centre’s mainstream medical care and treatment, and collaborative research into new anticancer treatments with the US Ludwig Institute for Cancer Research.
Integrating Complementary Medicine into Mainstream Cancer Care: Bridging the Gap Between Patients and Doctors and Making the Move from CAM Toward Integrative Oncology

Integrative cancer care or oncology is a patient-centred approach that nurtures the physical, emotional and spiritual well-being of cancer patients by integrating safe, evidence-based complementary therapies with conventional anticancer treatments, using a multidisciplinary approach that assesses and treats the patient as a whole rather than addressing their disease alone. Complementary therapies used by cancer patients are diverse in their origin, premise, practice, efficacy and safety. In Australia, CAMs may be categorised by the Therapeutic Goods Administration (TGA) as registered (prescribed or non-prescribed medications which meet Australian standards of quality, safety and efficacy) or listed (low risk products that are not routinely evaluated with respect to a manufacturer’s claims before marketing, but are subject to a random audit after listing). Listed medicines consist almost entirely of CAMs, which implies that they are produced according to appropriate standards for quality and safety but guarantees nothing in regard to their efficacy. Cancer patients and other members of the public are mostly unaware of such distinctions and may believe that a complementary (or alternative) medicine listed by the TGA has been assessed as both effective and safe and approved for use by the Federal Government. Additionally, many complementary therapies have long histories as components of ancient traditional medical practices, but have only been subjected to rigorous scientific investigation in the last 10-20 years. More research is required to evaluate or confirm the efficacy and safety of many of these therapies.

As stated previously, evidence from high quality cancer clinical trials indicates that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving QoL and psychological functioning. There is evidence of potential harm also (Tables 3 and 4). Herbal medicines, nutritional supplements and other natural therapies may pose direct safety risks because of their potential adverse effects or interactions with conventional anticancer treatments (chemotherapy, radiotherapy, surgery, hormonal therapies) and other medications. Some should not be used under any circumstances irrespective of potential benefit (e.g. St. John’s wort), while others may be beneficial when cancer patients are not undergoing these treatments and have no other contraindications.
It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate CAMs, in order to receive benefit while avoiding harm. Unfortunately, most physicians have limited knowledge of the safety and efficacy of specific complementary and alternative therapies and have not had any formal training in the CAM area. Furthermore, few oncology health professionals feel comfortable discussing CAM, and are concerned that they cannot effectively communicate with patients or have the skills to help them maintain hope. Surveys indicate that clinicians desire greater access to evidence-based CAM information, to improve the quality of their care, and to enhance communication with patients. Due to safety risks associated with CAM, clinicians are strongly encouraged to routinely ask patients about complementary and alternative therapy use.

Several recommended approaches for discussing CAM with cancer patients have been published, including a set of communication guidelines. These approaches and guidelines to effective communication generally involve: (1) eliciting the patient’s perspective of his or her illness; (2) being open-minded/non-judgmental and respectful in regard to cultural and linguistic diversity and different belief systems; (3) asking patients questions about CAM use at critical points in their cancer experience; (4) actively listening to patients and responding to their emotional state in exploring the details of CAM use or motivations to use it; (5) discussing relevant concerns while respecting the patient’s beliefs and emphasising that “natural” does not necessarily equate with safety in explaining known safety risks; (6) providing patients with balanced, evidence-based information and advice about specific complementary and alternative therapies; and (7) providing close clinical follow-up and psychological support of patients using CAM, even if they choose therapies which their clinician disagrees with.

Conclusion

Complementary therapies or CAM, as they are commonly referred to by patients and clinicians, are much sought after by Australian cancer patients as a means of coping with the physical and emotional impact of their disease and/or treatment. Irrespective of whether doctors like them or believe in them, patients will use them. If physicians in the medical profession are to provide cancer patients with the best care and advice possible, then they cannot ignore this sign of the times.
Whether termed integrative cancer care or complementary medicine, cancer physicians in Australia should strongly consider offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services. Conceivably, this will influence patients to continue with mainstream care and help them avoid any potential harm that may occur with autonomous CAM use. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment and care.

Acknowledgements

I would like to thank Professor Ian Olver (Guest Editor), Professor Peter Drummond and Mr Paul Katris for their comments on an early draft of this article.

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discussing complementary and alternative medicine in a conventional oncology 
setting: communication recommendations for clinicians. Patient Educ Couns. 
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Appendix A: Methodology (Study 1)

Appendix A contains a superseded methodology chapter (sans a reference list) written in thesis quality. It is only included for interested readers who seek more extensive methodological detail than the study 1 manuscript provides in chapter 2.
CHAPTER 6
6 METHODOLOGY
6.1 Ethics Approval
This study was approved by the ethics committees of Royal Perth Hospital and Murdoch University, and was conducted in compliance with National Health and Medical Research Council (NHMRC) guidelines for human research (NHMRC, 1999).

6.2 Patients
The study participants consisted of a heterogeneous group of 200 Western Australian adult cancer patients attending a medical oncology outpatient clinic. All patients provided voluntary written and informed consent and, at the time of recruitment, were awaiting the commencement of chemotherapy or radiation therapy as part of individualised cancer treatment.

6.3 Setting
All participants attended the Medical Oncology outpatient clinic at Royal Perth Hospital in Perth, Western Australia between September 1997 and December 2002. At the clinic, four consultant oncologists, two registrars, and two chemotherapy nurses dealt with 200-250 outpatients per week. Every six months registrars in the clinic were usually replaced as part of regular rotations in their medical training. Of the outpatients seen each week, approximately 5-10 patients were new presentations to the clinic, two thirds comprised regular follow-up visits related to ongoing cancer treatment, and the remainder attended review appointments for check-ups having completed treatment previously. In a year, over 4000 chemotherapy administrations were delivered to patients and a further 800 procedures performed.

6.4 Eligibility Criteria
Patients were eligible for this study if they met the following criteria–

*Age:* Adults were aged 18 years or over.

*Health Insurance Coverage:* Public and private health care cancer patients alike attended Royal Perth Hospital and were accepted for study participation.
Diagnosis: Only patients with a formal cancer diagnosis via histological or cytological confirmation of disease were eligible for the study.

Disease History/Status: Patients were not excluded from study participation on the basis of disease history or status (for example, if they had been previously diagnosed with cancer or had a current diagnosis of metastatic cancer).

Prognosis: Patients were not excluded from study participation on the basis of poor prognosis except on the advice of the attending medical oncologist.

Cancer Treatment: Patients were excluded if they had received prior cancer treatment (except surgery) for their current episode of cancer. Surgery was the exception as it was deemed too difficult to make contact with patients in the short intervals that frequently separated diagnosis and surgery. Additionally, any impairment in psychosocial adjustment or QOL observed at this point may have represented a normal and transient response of individuals to the bad news of diagnosis, rather than the existence of clinically-relevant cancer- or treatment-related problems with the potential for far-reaching effects. Patients were also excluded if they were not planned for chemotherapy; if treatment was not planned to last at least 8 weeks; or if cancer treatment was not overseen by Royal Perth Hospital for the entire duration.

Literacy: Patients were required to understand spoken English and read and write English sufficiently to provide written informed consent and answer open-ended items in questionnaires. The ability to speak fluent English was not essential for study participation provided reading and writing levels were adequate.

Psychopathology/Medical Condition: Patients with significant psychopathology or cognitive impairment were excluded if their condition was severe enough to prevent them providing rational and coherent written responses in the questionnaires. Such individuals, including those experiencing senile and other dementing states, were excluded on the basis of information provided by attending medical staff or because of behaviours identified during the study by the author, a clinical psychologist registrar. Also, patients who were unwell or had physical impairment impeding the completion of questionnaires were
assisted by the author, who asked questions verbally and transcribed responses, as appropriate.

6.5 Patient Recruitment
Using the eligibility criteria described, participants were actively recruited from a sequential series of cancer patients attending the Medical Oncology clinic at Royal Perth Hospital between August 1997 and June 1999. All patients received chemotherapy and many underwent other treatment modalities also.

Four consultant medical oncologists and twelve registrars were involved in the course of the study. Each were verbally briefed and provided with a written summary outlining the study and their role. The primary role of the medical oncologists was to complete QOL rating and medical data forms for both experimental and control patients when required (see Appendix B). Additionally, if time permitted, they were encouraged to introduce the study to prospective patients in consultations immediately prior to the initiation of treatment, and then to direct patients to the author for further explanation and elicitation of informed consent. The physicians were instructed not to discuss any details regarding research methods with patients and to direct any related enquiries to the author.

The author’s role was one of a full-time research assistant. For the bulk of the study, he worked in that capacity as a member of staff at the Department of Medical Oncology, Royal Perth Hospital. Identification of potential study participants was the responsibility of the author, who consulted outpatient appointment and medical oncology inpatient lists, medical oncologists and other staff, and medical records to ascertain patient eligibility. Prospective participants were approached about the study by the author as close to the initiation of cancer treatment as possible, either at the Medical Oncology clinic or on hospital wards if they were inpatients. Each patient was explained the study, given a study information sheet to read to help decide about participation, and was given the opportunity to ask questions. If patients agreed to proceed with the study, they were asked to complete a consent form, which was signed and dated by the author also, and patients were allocated an identifying participant number. Alternatively, if patients declined to participate, they were asked the reason why so that it could be recorded for research purposes, and were subsequently assigned as a control participant with an identifying number.
6.6 Design

The study employed a prospective, longitudinal, observational design (see Figure A1 for a graphical overview of the study). All experimental patients were assessed at four times, pretreatment (baseline), on-treatment (8 weeks into treatment), post-treatment, and follow-up (6 months), using a number of repeated measures administered to patients and their medical oncologists (see Table A1). To examine sample bias, physician ratings of QOL and physical health were gathered for control participants at these times also, in addition to demographic data.

At the pretreatment assessment, all patients had received a formal diagnosis of cancer and were waiting to begin chemotherapy and/or radiation therapy. Most patients completed the pretreatment assessment on the day of starting chemotherapy or radiation therapy. The on-treatment assessment was undertaken 8 weeks after the start of chemotherapy or radiation therapy, allowing for a leeway of 1 week. The post-treatment assessment occurred at the end of cancer treatment (excluding hormone therapy), with a 1 week leeway. The majority of patients completed the post-treatment assessment on their final day of cancer treatment. The follow-up assessment was conducted 6 months after the termination of treatment, with a 1 week leeway. Physician assessments of the patients were completed concurrently at these times, almost without failure. All patients completed the pretreatment assessment in the presence of the author at the Medical Oncology clinic to ensure that questionnaires were understood and that assistance could be given if required. On subsequent assessments, patients completed questionnaires, whenever possible, during appointments at the Medical Oncology clinic. When circumstances prevented this, patients were permitted to take questionnaires home, and were reminded to complete them independently and to read the instructions in bold type before each section. Patients were asked to return the questionnaires at their next appointment if it was within 1-2 weeks, or via post using a supplied reply-paid envelope if it was longer than 2 weeks.
6.7 Assessment Measures

6.7.1 Demographic and Disease- and Treatment-related Variables

Data concerning demographics (age, sex, nationality, current employment status, level of education) and disease- and treatment-related variables (previous cancer history, primary diagnosis, treatment intent, types of treatment received) was collected from multiple sources, including patients, oncologists and medical records, for all patients approached to participate in the study.

6.7.2 Questionnaires

Patients were administered questionnaires primarily comprising standardised instruments assessing psychosocial distress and health-related quality of life (QOL; see Table A1).
Short forms of instruments were used where available and psychometrically prudent to ease the burden on patients of completing lengthy questionnaires. Individual components of the 100-item assessment battery (see Appendix B) are discussed below.


The EORTC QLQ-C30 is a self-administered, cancer-specific, multidimensional measure of QOL, designed for cross-cultural use in clinical trials (Aaronson et al, 1993). It assesses core QOL domains relevant across a wide range of cancer sites and treatments, and is complemented by modules specific to particular types of cancer (e.g. breast, lung, ovarian). In the present study, the QLQ-C30 was used as the primary measure of QOL. Additionally, its psychosocial scales, Emotional, Cognitive, Role and Social Functioning, served as secondary measures of psychosocial distress, and Emotional Functioning was used as a validation check for depression and cancer-specific distress assessed by dedicated instruments described below. The QLQ-C30 Version 2.0 contains 30 items, 24 of which are arranged into 9 multi-item scales, representing various aspects or dimensions of QOL: five functional scales, Physical (PF), Role (RF), Emotional (EF), Cognitive (CF), and Social (SF); three symptom scales, Fatigue (FA), Nausea and Vomiting (NV) and Pain (PA); and a Global Health Status/QOL scale. The remaining items correspond to six single-item scales assessing other common cancer symptoms (for example, sleep disturbance, appetite loss) and the perceived financial impact of disease and treatment. The QLQ-C30 takes approximately 11 minutes to complete (Aaronson et al, 1993). Literacy requirements for respondents are modest (Sharp et al, 1999) and mode of administration (self-administration versus interview) has a negligible effect on score distributions (Aaronson et al, 1993).

At each assessment time, patients completed a modified version of the QLQ-C30 comprising 38 items. Items were rated for the preceding 7 days using dichotomous scales (yes/no) for the PF items and 4-point Likert scales (1 = "not at all", 2 = "a little", 3 = "quite a bit", 4 = "very much") for the remaining items. The content of the modified QLQ-C30 is described in more detail below.
### Table A1  Assessment instruments used in the present study

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Target Group</th>
<th>Description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) [38 items]</td>
<td>Cancer patients</td>
<td>Self-report measure. Assesses QOL domains. Uses dichotomous and 4-point Likert scales. 5 Functional scales 3 Symptom scales 6 Single-item scales 1 Global Health Status/QOL scale (replaced by the QOL Uniscale and GH Uniscale) * 4 items replaced; 4 items and 1 symptom scale added</td>
<td>Range = 0-100  Higher scores = better functioning OR more severe symptomatology</td>
</tr>
<tr>
<td>Quality of Life (QOL) Uniscale [1 item]</td>
<td>Cancer patients</td>
<td>Self-report measure of global quality of life. Used a modified 10-point Likert/visual analogue scale.</td>
<td>Range = 1-10  Higher scores = better global quality of life</td>
</tr>
<tr>
<td>Global Health (GH) Uniscale [1 item]</td>
<td>Cancer patients</td>
<td>Self-report measure of overall physical health. Used a modified 10-point Likert/visual analogue scale.</td>
<td>Range = 1-10  Higher scores = better overall physical health</td>
</tr>
<tr>
<td>Beck Depression Inventory–Short Form (BDI-SF) [13 items]</td>
<td>Medical patients</td>
<td>Self-report measure assessing cognitive-affective depression. BDI somatic items removed. Uses 4-point Likert scales.</td>
<td>Range = 0-39  Higher scores = greater depressive symptomatology</td>
</tr>
<tr>
<td>Impact of Event Scale–Intrusion (IES-I) [7 items]</td>
<td>Traumatised populations</td>
<td>Self-report measure. Assesses cognitive-emotional distress related to a specific stressor. Uses 4-point Likert scales.</td>
<td>Range = 0-35  Higher scores = greater distress</td>
</tr>
<tr>
<td>Eysenck Personality Questionnaire Revised Short Scale–Neuroticism (EPQRS-N) [12 items]</td>
<td>General population–adults</td>
<td>Self-report measure of neuroticism. Items are dichotomous (yes/no).</td>
<td>Range = 0-12  Higher scores = higher levels of neuroticism</td>
</tr>
<tr>
<td>Psychological Adjustment to Illness Scale (Self-Report)–Vocational Environment (PAIS-VE) [6 items]</td>
<td>Medical populations including cancer patients</td>
<td>Self-report measure. Assesses the vocational impact of medical illness including satisfaction with job and work performance. Uses 4-point scales.</td>
<td>Range = 0-18  Higher scores = poorer overall vocational adjustment</td>
</tr>
<tr>
<td>Marital Communication Problems Scale (MCPS) [4 items]</td>
<td>Cancer patients</td>
<td>Self-report measure. Assesses couple communication. Uses 4-point scales.</td>
<td>Range = 1-4  Higher scores = poorer couple communication</td>
</tr>
<tr>
<td>Qualitative Items [4 items]</td>
<td>Cancer patients</td>
<td>Open-ended, self-report measure probing cancer-related problems and use of non-traditional therapies.</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Global Health Status/QOL (2 items): This scale was omitted and replaced by the Global Health Uniscale and the Quality of Life Uniscale (see sections 6.7.2.2 and 6.7.2.3).

Functional Scales

Physical Functioning (8 items): This scale evaluated whether patients were capable of undertaking physical activities ranging from the fundamental (for example, eating, washing, dressing) to the strenuous (for example, taking long walks, lifting heavy objects). Three items were appended. One concerned the extent to which patients were forced indoors by illness and another asked if they had felt ill overall. The third item was positively worded and asked how well they physically felt.

Role Functioning (2 items): This scale assessed whether any limitations had been imposed on patients’ work or leisure activities by cancer and its treatment.

Emotional Functioning (6 items): This domain examined the psychological impact of cancer and its treatment on patients in terms of depression, anxiety and stress. Two items pertaining to loneliness were appended for greater breadth.

Cognitive Functioning (2 items): These items probed any difficulties patients may have encountered with memory and concentration in performing everyday tasks.

Social Functioning (2 items): This domain dealt with the impact that patients’ medical condition or treatment had on family life and social activities.

Symptom Scales

Nausea and Vomiting (2 items): Asked patients if they had vomited or felt nauseated.

Pain (3 items): Evaluated the incidence of pain and its interference in daily activities. One item was appended asking patients if any measures had been taken to achieve relief and with what effect.

Fatigue (3 items): Assessed the incidence of fatigue and how much rest was needed. One positively worded item regarding how energetic patients felt was also appended.
Sexual Functioning (3 items): This appended scale examined the impact of cancer and its treatment on sexual interest and performance. Additionally, patients were asked whether they had explored methods of sexual expression to complement or replace intercourse.

Single-Item Scales
Seven single-item scales focused on additional cancer symptoms. These included sleep disturbance, appetite loss, alopecia, weight gain, weight loss, hot flushes, and skin changes.

It should be noted that all appended items were taken from standardised EORTC QLQ disease-specific modules (Aaronson et al, 1987).

Raw scale scores of the QLQ-C30 were calculated by summing the ratings of each item and dividing by the number of items (Fayers, Aaronson, Bjordal & Sullivan, 1997). Subsequently, they were linearly transformed to scores ranging from 0 to 100 as specified in the QLQ-C30 scoring manual (Fayers et al, 1997). Higher scores on the functional scales represented better functioning and hence greater QOL. On the symptom and single-item scales they indicated more frequent and/or severe symptom experience and hence lower QOL. In the case of missing items within a scale, multivariate techniques were used to estimate the most likely value given information about an individual patient’s previous responses to the same item (Fayers et al, 1997).

A change of at least 10 points from one assessment time to another represented a clinically significant change in patients’ QLQ-C30 scale scores. QOL researchers have held that the clinical meaningfulness of an observed change in QOL scores should be judged via a comparison to the minimal clinically important difference (MCID), which is defined as ‘the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management.’ (Jaeschke, Singer & Guyatt, 1989, p408). Intuitively, a MCID of 10 points, which represents a change of 10% on QLQ-C30 scales ranging from 0-100, is appealing. However, this criterion has been psychometrically determined by a quantitative review of 14 collated QLQ-C30 studies that grouped patients according to disease- and treatment-related variables (King, 1996), and a study that formally assessed clinically significant changes in QOL as perceived by cancer patients (Osoba, Rodrigues,
Myles & Zee, 1998). Questionnaires examining QOL in other chronic illnesses have also interpreted a change of at least 10 points to be clinically significant (Jaeschke et al, 1989; Ware, Kosinski & Keller, 1994; Juniper et al, 1994).

It should be noted, however, that the MCID differs with context. In adjuvant treatment settings, it may be defined as the smallest decrease in QOL that cancer patients will tolerate to gain an increased chance of survival (Coates, 1993). Alternatively, for patients receiving palliative treatment, it may be the smallest improvement in QOL due to say, relief from dysphagia, despite other treatment side effects such as fatigue and alopecia.

Reliability
It has been established that a Cronbach’s alpha coefficient of at least 0.7 indicates acceptable internal consistency for multi-item questionnaires (Cronbach, 1951; Nunnally, 1978). The internal consistency of the functional and symptom scales of the EORTC QLQ-C30 (Version 2.0) has ranged from moderate to excellent (r = 0.55-0.90) across 6 studies involving heterogeneous and homogenous cancer populations (Aaronson et al, 1993; Ringdal & Ringdal, 1993; Bjordal, Kaasa & Mastekaasa, 1994; Fossa, 1994; Osoba, Zee, Warr, Kaizer & Latreille, 1994; Osoba et al, 1997a). Scales that exhibited the most consistently high internal reliability were Fatigue (r = 0.80-0.91), Emotional Functioning (r = 0.73-0.85) and Pain (r = 0.70-0.85). Scales that most commonly yielded less than satisfactory internal consistency were Cognitive Functioning (r = 0.56-0.73) and Nausea and Vomiting (r = 0.55-0.84).

Similar results have been reported in more recent large-scale validation studies of the QLQ-C30 (Version 2.0). In a general population study of 1965 Norwegian people, Pain and Fatigue had the highest internal consistency (α > 0.85), whilst Cognitive Functioning (α = 0.65) and Nausea and Vomiting (α = 0.67) had the lowest (Hjermstad, Fayers, Bjordal & Kaasa, 1998). In a study of 489 older African American and Caucasian primary care patients, good internal consistency was demonstrated for all QLQ-C30 functional and symptom scales (α ≥ 0.77) except Cognitive Functioning (r = 0.4-0.69) and Nausea and Vomiting (α = 0.49-0.51; Ford, Havstad & Kart, 2001). Additionally, in a study of 2000 cancer patients, all QLQ-C30 scales except Cognitive and Role Functioning were reported to have acceptable internal reliability (α > 0.7; Ringdal et al, 1999). In the current study, the
internal consistency of the QLQ-C30 functional and symptom scales ranged from moderate to excellent \((\alpha = 0.65-0.91)\) across the four assessment times, with one exception. The strongest scales were Role Functioning \((\alpha = 0.86-0.91)\) and Emotional Functioning \((\alpha = 0.86-0.90)\). Consistent with previous studies, Nausea and Vomiting \((\alpha = 0.53-0.78)\) was the weakest scale, whilst Social Functioning \((\alpha = 0.66-0.76)\), Pain \((\alpha = 0.66-0.81)\) and the appended Sexual Functioning scale \((\alpha = 0.65-0.89)\) narrowly failed to meet criterion at various assessment times.

Few studies have examined the test-retest reliability of the QLQ-C30. In one study of 190 cancer outpatients with stable disease, 4 day test-retest reliability was high for all QLQ-C30 functional scales \((r = 0.82-0.91)\); good for the symptom scales \((r > 0.8)\) with one exception, Nausea and Vomiting \((r = 0.63)\); and satisfactory to good for the single-item scales \((r = 0.72-0.84); Hjermstad, Fossa, Bjordal & Kaasa, 1995\). In another study of 102 cancer inpatients, test-retest reliability coefficients were high for all the QLQ-C30 scales \((r = 0.78-0.95)\) for an interval ranging from 1.5-5.0 hours (Velikova et al, 1999). Finally, satisfactory test-retest reliability \((r > 0.7)\) of the QLQ-C30 scales was reported for 105 newly-diagnosed or recurrent malignant glioma patients with a retest interval of several weeks (Osoba et al, 1997b).

**Validity**

Studies employing factor analysis and multitrait scaling have supported the construct validity of the QLQ-C30. In the original validation study by Aaronson and colleagues (1993) involving 305 inoperable lung cancer patients in 13 countries, the QLQ-C30 scales, in general, exhibited moderate intercorrelations before and during treatment, thus indicating that, although related, they assessed distinct components of the QOL construct. Factor analysis demonstrated reasonably good agreement with the hypothesised factor structure of the QLQ-C30 in a sample of 535 mixed cancer patients and subsamples of lung, breast, and ovarian cancer patients (Osoba et al, 1994). In another study of 120 palliative care cancer patients, an exploratory factor analysis of the QLQ-C30 yielded a 6-factor solution that explained 77% of the total variance (Kyriaki, Eleni, Efi, Ourania, Vassilios & Lambros, 2001). Additionally, the QLQ-C30 scales exhibited low to moderate intercorrelations, indicating that they measured distinctly separate QOL components (Kyriaki et al, 2001).
Related to construct validity are content and convergent validity. In one study of 171 newly-referred palliative care cancer patients, the QLQ-C30 exhibited good content validity in covering 10 out of the 12 most common symptoms and problems recorded in their medical records (Stromgren, Groenvold, Pedersen, Olsen & Sjogren, 2002). Several studies have examined the convergent validity of the QLQ-C30 scales using Spearman correlation coefficients. The statistical significance of a correlation coefficient may be gauged using the following criteria: <0.3 negligible; 0.3-0.44 moderate; 0.45-0.60 substantial, and >0.60 high (Burnand, Kernan & Feinstein, 1990). In one study of 110 low-income, metastatic prostate cancer patients, substantial to high convergent validity (r = 0.54-0.72) was found for Emotional, Physical and Role Functioning, but not for Social Functioning (r = 0.12), when compared to corresponding scales of the Functional Assessment of Cancer Therapy–General (FACT-G) inventory (Sharp et al, 1999). Similar results have been found for homologous or related subscales in studies comparing the QLQ-C30 and the Short Form-36 (breast and colorectal survivors, Apolone, Filiberti, Cifani, Ruggiata & Mosconi, 1998; 234 mixed cancer patients, Kuenstner, Langelotz, Budach, Possinger, Krause & Sezer, 2002), the Functional Living Index Cancer questionnaire (98 mixed patients, King, Dobson & Harnett, 1996; 200 mixed patients, Mercier, Bonneterre, Schraub, Lecomte & el Hasnaoui, 1998; Kuenstner et al, 2002), the General Health Questionnaire (126 head and neck cancer patients, Bjordal & Kaasa, 1992; 96 mixed patients, Niezgoda & Pater, 1993), the McGill Pain Questionnaire (96 mixed patients, Niezgoda & Pater, 1993), the Cancer Rehabilitation Evaluation System (96 mixed patients, Niezgoda & Pater, 1993), and the Sickness Impact Profile (96 mixed patients, Niezgoda & Pater, 1993). In another interesting study of 150 metastatic breast cancer patients participating in a randomised trial of supportive group therapy, a correlation matrix of the psychosocial scales of the QLQ-C30 (Role, Social, Emotional and Cognitive Functioning and Global Health Status/QOL) and other psychosocial measures was constructed to evaluate convergent validity (McLachlan, Devins & Goodwin, 1998). Substantial convergent validity was shown between Role Functioning and the PAIS Vocational (r = 0.57) and Domestic Environment (r = 0.52) subscales. Substantial to very high convergent validity was also demonstrated between Emotional Functioning and PAIS Psychological Distress (r = 0.68); the Profile of Mood States (POMS) total mood disturbance, tension and depression/dejection subscales (r > 0.74); the Mental Adjustment to Cancer anxious preoccupation subscale (r = 0.45); and IES-I (r = 0.55).
The two essential features of a QOL instrument for use in longitudinal studies or clinical trials are sensitivity to differences in clinical status (King, 2001), and responsiveness (i.e. the ability to detect change in QOL across time) (Lohr et al, 1996). The QLQ-C30 has generally shown good predictive validity in discriminating patient subgroups on the basis of particular QOL dimensions. In the original validation study, Aaronson and colleagues (1993) found that most of the functional and symptom scales of the QLQ-C30 clearly distinguished between patients differing in performance status, weight loss and treatment toxicity. Subsequent studies have examined a host of group variables in relation to the QLQ-C30, including age (Klee, Groenvold & Machin, 1997; Hjermstad et al, 1998), sex (Hjermstad et al, 1998), disease status (Hjermstad et al, 1998; Hammerlid & Taft, 2001), primary cancer diagnosis (Osoba et al, 1994), prognosis (Ringdal, Ringdal, Kvinsland & Götestam, 1994), disease stage (de Boer et al, 1994; Osoba et al, 1994, 1997b; Montazeri et al, 1999), performance status (de Boer, Sprangers, Aaronson, Lange & van Dam, 1994; Osoba et al, 1994, 1997b; Wisloff et al, 1996; Kobayashi et al, 1998; Montazeri et al, 1999; Bjordal et al, 2000; Kyriaki et al, 2001), response to treatment (Wisloff et al, 1996), and disease progression (King, Dobson & Harnett, 1995). Ignoring the QLQ-C30 single-item scales, Physical Functioning, Role Functioning and Fatigue have exhibited consistently high predictive validity in discriminating between patients in these studies. Moderate to good predictive validity has been demonstrated by Pain, Emotional Functioning and Social Functioning, whilst Cognitive Functioning and Nausea and Vomiting exhibited the weakest predictive validity.

The QLQ-C30 has shown generally good predictive validity in detecting changes in patients' QOL across time. In the original validation study, significant changes in the expected direction were found with respect to four of the eight QLQ-C30 functional and symptom scales (Physical and Role Functioning, Fatigue, Nausea and Vomiting) for lung cancer patients whose performance status had improved or declined during chemotherapy or radiation therapy (Aaronson et al, 1993). In a subsequent validation study of 535 mixed cancer patients, significant deterioration was observed after 8 days of chemotherapy in Physical, Role and Social Functioning, Global Health Status/QOL, Fatigue and Nausea and Vomiting, relative to pretreatment (Osoba et al, 1994). Recent validation studies have yielded more impressive results concerning the responsiveness of the QLQ-C30. In a study of 232 newly-diagnosed and recurrent head and neck cancer patients, significant
deterioration was reported from pretreatment to post-treatment on all QLQ-C30 scales except Emotional Functioning and two single-item scales (Bjordal et al, 2000). Finally, in a study of 120 cancer patients receiving palliative treatment, significant improvements were reported between pretreatment and 15 days on-treatment for all QLQ-C30 scales, with the biggest changes observed in Physical and Role Functioning, Global Health Status/QOL, Pain and Sleep Disturbance (Kyriaki et al, 2001).

6.7.2.2  Global Health (GH) Uniscale (adapted from Aaronson et al, 1993)
The GH Uniscale is a single item, self-report measure of overall physical health for cancer patients. In the present study, it served as a primary measure of QOL and as a validation check for the Physical Functioning scale of the QLQ-C30. At each assessment time, patients and their attending medical oncologists were asked to rate the patient’s physical health for the preceding 7 days on a modified version of the Global Health Status item of the EORTC QLQ-C30. The scale was converted from a 7-point Likert scale to a hybrid 10-point Likert/visual analogue scale (1 = “extremely bad”, 10 = “extremely good”) to improve validity, and appropriate changes in wording were made for the physicians’ version (see Appendix B). Higher scores indicated better overall physical health.

6.7.2.3  Quality of Life (QOL) Uniscale (adapted from Selby, Chapman, Etazadi-Amoli, Dalley & Boyd, 1984; Herr, Kornblith, & Ofman, 1992)
The QOL Uniscale is a single-item, self-report measure of the overall effect of cancer and its treatment on the QOL of a patient. In the present study, the QOL Uniscale was employed as a primary measure of QOL. More specifically, it was utilised as a global index of patients’ QOL that monitored change over time in response to cancer and its treatment. At each assessment time, the scale was rated by patients and their attending medical oncologists using a modified hybrid 10-point Likert/visual analogue scale designed to enhance validity. For patients, the QOL Uniscale scale was anchored at its ends by the statements, “My life is extremely unpleasant because of my state of health” (1) and “My life is normal for me, with no change because of my state of health” (10). The wording was appropriately modified in the physician’s version (see Appendix B). Higher scores indicated better QOL.
Reliability
Satisfactory test-retest reliability has been reported for the QOL Uniscale in recurrent
disease (r = 0.72, 9-12 hours interval; Selby et al, 1984) and newly-diagnosed metastatic
prostate cancer patients (1 month interval, no significant differences from baseline; Herr et

Validity
The QOL Uniscale has demonstrated very good predictive validity. In a study of a mixed
sample of 96 metastatic breast cancer and chemotherapy patients, patients’ QOL Uniscale
scores correlated highly with other QOL measures, including physicians’ QOL Uniscale
ratings (r > 0.7), Sickness Impact Profile total scores (r > 0.7), and Karnofsky Index scores
(r > 0.6) (Selby et al, 1984). Additionally, when compared to no-current-treatment control
patients, the QOL Uniscale was able to detect significant declines in clinical status over
time from one week to the next in mixed cancer patients receiving chemotherapy (Selby et
al, 1984), and at 6 months post-treatment in metastatic prostate cancer patients receiving
hormone therapy (Herr et al, 1992). These findings together with those of more recent
studies examining single-item cancer QOL scales (Hurny et al, 1996; Sloan et al, 1998;
Bernhard, Sullivan, Hurny, Coates & Rudenstam, 2001) support the use of the QOL
Uniscale in evaluating the impact that cancer and its treatment has on QOL over time for
patients.

6.7.2.4 Beck Depression Inventory– Short Form (BDI-SF) (Beck & Beck, 1972)
The Beck Depression Inventory is one of the most widely used measures of depression,
proving particularly useful as a screening tool in both psychiatric and non-psychiatric
populations (Beck & Steer, 1993). The short form of the BDI (BDI-SF) is an abridged, self-
administered 13-item self-report scale assessing the cognitive, affective and behavioural
symptoms of clinical depression to the exclusion of somatic symptoms manifested in
medical illness. The BDI-SF takes approximately 5 minutes to complete and respondents
require a grade 5-6 reading level (Groth-Marnat, 1990).

In the current study, the BDI-SF was used as a primary measure of psychosocial distress,
specifically assessing major depression amongst cancer patients. Patients completed the
BDI-SF embedded within the 21-item full form of the BDI (Beck, Ward, Mendelson,
Mock, & Erbaugh, 1961) to preserve construct validity (Berndt, 1979), and to allow comparison of short form and full form scores. Patients were asked to endorse one or more statements for each item on a 4-point Likert scale ranging from 0 (absence of symptom) to 3 (persistent or salient symptom) that best described how they had felt during the previous week including the day of assessment. Total scores were calculated by summing the highest responses for each item.

Depression levels were classified accordingly: (a) none/minor (0-4), (b) mild (5-7), (c) moderate (8-15), and (d) severe (16-39) (Beck & Beck, 1972). A cut-off score ≥8 (moderate or severe depression) was used to identify cases of major depression at each assessment time (Beck & Beck, 1972). This cut-off has been shown to maximise the sensitivity (percentage of cases correctly identified compared to a diagnostic interview) and specificity (percentage of non-cases correctly identified) of the BDI-SF with metastatic cancer patients (Chochinov, Wilson, Enns & Lander, 1997) and other medical populations, such as primary care patients (Volk, Pace & Parchman, 1993). A cut-off score of 5 has been used in other studies (for example, Kissane, Bloch, Onghena, McKenzie, Snyder & Dowe, 1996; McGuire, Kiecolt-Glaser & Glaser, 2002), but was rejected for the present study out of concern that it may be too sensitive for use with a physically ill sample such as cancer patients and realise an unacceptable level of false positives.

One of the biggest problems in assessing depression in medical populations is that scores are affected by the physical illness of patients. The BDI-SF circumvents this problem by removing all somatic items from the revised full form without compromising reliability or validity (Beck & Beck, 1972).

Reliability

In a meta-analytic study, internal consistency of the BDI full form was reported to range from 0.73 to 0.92, with a mean Cronbach alpha coefficient of 0.86 in psychiatric populations and 0.81 in non-psychiatric populations (Beck, Steer & Garbin, 1988). Similarly results have been found for the BDI-SF (Groth-Marnat, 1990; Reynolds & Gould, 1981; Gould, 1983). In the present study, Cronbach alpha coefficients ranged from 0.74 to 0.84, indicating satisfactory to good internal consistency for the BDI-SF across the four assessment times.
Correlations between the BDI-SF and the full form have ranged from 0.89 to 0.97 in populations, including general medical outpatients and depressed inpatients (Beck, Rial & Rickels, 1974), substance users (Reynolds & Gould, 1981) and university undergraduates (Gould, 1983). Consequently, the short form is a highly acceptable substitute for the full form. In regard to test-retest reliability, Beck and colleagues (1961) argued that meaningful results could not be derived for the BDI because repeated administrations involving long intervals would underestimate the reliability as a result of therapeutic changes or, alternatively, overestimate it because of memory effects in the case of short intervals. Nevertheless, many studies have estimated the test-retest reliability of the BDI full form ($r = 0.48-0.86$) and have shown that it is dependent on the interval separating repeated administrations and the composition of the sample (Beck, Steer & Garbin, 1988; Groth-Marnat, 1990; Richter, Werner & Bastine, 1994). Given high alternate form reliability, the test-retest reliability of the BDI-SF is likely to be influenced by similar factors, although this line of investigation has unfortunately been ignored by researchers.

**Validity**

The construct validity of the BDI-SF is very good. Studies examining its factor structure have consistently reported the presence of three underlying factors, negative self-esteem, anergy and dysphoria, corresponding to the cognitive, behavioural and affective components of depression (Reynolds & Gould, 1981; Foelker, Shewchuk & Niederehe, 1987; Leahy, 1992). High convergent validity ($r = 0.6-0.8$) has also been reported in relation to other measures of depression, such as the Self-Rating Depression Scale, Rosenberg Self-Esteem Scale and the UCLA Loneliness Scale for substance abuse and university undergraduate samples (Reynolds & Gould, 1981; Gould, 1983), and to clinician ratings for medical patients (Beck & Beck, 1972).

A meta-analysis of studies evaluating the psychometric properties of the BDI full form found that in addition to high content validity, the inventory had very good predictive validity in distinguishing between depressed and non-depressed individuals and detecting change in clinical status over time (Richter, Werner, Heerlein, Kraus & Sauer, 1998). Similar predictive validity has been demonstrated by the BDI-SF in studies discriminating depressed metastatic cancer patients (Chochinov et al, 1995) and medical clinic outpatients (Dreyfus, 1987) from non-depressed individuals, as well as controlled studies with
successful treatment outcomes involving depressed elderly outpatients (Scogin, Beutler, Corbishley & Hamblin, 1988) and chronic pain patients (Plesh, Curtis, Levine & McCall, 2000). This augurs well for the BDI-SF’s ability to discriminate depressed from non-depressed cancer patients in the current study.

6.7.2.5 Impact of Event Scale– Intrusion (IES-I) (Horowitz, Wilner & Alvarez, 1979)

The Impact of Event Scale (IES) is one of the most widely used cross-cultural measures of post-traumatic stress symptoms (Joseph, 2000). It consists of two subscales, Intrusion and Avoidance. The Intrusion subscale of the IES (IES-I) is a 7-item self-report scale measuring cognitive-emotional distress in response to a specific stressor, defined as having cancer in the present study. Intrusion was characterised by ‘unbidden thoughts and images, troubled dreams, strong pangs or waves of feelings and repetitive behaviour’ (Horowitz et al, 1979, p210). The IES-I takes 2-3 minutes to complete and respondents require a primary school reading level.

In the current study, the IES-I was used as a primary measure of psychosocial distress, chiefly assessing cancer-specific distress. It was also used to screen for post-traumatic stress symptoms and post-traumatic stress disorder (PTSD). At each assessment time, patients were asked to estimate the frequency of intrusive thoughts relating to having cancer that occurred in the preceding week using a 4-point Likert scale (1 = "not at all", 2 = “rarely”, 3 = “sometimes”, 4 = "often"). Modified scale values of 1-4 were used instead of original scale values of 0, 1, 3 and 5 to facilitate uniformity with previous measures completed by participants and thus avoid added burden or confusion. Total IES-I scores were calculated by summing ratings converted to original scale values (0-5). Levels of cognitive-emotional distress were classified accordingly: (a) low (0-8), (b) medium (9-19) and (c) high (20-35) (Horowitz, 1982). A cut-off score ≥9 (medium or high cognitive emotional distress) was used at each assessment time to identify cases of significant cancer-specific distress that may have warranted further investigation.

In addition, levels of post-traumatic stress symptoms were classified accordingly: (a) subclinical (0-3), (b) mild (4-11), (c) moderate (12-19), and (d) severe (20-35) (based on Corneil, Beaton & Solomon, cited in Hutchings & Devilly, 2001). A cut-off score ≥12
(moderate or severe post-traumatic stress symptoms) was used to indicate instances of significant post-traumatic stress symptoms and a cut-off score ≥20 signified probable caseness for PTSD.

The IES has been utilised in the normal adult population (Briere & Elliott, 1998) and a wide range of traumatised adult populations, including combat veterans (for example, Pitman, Orr, Altman, Longpre, Poire & Macklin, 1996), sexual assault victims (for example, Resick & Schnicke, 1992), the bereaved (for example, Zilberg, Weiss & Horowitz, 1982), motor vehicle accident survivors (for example, Bryant & Harvey, 1995), and natural disaster survivors (for example, Carr, Lewin, Webster, Hazell, Kenaerdy & Carter, 1995). The IES has also been widely used in clinical outcome studies involving drug trials (for example, Davidson, Roth & Newman, 1991) and psychological therapies (for example, relaxation training–Hossack & Bentall, 1996; behavioural therapy–Richards, Lovell & Marks, 1994; time-limited psychotherapy–Ford, Greaves, Chandler, Thacker, Sennhauser & Schwartz, 1997; eye movement desensitisation and reprocessing–Grainger, Levin, Allyn-Byrd, Doctor & Lee, 1997).

In regard to cancer, the IES has been utilised with breast (for example, Wenzel et al, 1999; Spiegel et al, 1999; Classen et al, 2001), prostate (Herr, Kornblith & Ofman, 1992; Kornblith, Herr, Ofman, Scher & Holland, 1994), Hodgkin’s lymphoma (Cella & Tross, 1986; Cella, Mahon & Donovan, 1990), malignant melanoma (Kelly, Smithers, Swanson, McLeod, Thomson & Walpole, 1995), and mixed cancer patients (Edgar, Rosberger & Nowlis, 1992; Baider, Peretz & Kaplan De-Nour, 1992; Baider, Peretz, Hadani & Koch, 2001). Additionally, the IES has been used with individuals at increased risk of developing breast (for example, Lerman, Seay, Balshem & Audrain, 1995; Thewes, Meiser & Hickie, 2001), prostate (Bratt et al, 2000), and bladder cancer (Hornsby, Sappington, Mongan, Gullen, Bono & Altekruse, 1985).

**Reliability**

Internal consistency of the IES-I has ranged from 0.72 to 0.92, with a mean Cronbach alpha coefficient of 0.86 for eighteen studies involving non-cancer populations (Sundin & Horowitz, 2002). Good results have also been reported for cancer (α = 0.78; Wenzel et al, 1999) and at-risk populations (α = 0.88; Thewes et al, 2001). In the present study,
Cronbach alpha coefficients ranged from 0.82 to 0.87, indicating that the IES-I had good levels of internal consistency across the four assessment times. The IES-I has also demonstrated satisfactory to excellent test-retest reliability over short intervals (≤ 2 months) for both traumatised (r = 0.89, Horowitz et al, 1979; r = 0.94, Weiss & Marmar, 1997) and at-risk cancer populations (r = 0.89, Zakowski et al, 1997; r = 0.75, Thewes et al, 2001).

**Validity**

Two qualitative reviews of the psychometric properties of the IES have found adequate support for the construct validity of the IES-I, albeit with a few notable exceptions (Joseph, 2000; Sundin & Horowitz, 2002). A number of studies have replicated the factor structure of the IES-I across a variety of populations including sea disaster survivors (Joseph, Williams, Yule & Walker, 1992; Joseph et al, 1993), bank hold-up victims (Hodgkinson & Joseph, 1995), combat veterans (Shevlin, Hunt & Robbins, 2000), the bereaved (Zilberg et al, 1982), malignant melanoma patients (Kelly et al, 1995), and women at-risk to breast cancer (Thewes et al, 2001). A few studies, however, have found evidence of a second intrusion factor characterised as sleep disturbance (Joseph, 2000; Amdur & Liberzon, 2001), but this may be due to differences in the factor analytic techniques employed (Cordova, Studts, Hann, Jacobsen & Andrykowski, 2000).

Amongst specific measures of PTSD, the IES-I has demonstrated substantial to high convergent validity in the normal population (Los Angeles Symptom Checklist- Intrusion, -Avoidance, -Arousal; r = 0.68, 0.60, 0.61, respectively; Trauma Symptom Inventory- Intrusive Experiences, -Defensive Avoidance, -Anxious Arousal; r = 0.67, 0.66, 0.49, respectively; Briere & Elliott, 1988), combat veterans (PTSD Inventory, r = 0.79; Solomon & Mikulincer, 1988; Mississippi Scale for Combat-Related PTSD, r = 0.56; Structured Clinical Interview for DSM-II Revised, r = 0.49; McFall, Smith, Roszell, Tarver & Malas, 1990), mixed military/civilian samples (Structured Clinical Interview- Total, -Intensity; r =0.75, 0.77, respectively; Minnesota Multiphasic Personality Inventory- PTSD, r = 0.76; Neal, Busuttil, Rollins, Herepath, Strike & Turnbull, 1994). This suggests that the IES-I is a valid measure of post-traumatic stress symptoms and may serve as a brief screening instrument for PTSD, but cannot be used as a measure of PTSD *per se*, most notably because it does not measure the hyperarousal symptoms of PTSD that have been included in recent diagnostic criteria (American Psychiatric Association, 1994).
The IES-I has also exhibited moderate to substantial convergent validity in relation to measures of generalised distress for a range of populations, including psychiatric patients (General Health Questionnaire- Anxiety, -Depression; \( r = 0.53, 0.44 \), respectively; Spurrell & McFarlane, 1995), nuclear accident survivors (Symptom Checklist-90 Revised- Anxiety, -Depression; \( r = 0.54, 0.48 \), respectively; Davidson & Baum, 1986), malignant melanoma patients (General Health Questionnaire- Anxiety, \( r = 0.43 \); Hospital Anxiety and Depression Scale- Anxiety, \( r = 0.40 \); Kelly et al, 1995), and at-risk breast cancer patients (State-Trait Anxiety Inventory- State, \( r = 0.24 \); General Health Questionnaire, \( r = 0.23 \); BDI, \( r = 0.22 \); Thewes et al, 2001). Correlations between the IES-I and generalised distress measures in these studies tended to be lower than correlations between the measures of generalised distress themselves, suggesting that the IES-I measures stressor-specific distress rather than generalised distress. These findings regarding convergent validity support the use of the IES-I in the current study to gauge cancer-specific distress and screen for PTSD.

Qualitative reviews have found that the IES has good predictive validity across a range of populations in terms of detecting changes in clinical status over time and discriminating different levels of stress reaction among individuals (Corcoran & Fischer, 1994; Briere, 1997; Sundin & Horowitz, 2002). Such predictive validity has been demonstrated by the IES-I also. For example, in one study of 111 breast cancer patients undergoing group psychotherapy, significant reductions in distress, as assessed by various psychosocial measures including IES Intrusion, Avoidance and total scores, were observed at post-treatment and at 3- and 6- months follow-up (Spiegel et al, 1999). Similar results using the IES-I have been reported across time in a number of populations including clinic outpatients (Horowitz et al, 1979), combat veterans (Kosten, Frank, Dan, McDougle & Giller, 1991; Rothbaum, Hodges, Ready, Graap & Alarcon, 2001), the bereaved (Corcoran & Fischer, 1994), relatives of breast cancer patients (Schwartz et al, 1998), surgical breast cancer patients (Tjemsland, Soreide & Malt, 1998), and holocaust survivors with cancer (Baider, Peretz & Kaplan De-Nour, 1997).

Research has also shown that the IES-I discriminates between groups exhibiting mild and more severe stress reactions. Horowitz and colleagues (1979) found significant differences on IES Intrusion, Avoidance and total scores between stress clinic outpatients and medical
students exposed to cadaver dissection. Similar differences in IES-I scores have been reported between combat veterans and comparable controls (Solomon & Kleinhauz, 1996), women with and without a family history of breast cancer (Valdimarsdottir, Bovbjerg, Kash, Holland, Osborne & Miller, 1995; Lloyd et al, 1996; Zakowski et al, 1997; Croyle, Smith, Botkin, Baty & Nash, 1997; McCaul, Branstetter, O’Donnell, Jacobson & Quinlan, 1998), advanced and localised malignant melanoma patients (Kelly et al, 1995), prostate cancer patients and their spouses following cancer treatment (Kornblith et al, 1994), younger and older women after breast cancer treatment (Wenzel et al, 1999), and male and female Hodgkin’s lymphoma survivors (Norum & Wist, 1996). Finally, research has shown that higher scores on the IES-I may predict greater subsequent psychosocial distress. For example, IES-I scores at 2 months predicted PTSD at 6 months in burn victims (Perry, Difede, Musngi, Frances & Jacobsberg, 1992). Additionally, the IES-I alone or in combination with other psychosocial measures has identified gastrointestinal cancer patients (Nordin & Glimelius, 1999) and women with familial breast cancer (McCaul et al, 1998) that are at-risk to delayed psychosocial distress.

6.7.2.6 Eysenck Personality Questionnaire Revised Short Scale—Neuroticism (EPQRS-N) (Eysenck & Eysenck, 1991)

The adult version of the Eysenck Personality Questionnaire Revised (EPQR) is a self-report inventory evaluating normal and abnormal personality. It is based on factor analytic research and measures three orthogonal factors or personality traits, Neuroticism (N), Extraversion (E) and Psychoticism (P). The short form of the EPQR Neuroticism scale (EPQRS-N) is an abbreviated 12-item scale used to measure neuroticism or emotionality. Eysenck and Gudjonsson (1989) characterised the neurotic individual as an anxious, depressed, tense, irrational, shy, moody and emotional person, who suffers from feelings of guilt and low self-esteem. The EPQRS-N takes 2-3 minutes to complete and respondents require a primary school reading level.

In the present study, the EPQRS-N was employed as a secondary measure of psychosocial distress. Neuroticism was assessed at pretreatment only to determine whether it was a predictor of psychosocial distress experienced by patients during or following cancer treatment. Studies have shown that there is a significant relationship between neuroticism and psychosocial distress, including the development or recurrence of sub-clinical or
clinical depression (Christie & Venables, 1973; Hill, Kemp-Wheeler & Jones, 1986; Hill & Kemp-Wheeler, 1986; Gilbert & Reynolds, 1990; Berlanga, Heinze, Torres, Apiquian & Caballero, 1999; Roberts & Kendler, 1999; Schroevers, Sanderman, van Sonderen & Ranchor, 2000), PTSD (Holeva & Tarrier, 2001), attempted suicide (Colson, 1972), and general psychological distress (Jang, Livesley & Vernon, 1999). Similar relationships between neuroticism and psychosocial distress exist in cancer patients. Prospective studies have shown that patients with high neuroticism scores developed significantly greater psychosocial distress in the short and longer term (Morris et al, 1977; Thomas, Mehden & Jehu, 1987; Schroevers et al, 2000; Ranchor, Sanderman, Steptoe, Wardle, Miedema & Ormel, 2002).

Patients were asked to respond to dichotomous items of the EPQRS-N with an answer of “yes” (1) or “no” (0). Neuroticism scores ranged from 0 to 12 and were calculated by summing “yes” responses. High N scores indicated nervousness, depression, maladjustment and excessive emotionality, whilst low scores signified emotional stability (Eysenck & Eysenck, 1991).

The EPQ and EPQR have been used in a myriad of normal (for example, Loo, 1979; Artistic & Laicardi, 2002), psychiatric (for example, Berlanga et al, 1999) and medical populations (for example, Wilhelmsen, Haug, Ursin & Berstad, 1994), including cancer patients (for example, Yamaoka et al, 1998; Walker et al, 1999). Similarly, the EPQRS-N has been used in a wide variety of populations including normal adults (for example, Eysenck, Eysenck & Barrett, 1985; Barrett & Eysenck, 1992), university undergraduates (for example, Francis, Philipchalk & Brown, 1991; Glicksohn & Abulafia, 1998), the elderly (Mackinnon et al, 1995), young offenders (McMurran, Hollin & Bowen, 1990), trauma victims (Chung, Easthope, Chung & Clark-Carter), psychiatric inpatients (for example, Raine & Manders, 1988; Pearson, 1990; Wade et al, 1995), and medical populations (for example, Hepburn, Deary, MacLeod & Frier, 1994; Miles, Shevlin & McGhee, 1999).

Reliability
Internal consistency of the EPQRS-N has ranged from 0.80 to 0.84 in normal adults (Eysenck et al, 1985) and individuals with skin disease (Miles et al, 1999), with no
significant gender differences reported. In the current study, the EPQRS-N exhibited good internal consistency at pretreatment with a Cronbach alpha coefficient of 0.81.

Correlations between the EPQRS-N and the standard scale have ranged from 0.94 to 0.96 (Francis et al, 1991; Barrett & Eysenck, 1992) across cultures, including an Australian student sample (Francis et al, 1991). Consequently, the EPQRS-N is a highly acceptable substitute for the standard scale. One month test-retest reliabilities of 0.76 (males) and 0.81 (females) have been reported for the EPQR-N standard scale in a general population sample (Eysenck & Eysenck, 1991). Similar results were found for the EPQRS-N in a study of 92 university students ($r = 0.79$, 6 month interval; Hosokawa & Ohyama, 1993).

**Validity**

The most impressive feature of the original EPQ is its construct validity (Kline, 1993). For example, in one factor analytic study the three factors of the EPQ were confirmed and shown to be almost completely orthogonal (Barrett & Kline, 1980). Factor analysis of the EPQRS in general population and student samples has supported the same underlying factor structure, including Neuroticism (Hosokawa & Ohyama, 1993; Glicksohn & Abulafia, 1998). The EPQRS-N has also demonstrated substantial to excellent convergent validity in relation to the longer Eysenckian Neuroticism scales, the Junior Eysenck Personality Inventory ($r = 0.81$), the Junior EPQ ($r = 0.78$) and the EPQ ($r = 0.95$), in a young sample (Francis & Pearson, 1988); and the Neuroticism scores of the Maudsley Personality Inventory ($r = 0.62$) and the high anxiety ($r = 0.62$), high ergic tension ($r = 0.57$), and guilt proneness scales ($r = 0.50$) of the Sixteen Personality Factor (16PF) inventory, in university student samples (Hosokawa & Ohyama, 1993).

The Eysenckian Neuroticism scales have demonstrated good predictive validity with respect to discriminating different levels of emotionality or risk/occurrence of other kinds of psychosocial distress. For example, one study found that university undergraduates with high EPQ-N scores experienced more intense emotional states than low scorers (Bachorowski & Braaten, 1995). In another study, high trait neuroticism, as measured by the EPQ-N, distinguished breast cancer patients who had psychosocial distress (anxiety and depression) from those who did not when interviewed at the time of local recurrence (Jenkins, May & Hughes, 1991). Neuroticism in combination with a previous psychiatric
history was also found to be predictive of risk to psychosocial distress in breast cancer patients at local recurrence (Jenkins et al, 1991). Similar power, often in combination with other variables, has been demonstrated by the Eysenckian Neuroticism scales in predicting vulnerability to, or recurrence of, major depression (Roy, 1999; Roberts & Kendler, 1999; Berlanga et al, 1999) and predicting the development of PTSD following trauma (Holeva & Tarrier, 2001). These findings of good predictive validity bode well for the primary use of the EPQRS-N in the present study, namely, the prediction of psychosocial distress in cancer patients during or following cancer treatment.

6.7.2.7 Psychological Adjustment to Illness Scale (Self-Report)– Vocational Environment (PAIS-VE) (Derogatis & Lopez, 1983)

The self-report version of the Psychosocial Adjustment to Illness Scale (PAIS-SR) is a questionnaire comprising 7 subscales that assesses the quality of a patient’s psychosocial adjustment to a current medical illness or the residual effects of a previous illness (Derogatis & Lopez, 1983). The Vocational Environment subscale of the PAIS (PAIS-VE) is a 6-item self-report scale assessing the vocational impact of medical illness, including perceived job performance, vocational impairment, job satisfaction, time lost, changes in vocational interest and work goals, and problems with co-workers. The PAIS-VE takes 2-3 minutes to complete and respondents require a primary school reading level.

In the current study, the PAIS-VE was utilised as a primary measure of QOL, which evaluated the specific, but often ignored, QOL domain of vocational adjustment for cancer patients who worked or studied in some capacity during the course of the study. Vocation was defined as paid or unpaid work or study not related to family or home duties. This narrow definition was purposeful in order to capture an aspect of patients’ QOL that was distinctly different to that examined by the EORTC QLQ-C30, yet was likely to have been an integral part of life outside family and home life for those who worked prior to cancer diagnosis. Patients completed the PAIS-VE at each assessment time, if applicable, and rated items for the preceding 30 days using a 4-point Likert scale (a-d corresponded to 0-3 with scale reversal occurring for alternate items to reduce response bias). Higher ratings on the PAIS-VE indicated poorer vocational adjustment. Raw scores were summed and converted to standardised T-scores using norms provided in the test manual for mixed cancer patients (Derogatis & Lopez, 1983). Non-respondents received a raw score of 0 and
were assigned a standardised T-score using the mixed cancer patient norms (Derogatis & Lopez, 1983). However, for reasons of greater precision and interpretation, raw scores were maintained to evaluate changes over time.

**Reliability**

The reliability of the PAIS-SR has been established in a variety of medical populations, including cancer patients (Derogatis, 1986). Satisfactory internal consistency for the PAIS-VE was reported in the test manual for 69 cardiac patients ($\alpha = 0.76$; Derogatis & Lopez, 1983). Good results were also found in a large study of 502 mixed cancer patients ($\alpha = 0.84$; Merluzzi, & Martinez Sanchez, 1997), whilst only moderate to satisfactory internal consistency was indicated in a longitudinal study of 128 post-surgical breast cancer patients ($\alpha = 0.64$-$0.75$) and 121 partners ($\alpha = 0.59$-$0.66$) involving four assessments ranging from 7-10 days to 90 days post-surgery (Murphy, 1994). In the present study, Cronbach alpha coefficients ranged from 0.65 to 0.75, indicating that the PAIS-VE had moderate to satisfactory internal consistency across the four assessment times. Unfortunately, test-retest reliability of the PAIS-VE (or any of the other PAIS subscales) has not been reported in the test manual or elsewhere.

**Validity**

Factor analytic studies have confirmed the construct validity of the PAIS. In one study of 120 lung cancer patients, seven factors corresponding to the PAIS subscales accounted for 63% of the total variance in the factor matrix, of which the PAIS-VE contributed 10% (Derogatis & Lopez, 1983). Furthermore, all 6 items of the PAIS-VE loaded heavily on it ($r > 0.5$) and not on other PAIS subscales. Similar results were also found in large studies involving 502 mixed cancer patients (Merluzzi, & Martinez Sanchez, 1997), 557 gastrointestinal disorder patients (Wilhelmsen, Bakke, Tangen Haug, Endresen & Berstad, 1994), and 280 chronic disease patients (Rodrique, Kanasky, Jackson & Perri, 2000). Moderate to substantial convergent validity of the PAIS-VE has been reported in relation to other adjustment measures, including the Global Adjustment to Illness Scale ($r = 0.54$; Derogatis, Abeloff & Melisaratos, 1979), Symptom Checklist-90 Revised ($r = 0.39$; Derogatis et al, 1979), Affect Balance Scale Index ($r = 0.46$; Derogatis et al, 1979), Sickness Impact Profile ($r = 0.54$; Merluzzi & Martinez Sanchez, 1997), and Karnofsky Performance Scale ($r = 0.44$; Merluzzi & Martinez Sanchez, 1997) in breast cancer.
patients; the Cancer Behavior Inventory (r = 0.38) and Mental Health Index (r = 0.5) in mixed cancer patients (Merluzzi & Martinez Sanchez, 1997), and physician assessments of vocational rehabilitation in chronic haemodialysis patients (Kaplan De-Nour, 1982). Additionally, the PAIS-VE has demonstrated weaker correlations with more diverse measures, such as the Patient’s Attitudes, Information and Expectancies Scale (r = 0.28; Derogatis et al, 1979) and the Interview Schedule for Social Interaction (r = 0.15; Merluzzi & Martinez Sanchez, 1997).

Several studies have investigated the predictive validity of the PAIS. For example, of all the PAIS subscales, the PAIS-VE was shown to be most sensitive to differences in adjustment observed 1 to 3 months after lung cancer screening between patients who returned positive tests (n=128) and those that returned negative results (n=86; p<0.01; Derogatis et al, 1979). Additionally, the PAIS-VE has been an indicator of significantly greater psychosocial distress amongst cancer patients with new recurrences relative to normative samples of cancer patients (Mahon, Cella & Donovan, 1990). The PAIS-VE has also demonstrated predictive validity in relation to changes in clinical status over time. In one longitudinal study, metastatic cancer patients exhibited significant increases in vocational problems as measured by the PAIS-VE over time (Kaye & Gracely, 1993). Conversely, significant reductions in vocational problems were observed at 6 and 12 months post-surgery in 89 heart bypass patients (Langeluddecke, Fulcher, Baird, Hughes & Tennant, 1989).

6.7.2.8 Marital Communication Problems Scale (MCPS; Herr et al, 1992)

The MCPS is perhaps the only communication scale tailored to cancer patients. The MCPS is a 4-item self-report scale that assesses the degree to which cancer patients and their partners can openly discuss their feelings with each other. It takes 1-2 minutes to complete and respondents require a primary school reading level.

In the present study the MCPS was employed as a secondary measure of psychosocial distress and QOL. It was administered at pretreatment only to determine whether it was a predictor of subsequent psychosocial distress or impaired QOL amongst cancer patients. Controlled studies (for example, Dorval, Maunsell, Taylor-Brown & Kilpatrick, 1999; Joly et al, 2002) and qualitative reviews (for example, Taylor-Brown, Kilpatrick, Maunsell &
Dorval, 2000) have shown that pre-existing relationship difficulties or dissatisfaction predict further relationship problems during cancer treatment and in survival, and that the rate of relationship breakdown amongst cancer survivors does not differ significantly from the normal population.

Patients rated MCPS items on a 4-point scale (1 = "not at all", 2 = “a little”, 3 = “moderately”, 4 = "very much") with scoring reversed on alternate items to reduce response bias. MCPS scores ranged from 1-4 and were the calculated mean of summed ratings. Higher scores indicated greater communication problems between cancer patients and their partners.

**Psychometric Properties**

Construction of the MCPS was based largely on expert opinion, with the authors selecting three items from existing standardised scales, the Cancer Inventory of Problem Situations (Heinrich, Schag & Ganz, 1984), ENRICH (Olson, Fournier & Druckman, 1985) and the McMaster Family Assessment Device (Epstein, Balswin & Bishop, 1983), and appending an item of their own (Kornblith, Herr & Ofman, 1994). Internal consistency of the scale was unacceptable (Cronbach, 1951; Nunnally, 1978), with Cronbach alpha coefficients of 0.47 for prostate cancer patients and 0.52 for spouses (Kornblith et al, 1994). In the current study, however, a Cronbach alpha coefficient of 0.73 was attained at pretreatment, which is most acceptable given the brevity of the MCPS and its restricted use as a secondary measure.

**6.7.2.9 Qualitative Items**

Qualitative items soliciting written comments from patients were included. Patients were asked what the most important problem was for them in the previous few weeks. Additionally, they were asked what complementary and alternative therapies (if any) had been tried since diagnosis and to describe the benefits of their use. Qualitative data was collated by two independent raters, who extracted themes from patients’ written responses and compiled descriptive statistics for them. One rater was a cancer researcher in public health and the other was a postgraduate student in psychology. Both raters were recruited on a voluntary basis via the Western Australian Clinical Oncology Group.
6.8 Pilot Study

Prior to the commencement of the main study, a pilot study evaluating the relevance and acceptability of the assessment battery was undertaken with 12 mixed cancer outpatients at Medical Oncology, Royal Perth Hospital. The assessment battery used was the same as described above, except that the Neuroticism Extraversion Openness Five-Factor Inventory—Neuroticism (NEO FFI-N) scale (Costa & McRae, 1992) was included instead of the EPQRS–N and the State-Trait Anxiety Inventory—State (STAI-S) scale (Spielberger, 1983) was additionally incorporated. The NEO FFI-N is a standardised, self-administered 12-item scale measuring neuroticism or the tendency to experience negative emotions, such as anxiety, depression and hostility (Costa & McRae, 1992). Patients rated items on a 5-point Likert scale ranging from “strongly agree” (1) to “strongly disagree” (5). The STAI-S is a standardised, 20-item self-report measure of anxiety or the current level of tension and apprehension (Spielberger, 1983). Items were rated on a 4-point Likert scale ranging from “not at all” (1) to “very much so” (4).

All patients approached to participate were explained that the purpose of the pilot study was to gain feedback regarding the suitability of a questionnaire to be used in a forthcoming study that evaluated the experiences of cancer patients undergoing treatment. They were advised that participation was voluntary, would have no direct benefit for them, and that refusal would not compromise their medical treatment. No patient refused to participate.

Patients were equally divided according to gender, all aged ≥ 50 years, and were predominantly married, retired, of Anglo-Saxon descent and educated to a secondary school level or better. All patients had undergone ≥ 3 months of chemotherapy and had received and/or were receiving other cancer treatments also.

Patients were asked to complete assessment batteries containing 120 items. For comparison of completion rates, six patients were randomly assigned to complete the questionnaires at the clinic and the other six were asked to complete them at home and return them at their next clinic appointment. All patients were given a brief explanation of the questionnaire, including the general layout and the broad areas assessed, and were advised that it was necessary to read the instructions in bold type at the start of each section before answering the questions. Assistance was given as required to patients who completed questionnaires at
the clinic, whilst patients who took them home were told to leave out questions that confused them and that they would be given help upon return to the clinic.

Upon return of questionnaires, verbal feedback was solicited from all patients irrespective of completion. All the patients who filled in questionnaires at the clinic completed them adequately (6/6) compared to only half the patients who took them home (3/6). Reasons for non-completion included treatment-related illness and excessive questionnaire length. All patients who completed questionnaires found that the layout and response format of the questionnaire was generally good, and that the content was highly relevant and comprehensively covered issues relating to cancer patients’ QOL and psychosocial adjustment. Patients did not make any suggestions for inclusion of additional material when asked. The majority of completers (7/10) also found that the length of the questionnaire was within reason, although felt 50-75 items would maximise study participation. Finally, patients who completed questionnaires at the clinic took 20-25 minutes.

The most important negative feedback received concerned the NEO FFI-N scale. The majority of patients felt that the scale was made unnecessarily difficult by the lengthy, complicated instructions and the 5-point Likert scale. They reported that they either had to frequently refer back to the instructions or ask the author for clarification in order to complete the section properly. The author concurred with the latter given that all requests for assistance with the questionnaire were for the NEO FFI-N section.

The results of the pilot study were discussed with the clinic’s two most senior consultant medical oncologists. Firstly, it was agreed that the EPQRS-N should be used to replace the NEO FFI-N as a brief neurotic personality measure given its good face validity and comparable psychometric rigour and length. Secondly, it was decided that the questionnaire should have a maximum length of 100 items, although the medical oncologists felt that even a 100-item questionnaire may be too burdensome for some cancer patients. They advocated the culling of both the BDI and STAI-S. The author felt that exclusion of the STAI-S scale was warranted given that the Emotional Functioning scale of the EORTC QLQ-C30 has been shown to predominantly assess anxiety (Skarstein, Aass, Fossa, Skovlund & Dahl, 2000). However, the author rejected the removal of the BDI because the only other measure tapping depression in the questionnaire, the QLQ-C30 Emotional
Functioning scale, lacked the BDI’s psychometric rigour in screening for depression (Skarstein et al, 2000). The medical oncologists subsequently requested that the author consult on this issue with a psychiatrist that had previously worked at the clinic. The psychiatrist concurred with the author and this was accepted by the medical oncologists. Subsequently, the 100-item questionnaire contained in Appendix B was finalised for use in the main study.
Appendix B: Study 1 Questionnaires

The Physician Ratings questionnaire employed in this study appears below. It was completed at each assessment time by the patient’s attending medical oncologist.

PATIENT'S INITIALS ________________________
DOCTOR: _____________________________
UMRN: ________________
CHECKPOINT:_________

DATE: ___ / ___ / ___

1. **Overall** how do you feel the patient’s life has been affected by the state of his/her health as of today? (Please circle the number on the line below.)

   1------2------3------4------5------6------7------8------9------10
   A Lot Not at All

2. How would you rate the patient’s overall physical condition during the past week? (Please circle the number on the line below.)

   1------2------3------4------5------6------7------8------9------10
   Extremely Bad
   Extremely Good
The full questionnaire for patients employed in this study is reproduced below. It was administered in its entirety at the pretreatment (baseline) assessment time point only. Questions 37-40 (marital/partner communication), 76-87 (premorbid neuroticism) and 91-99 (demographics) were omitted at subsequent assessments as they were only pertinent to baseline assessment.

PATIENT'S INITIALS ___________________ DATE: __ / __ / ___ Subject No.: ______

CANCER PATIENTS' QUALITY OF LIFE QUESTIONNAIRE

We are interested in understanding better how cancer may have affected your life. For each of the questions listed below, please circle the number that best applies to you. The information that you provide will remain strictly confidential.

Because of your present condition?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you need help with eating, dressing, bathing or using the toilet?</td>
</tr>
<tr>
<td>2.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you have to stay in bed or a chair for most of the day?</td>
</tr>
<tr>
<td>3.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you have to stay indoors most or all of the day?</td>
</tr>
<tr>
<td>4.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you have any trouble either walking a short distance or climbing one flight of stairs?</td>
</tr>
<tr>
<td>5.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you have trouble either taking a walk or climbing a few flights of stairs?</td>
</tr>
<tr>
<td>6.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Do you have any trouble bending, lifting, or stooping?</td>
</tr>
<tr>
<td>7.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Are you limited in any way in doing your work or household jobs?</td>
</tr>
<tr>
<td>8.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Does your condition keep you from working at a job or doing household jobs?</td>
</tr>
</tbody>
</table>

During the past week:

<table>
<thead>
<tr>
<th>Not at All</th>
<th>A Little</th>
<th>Moderately</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Did you feel energetic?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Were you physically well?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Please go on to the next page
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Moderately</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Did you have any trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. All in all, did you feel ill?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Did you have pain in other parts of your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16a. Did you have any treatment for pain?</td>
<td>NO: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16b. If YES, How much did it help?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Did you have hot flashes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Have you had any skin changes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Have you had any weight gain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had any weight loss?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Have you had any secondary hair loss that is, your beard or pubic hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Have you lost muscle bulk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you lack appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Were you nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Did you vomit?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Did your condition limit your interest in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Did your condition interfere with your enjoyment of sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4 N/A</td>
</tr>
<tr>
<td>28. Have you used other methods of sexual expression with your partner, other than or in addition to sexual intercourse?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4 N/A</td>
</tr>
<tr>
<td>29. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>31. Did you feel lonely?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
During the past week:

34. Did you feel lonely even when you were with people?  
   Not at All A Little Moderately Very Much  
   1  2  3  4

35. Has your condition interfered with your family or social life?  
   Not at All A Little Moderately Very Much  
   1  2  3  4

36. Has your medical treatment interfered with your family or social life?  
   Not at All A Little Moderately Very Much  
   1  2  3  4

Below are some statements about relationships. For each please circle the answer that reflects how often the statement is true of your relationship with your spouse/partner.

<table>
<thead>
<tr>
<th>Statements:</th>
<th>Not at All</th>
<th>A Little</th>
<th>Moderately</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>37. It is easy for me to express my true feelings to my spouse/partner</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. My spouse/partner can't tell what I am feeling from what I am saying</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. I can talk openly with my spouse/partner about my fears about cancer and what might happen</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. So as not to upset my spouse/partner, I find it easier to discuss my problems with other people</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Below is a list of questions related to the impact your illness may have had on your employment situation. If you were employed at the time of your diagnosis please complete the following questions by circling the answer most appropriate to yourself.

41. Do you have a job, either paid and/or unpaid that is outside of the home?
   a) No (please go to Question 48)
   b) Yes (Continue straight on)

42. Has this event interfered with your ability to do your job
   a) No problems with my job
   b) Some problems, but only minor ones
   c) Some serious problems
   d) Illness has totally prevented me from doing my job

Please go on to the next page
43. How well do you physically perform your job now?
   a) Poorly
   b) Not too well
   c) Adequately
   d) Very well

44. During the past 30 days, have you lost any time off work because of this condition?
   a) 3 days or less
   b) 1 week
   c) 2 weeks
   d) More than two weeks

45. Is your job as important to you now as it was before this all started?
   a) Little or no importance to me now
   b) A lot less important
   c) Slightly less important
   d) Equal or greater importance than before.

46. Have you had to change your goals concerning your job as a result of these events?
   a) My goals are unchanged
   b) There has been a slight change in my goals
   c) My goals have changed quite a bit
   d) I have changed my goals completely

47. Have you noticed any increase in problems with your co-workers since these events?
   a) A great increase in problems
   b) A moderate increase in problems
   c) A slight increase in problems
   d) None

Below is a list of comments made by people after stressful events, such as having cancer.
Please check each item, indicating how frequently these comments were true for you during the past week about your illness.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Not at All</th>
<th>A Little</th>
<th>Moderately</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. I thought about it when I didn’t mean to.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. I had trouble falling or staying asleep because of pictures or thoughts about it that came into my mind.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. I had waves of strong feelings about it.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. I had dreams about it.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
52. Pictures about it popped into my mind
   1 Not at All  2 A Little  3 Moderately  4 Very Much

53. Other things kept making me think about it.
   1 Not at All  2 A Little  3 Moderately  4 Very Much

54. Any reminder brought back feelings about it.
   1 Not at All  2 A Little  3 Moderately  4 Very Much

This section consists of 21 groups of statements. After reading each group of statements carefully circle the number (0, 1, 2 or 3) next to the one statement in each group which best describes the way you have been feeling the past week, including today. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

55. 0 I do not feel sad
     1 I feel sad
     2 I am sad all the time and I can’t snap out of it
     3 I am so sad or unhappy that I can’t stand it

56. 0 I am not particularly discouraged about the future
     1 I feel discouraged about the future
     2 I feel I have nothing to look forward to
     3 I feel that the future is hopeless and that things cannot improve

57. 0 I do not feel like a failure
     1 I feel that I have failed more than the average person.
     2 As I look back on my life, all I can see is a lot of failures
     3 I feel I am a complete failure as a person

58. 0 I get as much satisfaction out of things as I used to
     1 I don’t enjoy things the way I used to
     2 I don’t get real satisfaction out of anything anymore
     3 I am dissatisfied or bored with everything

59. 0 I don’t feel particularly guilty
     1 I feel a good part of the time
     2 I feel quite guilty most of the time
     3 I feel guilty all the time

60. 0 I don’t feel I am being punished
     1 I feel I may be punished
     2 I expect to be punished
     3 I feel I am being punished

61. 0 I don’t feel disappointed in myself
     1 I am disappointed in myself
     2 I am disgusted with myself
     3 I hate myself

Please go on to the next page
62. 0 I don’t feel I am any worse than anybody else
1 I am critical of myself for my weaknesses or mistakes
2 I blame myself all the time for my faults
3 I blame myself for everything bad that happens

63. 0 I don’t have any thoughts of killing myself
1 I have thoughts of killing myself, but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

64. 0 I don’t cry any more than usual
1 I cry more now than I used to
2 I cry all the time now
3 I used to be able to cry, but now I can’t cry even though I want to

65. 0 I am no more irritated now than I ever am
1 I get annoyed or irritated more easily than I used to
2 I feel irritated all the time now
3 I don’t get irritated at all by the things that used to irritate me

66. 0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost of my interest in other people
3 I have lost all my interest in other people

67. 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty in making decisions than before
3 I can’t make decisions at all anymore

68. 0 I don’t feel I look any worse than I used to
1 I am worried that I am looking old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive

69. 0 I can work about as well as before
1 It takes an extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can’t do any work at all

70. 0 I can sleep as well as usual
1 I don’t sleep as well as I used to
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

71. 0 I don’t get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

Please go on to the next page
72. 0 My appetite is no worse than usual
    1 My appetite is not as good as it used to be
    2 My appetite is much worse now
    3 I have no appetite at all anymore

73. 0 I haven’t lost much weight, if any, lately
    1 I have lost more than 5 pounds
    2 I have lost more than 10 pounds
    3 I have lost more than 15 pounds

I am purposely trying to lose weight by eating less. Yes       No

74. 0 I am no more worried about my health than usual
    1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation
    2 I am very worried about physical problems and it’s hard to think of much else
    3 I am so worried about my physical problems that I cannot think about anything else

75. 0 I have not noticed any recent change in my interest in sex
    1 I am less interested in sex than I used to be
    2 I am much less interested in sex now
    3 I have lost interest in sex completely

Please answer each question in this section by putting a circle around the ‘YES’ or ‘NO’ following the question. There are no right or wrong answers, and no trick questions. Work quickly and do not think too long about the exact meaning of the questions.

76. Does your mood often go up and down? Yes   No
77. Do you ever feel ‘just miserable’ for no reason? Yes   No
78. Are you an irritable person? Yes   No
79. Are your feelings easily hurt? Yes   No
80. Do you often feel ‘fed-up’? Yes   No
81. Would you call yourself a nervous person? Yes   No
82. Are you a worrier? Yes   No
83. Would you call yourself tense or ‘highly-strung’? Yes   No
84. Do you worry too long after an embarrassing experience? Yes   No
85. Do you suffer from ‘nerves’? Yes   No
86. Do you often feel lonely? Yes   No
87. Are you often troubled by feelings of guilt? Yes   No

Please go on to the next page
88. **Overall** how do you feel your life has been affected by the state of your health as of today? (Please circle the number on the line below.)

1------2------3------4------5------6------7------8------9------10

My life is ____________

extremely ____________

unpleasant ____________

because of ____________

the state of ____________

my health ____________

My life is ____________

normal for ____________

me with no ____________

changes ____________

because of ____________

the state of ____________

my health ____________

89. How would you rate your physical condition during the **past week**? (Please circle the number on the line below.)

1------2------3------4------5------6------7------8------9------10

Extremely ____________

Bad ____________

Extremely ____________

Good ____________

90. We would also like to know which problem you felt was the most important for you during the past few weeks. Please write about it in your own words in the space below. If space does not permit your comments please also use the back page:

Problem:

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91. Since your diagnosis, have you tried any complementary and alternative therapies? Y/N

92a. If YES, please state below what and describe what you get out of them:

..............................................................................................................................................................................
..............................................................................................................................................................................
..............................................................................................................................................................................
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..............................................................................................................................................................................
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..............................................................................................................................................................................

92b. If NO, have you thought about it? Y/N

Please go on to the next page
The last few questions relate to your background.

Please fill in or tick the appropriate answer.

93. How old were you on your last birthday? ___________ years.

94. What is your marital status?

   __(1) Single, never married
   __(2) Married
   __(3) Separated
   __(4) Divorced
   __(5) Widowed

95. What is your current employment status?

   __(1) Working full-time
   __(2) Working part-time
   __(3) Retired
   __(4) Unemployed
   __(5) Other (please specify) ______________________________

96. What is the highest level of education you have completed?

   __(1) Primary School (12 years of age)
   __(2) Year 10/Third Year High School/Achievement Certificate (15 years of age)
   __(3) Year 12/Completed High School/TEE/Leaving Certificate (17 years of age)
   __(4) TAFE or Trade Qualification
   __(5) University or College Degree

97. What is your ethnic background? ________________________________

98. Have you had cancer previously?  Y/N

99. Please state the site of the cancer you have right now? __________________________

100. What treatment, if any, have you received for your cancer prior to filling in this questionnaire (for example, surgery, chemotherapy, radiotherapy etc.)? _______________________________

THANK YOU VERY MUCH FOR YOUR HELP!
Appendix C: Complementary and Alternative Medicine Used by Patients with Cancer– Evidence for Efficacy and Safety (Draft Manuscript – Study 2)

Appendix C contains an earlier revision of the study 2 manuscript provided in chapter 3. It contains omitted summary tables and a significant amount of material that was otherwise culled due to its duplication in other chapters of the edited handbook in which it was published (as determined by peer review), and concerns about the length of chapters held the publisher.
COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) USED BY PATIENTS WITH CANCER: EVIDENCE FOR EFFICACY AND SAFETY

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Abstract

Many cancer patients use complementary and alternative medicine (CAM) in an effort to control symptoms and to prevent and treat disease. Recent estimates suggest an overall prevalence for complementary medicine use of 14% to 65% among Australian adults diagnosed with cancer (with estimates as high as 80% to 91% in the US and Europe), and 8% to 14% for alternative medicine use among adult cancer patients. Given the increasing desire of cancer patients to use CAM, it is important that clinicians have a good understanding of the evidence available for the efficacy and safety of specific complementary and alternative therapies.

CAMs may be classified into 5 categories: whole medical systems, mind-body techniques, biologically-based practices, manipulative and body-based practices, and energy therapies. The present systematic review aims to provide an overview of the current evidence pertaining to the efficacy and safety of a range of CAMs in each of these categories used by
cancer patients (upon diagnosis, during conventional treatment, in response to disease progression or recurrence, or during remission/survivorship) in Australia and elsewhere. Where possible, evidence from meta-analytic and systematic reviews is utilised. Complementary and alternative therapies considered include homeopathy, traditional Chinese medicine, mind-body techniques (ranging from relaxation and meditation to yoga and tai chi through to music therapy and religious/spiritual coping and prayer), biologically-based practices broadly comprising nutritional supplements (e.g. antioxidants, shark cartilage) and Chinese and Western herbal medicine (e.g. ginseng and St. John’s wort, respectively), manipulative and body-based practices (massage, acupuncture, exercise), and energy therapies (biofield therapies including Qigong and touch therapies such as Reiki; bioelectromagnetic therapies including microwave/UHF/Tronado therapy).

Currently, there is evidence from high quality clinical trials that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving quality of life and psychological functioning (e.g. relaxation). There is evidence of potential harm also. Nutritional supplements, herbal preparations, and other natural therapies among the biologically-based practices may pose direct safety risks because of their potential adverse effects or interactions with conventional anticancer treatments and other medications. Some should not be used under any circumstances in cancer patients irrespective of potential benefit (e.g. St. John’s wort), while others may be beneficial when patients are not undergoing these treatments and have no other contraindications (e.g. valerian for short-term amelioration of sleep problems in non-surgical cancer patients). Alternative therapies promoted as “cures” in place of conventional treatments (e.g. shark cartilage) have the potential to cause patients (and their loved ones) the most harm, however, when they forego evidence-based cancer treatments that are likely to be more effective.

It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies, in order to receive benefit while avoiding harm. Additionally, as a consequence of the safety risks associated with CAM use, clinicians are strongly encouraged to routinely ask patients about complementary and alternative therapy use.
In conclusion, whether termed complementary medicine or integrative oncology, cancer physicians in Australia should strongly consider offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services. Conceivably, this will influence patients to continue with mainstream care and help them avoid any potential harm that may occur with autonomous CAM use. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment and care.

1. Introduction
A multitude of complementary and alternative medicines (CAMs) are in contemporary use, which the US National Center for Complementary and Alternative Medicine (NCCAM) has classified into 5 categories, whole medical systems, mind-body techniques, biologically-based practices, manipulative and body-based practices, and energy therapies (Table 1). The evidence for popular CAM approaches in these categories that are used in Australia and elsewhere by cancer patients will be reviewed below.

2. Popular CAM Approaches and Evidence for Use
2.1 Whole medical systems
Whole medical systems are complete systems of diagnosis and practice, which have some overlap with the other four categories. Several whole medical systems exist including those that have been developed in Western cultures (e.g. homeopathy), as well as non-Western cultures (e.g. traditional Chinese medicine, Ayurveda).

2.1.1 Homeopathy
Homeopathy is based on the proposed law of similars that “like cures like”, whereby low concentrations of substances that cause symptoms in healthy individuals can be used to treat patients with similar symptoms. Homeopathic medicines are generally safe in terms of adverse effects and interactions with conventional treatments. A systematic review of 53 studies found that homeopathic medicines prescribed by trained practitioners in low concentrations are probably safe and unlikely to cause serious adverse events, with the main risks being indirect and stemming from inexperienced practitioners (e.g. misdiagnosis).1
Homeopathy is predominantly used in supportive and palliative care for cancer patients, mainly to strengthen the body in battling cancer, improve general well-being and relieve cancer pain. Two systematic reviews of controlled trials have found that homeopathic medicines appeared to improve symptom management during chemotherapy and radiotherapy (specifically chemotherapy-induced stomatitis and acute radiotherapy-induced dermatitis). While producing encouraging preliminary evidence, the authors in both reviews expressed concern about the general lack of evidence and the clinical heterogeneity of the studies and cautioned that further research was required before any definitive recommendations on use to cancer patients could be made.

2.1.2 Naturopathy
Naturopathy is an alternative medical system based on the core beliefs that nature has the ability to heal and that the human body has the vital ability to maintain and heal itself. Naturopaths favour natural remedies and minimally-invasive approaches in preference to surgery and drugs. Practitioners use a wide variety of treatment modalities including dietary and lifestyle changes (e.g. eating more whole and unprocessed foods, abstaining from alcohol and sugar, stress reduction); vitamins, minerals and nutritional supplements; herbal medicine; homeopathy; mind-body techniques (e.g. meditation, yoga, counselling); and manipulative and body-based therapies (e.g. hydrotherapy, physical exercise). Given the overlap of naturopathic remedies with other categories of CAM, they will be reviewed in their respective sections below.

2.1.3 Traditional Chinese medicine
Traditional Chinese medicine (TCM) is based on the concept that the human body is a dynamic universe of interconnected energy systems and aims to maintain balance, harmony and order of these systems to ensure healthy functioning of the body. TCM treatments include acupuncture and related techniques (e.g. acupressure, moxibustion), Chinese herbal medicine, massage (e.g. tui na, cupping), exercise and breathing techniques (e.g. Qigong), and dietary and lifestyle advice. In Australia, the most popular forms of TCM are Chinese herbal medicine and acupuncture.

TCM is predominantly used by cancer patients to improve immunological function, symptom management (i.e. of general constitutional symptoms such as fatigue, pain and
depression, and specific symptoms such as gastrointestinal distress, appetite loss and myelosuppression) and overall well-being, as well as to enhance the effects of conventional treatments in chemotherapy and radiotherapy. In a review of randomised controlled trials (RCTs) and observational studies of TCM in supportive cancer care, the authors concluded that overall there was sufficient preliminary evidence to undertake high quality clinical trials to evaluate the effects on QoL and survival of integrating TCM into conventional oncology care (see below for discussion of specific TCM treatments).

2.2 Mind-body techniques
Mind-body techniques involve individuals learning coping strategies to deal with emotional distress that may be manifested in physical symptoms. Techniques include practitioner-administered therapies such as hypnotherapy and mindfulness-based stress reduction, and self-help strategies such as relaxation, meditation and creative therapies (including art, music and dance therapy). Some techniques that were considered CAM in the past have become mainstream (e.g. patient support groups), but are discussed below nonetheless because they complement conventional anticancer treatment.

2.2.1 Relaxation
Relaxation techniques originated in the early 1900s in the U.S. and Europe. They are designed to elicit a state of mental and physical relaxation, most commonly by focusing attention on the sensations associated with systematically tensing and relaxing muscle groups as in progressive muscle relaxation (PMR), or achieve a hypometabolic state of reduced sympathetic arousal (e.g. via autogenic training, PMR augmented with diaphragmatic breathing and/or guided imagery). Relaxation techniques often involve diaphragmatic or deep breathing (slow, deep rhythmic breathing) to aid in the release of muscle tension, and may incorporate guided imagery/visualisation (evoking images, usually sensory or affective) to calm the mind.

Relaxation is generally safe and adverse events are rare. Common side-effects include intrusive thoughts, sense of losing control, unsettling sensory experiences, and muscle cramps and spasms. Other adverse effects may include feelings and sensations of unfamiliarity or vulnerability, intrusive images, dizziness, floating, depersonalisation, dissociation, paradoxical increases in tension or anxiety, irritability, hallucinations, panic,
and abreaction (anxiety release through the reliving of traumatic events). Some of these side-effects are to be expected transiently in the short-term, however, and such symptoms of relaxation-induced anxiety may be used therapeutically if individuals can learn to relax during these experiences and thus facilitate greater coping in stressful life situations when they arise (e.g. [Smith, Woolfolk and Lehrer]). In any case, only about 4% of clients seen by psychologists have treatment terminated due to side-effects of relaxation. Additionally, relaxation-induced anxiety, abreaction and other adverse effects occur less frequently in PMR than in autogenic training, PMR + guided imagery, or meditation (e.g. [Heide and Borkovec, Norton et al, Grigsby, Pitman et al]). Nevertheless, relaxation techniques should be used with caution or are best avoided in cancer patients with (a history of) psychosis (e.g. schizophrenia) or post-traumatic stress disorder. Additionally, autogenic training and PMR is best avoided in patients with poorly-controlled cardiovascular disease as tensing muscles may cause heart rate and blood pressure fluctuations via the Valsalva response.

Turning to efficacy, a meta-analysis of 15 RCTs involving patients undertaking acute non-surgical cancer treatment (chemotherapy, radiotherapy, bone marrow transplantation, hyperthermia) revealed that relaxation exerted significant positive effects on nausea, pain, physiological arousal (blood pressure, heart rate), anxiety, depression and hostility. A more recent meta-analysis of 25 controlled trials and observational studies also found reasonably strong evidence for the efficacy of relaxation-based interventions in reducing cancer pain, while recent systematic reviews derived some support that relaxation reduced pain, nausea and vomiting and anticipatory nausea and vomiting, respectively.

2.2.2 Meditation
Meditation is an ancient Eastern practice that has been popularly adopted worldwide. It involves training the mind to focus on breathing or a specific object/image in an effort to free it of all thought (concentrative meditation), or to focus on sensations experienced in the present moment in a non-judgmental and accepting manner to establish a stable, non-reactive awareness to the physical or psychological symptoms associated with them (mindfulness meditation). Most meditation practices were developed within a religious or spiritual context and the ultimate goal is to achieve some form of spiritual/personal growth or transcendental experience and find a system of values and philosophy of life,
whereas many approaches in behavioural medicine (e.g. relaxation, biofeedback) are designed as treatments for particular disorders. There are many forms of meditation (e.g. Sahaja yoga meditation, Vipassana meditation), but the two most researched practices are mindfulness and transcendental meditation [involves a silent word or phrase (a mantra) being repeated in order to calm (and ultimately transcend) the ordinary flow of internal mental dialogue].

Meditation is generally safe and serious adverse events are rare, but it is not without side-effects. Common adverse effects include relaxation-induced anxiety and panic, restlessness, frustration, paradoxical increases in tension, depersonalisation or derealisation (which can recur after meditation), antisocial behaviour and flattened affect. Other adverse effects during and after meditation may include reduced motivation in life, boredom, difficulty in returning to normal everyday life after meditation retreats, pain, impaired reality testing, confusion and disorientation, feeling “spaced out”, depression, increased negativity, being more judgmental, a sense of ineptitude, greater awareness of one’s own poor self-esteem or unfortunate life circumstances, feelings of guilt or defencenessness, uncomfortable kinaesthetic sensations, mild dissociation, hallucinations, psychotic episodes, grandiosity, elation, destructive behaviour, suicidal ideation or attempts, recovery of repressed memories, and feeling addicted to meditation.

A number of these side-effects, however, are not only expected to be temporary and transient, but are considered integral to meditation by some proponents (e.g. it is part of the process of observing both positive and negative experiences in a non-judgmental manner, which is a core aspect of mindfulness). The ability of meditation instructors to handle such experiences is likely to be important in determining whether they become valuable learning opportunities or, alternatively, adverse events. In any case, most studies reporting safety concerns about meditation have involved transcendental or Vipassana meditation and most side-effects have been observed in longer-term retreats (e.g. 10 days) and/or intensive meditation (e.g. 3 hour sessions), which are not formally recommended for “novice” patients of some meditation practices such as mindfulness. Moreover, only 7.4% of long-term meditators in one study reported severe adverse effects. Nevertheless, meditation practices (transcendental or Vipassana meditation, in particular) should be used with caution or are best avoided in cancer patients with (a history of) psychosis (e.g.
schizophrenia), schizoid or schizotypal personality disorder, bipolar disorder, dissociative states, or hypochondriac and somatisation disorders. Additionally, meditation is contraindicated in patients experiencing physical exhaustion caused by fasting and sleep reduction during longer-term, unguided and intensive meditation.

Mindfulness-based stress reduction (MBSR) is the most studied meditation technique among cancer patients and combines mindfulness meditation with Hatha yoga. A meta-analysis of 3 RCTs and 7 observational studies suggested that MBSR may improve breast cancer patients’ psychological adjustment to illness (i.e. ameliorating anxiety, stress, fatigue, general mood and sleep disturbance), but found less convincing evidence to support improvement of physical health. Additional larger RCTs involving other cancer populations were recommended to validate these results. Similar conclusions were also drawn in recent systematic reviews involving cancer patients using MBSR or mindfulness meditation alone.

2.2.3 Hypnotherapy

Hypnotherapy is a psychological approach that induces a state of aroused consciousness in which suggestions are made to an individual to facilitate behaviour change or symptom relief. An induction procedure, often involving relaxation/imagery techniques, is used prior to suggestion. The efficacy of hypnotherapy is associated with an individual’s level of suggestibility, particularly in achieving long-term symptom relief. Hypnotherapy is generally safe when administered by qualified practitioners, but some individuals might experience transitory side-effects during or after hypnosis. These adverse effects include headaches, drowsiness, confusion, dizziness, or nausea and, less frequently, anxiety or panic; they occur in 5% to 31% of individuals who undertake hypnotherapy. Serious adverse events are rare and typically involve exacerbation of psychological symptoms (e.g. abreaction in post-traumatic stress disorder; induction of “false memories” in psychologically vulnerable individuals), which is usually caused by the misapplication of hypnotherapeutic techniques or poor clinical practice (e.g. not preparing patients sufficiently). Nevertheless, the World Health Organization and others caution against the use of hypnotherapy in individuals with (a history of) psychosis, personality disorders or organic psychiatric conditions.
Hypnotherapy has been used to manage a variety of symptoms in cancer patients, including nausea and vomiting, chronic pain, acute procedural or peri-/postoperative pain and anxiety. A meta-analysis of 6 RCTs (one in adults, five in children) has suggested that hypnotherapy is effective in reducing anticipatory and chemotherapy-induced nausea and vomiting in paediatric patients alone. Further RCTs involving larger samples in children were recommended, as were more RCTs for adult cancer patients given their paucity in the literature. A US National Institutes of Health Technology Assessment Panel concluded that there was strong evidence that hypnotherapy alleviated chronic pain, including cancer-related pain. Similarly, a systematic review examining 6 RCTs suggested that much support exists for the use of hypnotherapy in cancer pain management. Furthermore, a more recent systematic review found that hypnotherapy improved cancer pain without exception in a small number of controlled and observational studies, although further large RCTs are required to confirm this positive trend. Finally, systematic reviews of RCTs and observational studies have demonstrated that hypnotherapy is a potentially valuable treatment for acute procedural pain and distress in adult and paediatric cancer patients, although limitations of the studies identified (e.g. non-reporting of the method of randomisation, outcome measures used may not be clinically-relevant) suggest that further RCTs should be performed.

2.2.4 Yoga

Yoga is a series of practices that incorporate eight disciplines, including physical poses and postures, breath control and meditation, with the goal of uniting the mind, body and spirit for improved physical/mental health and self-awareness. There are many types of yoga, with Hatha yoga (a gentle form most commonly practiced in Western countries) and Tibetan yoga being the most studied in recent years. Yoga has been well-tolerated in studies and no serious adverse effects [e.g. ligament/joint damage from overstretching; nerve/vertebral disc damage, stroke or blood vessel blockage due to (prolonged) postures; eye damage and blurred vision, including worsened glaucoma, caused by increased intraocular pressure with headstands] have been reported in cancer and other chronic disease populations, possibly owing to the use of gentle poses and stretching that could be performed even by patients with functional limitations. Nevertheless, complications may arise in certain circumstances, thus yoga should be avoided or used in a gentler, modified form under the guidance of an experienced instructor by individuals with balance problems;
uncontrolled hypertension, symptomatic anaemia, postural hypotension or lightheadedness/dizziness; fever, systemic infection or significant thrombocytopenia; certain eye conditions, including glaucoma and retinal detachment; severe osteoporosis, vertebral damage or cervical spondylosis; fragile or atherosclerotic neck arteries or a risk of blood clots; artificial joints or prosthetic devices (e.g. infusaport, colostomy bag, stents); pregnancy; and psychosis.333

Two systematic reviews of RCTs and observational studies provide preliminary support for the efficacy of yoga interventions in cancer patients and survivors.21,22 Positive effects were reported for a range of outcomes including sleep quality, mood, stress and overall QoL, but several methodological limitations prompted recommendations that further RCTs be performed employing larger samples, male and female non-breast cancer patients and yoga interventions targeting specific cancer symptoms or problems.

### 2.2.5 Tai chi

Sometimes referred to as “moving meditation”, tai chi is derived from TCM and incorporates slow movements and postures (similar to aerobic exercise), controlled breathing and meditation. Tai chi appears to be generally safe and no serious adverse effects have been reported in cancer and other chronic disease populations.23-25 The most common reported side-effects of tai chi, albeit rare, are sore muscles, sprains and electrical sensations.334 As with any form of exercise, individuals must be aware of their physical limitations. Therefore tai chi should be used with caution or avoided in patients with severe osteoporosis, joint problems, acute back pain, sprains or fractures, or whose physical functioning otherwise precludes certain exercises. Additionally, straining downward or holding low postures is contraindicated in patients with inguinal hernia; artificial joints or prosthetic devices (e.g. infusaport, colostomy bag, stents); pregnancy; or those recovering from abdominal surgery.334

Tai chi has been used by cancer patients to improve QoL, mood, flexibility, and balance.24 Two systematic reviews of controlled studies in supportive breast cancer care, however, have found insufficient evidence for the positive impact of tai chi on physical or psychological outcomes and QoL in patients.23,24 Given the small sample sizes and poor quality of the studies identified, further large RCTs involving breast and other cancer
populations are required. Additionally, tai chi should be compared to more conventional forms of exercise to determine whether it confers additional benefits to patients.

2.2.6 Music therapy
Music therapy is designed to facilitate communication and achieve therapeutic goals through the creative use of music. Using music alone or in combination with relaxation/imagery techniques, music therapists help individuals engage with different aspects of live or recorded music (i.e. via passive listening, singing, writing lyrics, or playing instruments). Many cancer centres worldwide (including Australia) offer music therapy, thus it is one of the few creative therapies that have been subjected to scientific evaluation. A recent meta-analysis of 183 studies across 11 medical specialties (with a heavy emphasis on cancer patients) revealed that music therapy resulted in significant improvements in pain, well-being, mood, and nausea and vomiting. Although the results suggest that music therapy is useful in an oncology setting, many of the studies used small samples and few were RCTs. More large RCTs are required, preferably comparing music therapy to relaxation/imagery techniques in an effort to determine whether music therapy per se is effective in improving the QoL of cancer patients. In the interim, however, music therapy could be supported for use in cancer patients given that few (if any) adverse events are associated with it.

2.2.7 Support groups
Support groups enable patients at any stage of their cancer experience to gain emotional support from others with similar experiences (and to reciprocate in kind) by sharing information, experiences and feelings in a caring environment. One of the main aims is to enhance the patient’s individual coping resources. Cancer support groups include a variety of different approaches (e.g. psychotherapy, psychoeducation, cognitive-behavioural therapy), types (e.g. face-to-face, telephone or internet support) and settings (e.g. community centres or hospitals, the patient’s home) encompassing health professional-led support groups and self-help groups.

A meta-analysis of 20 RCTs has suggested that participation in professional-led support groups results in significant improvements in cancer patients’ emotional well-being (depression, anxiety), adjustment to illness, QoL and marital satisfaction, but not survival.
Similarly, a more recent systematic review of 32 RCTs and 12 descriptive studies revealed that professional-led support groups produced positive effects in psychosocial functioning (less social isolation, felt more understood and hopeful) and morale and other QoL dimensions, but not survival. Despite these positive findings, a number of caveats were highlighted in each review including the overrepresentation of women with breast cancer (usually during survivorship rather than active disease) and the lack of community trials in the support group literature. Consequently, further RCTs examining professionally-led cancer support groups must be performed involving patients with different types of cancer and disease stages, preferably with a greater focus on men (particularly with prostate cancer given the prevalence of sexual problems) and facilitation of support groups in community settings (rather than within clinical trials where optimal resources are often available).

Benefit from peer/volunteer support programmes, however, is less apparent for cancer patients. A systematic review of 16 controlled trials and 26 descriptive studies indicated a high level of satisfaction with individual/group peer support programmes, but mixed evidence for psychosocial benefit. A systematic review of 10 controlled trials and 10 descriptive studies also found high satisfaction among participants in individual volunteer support programmes, but very limited evidence for psychosocial benefit given the lack of RCTs performed. As with professional-led support groups, more large RCTs involving patients with different types of cancer and disease stages are required to examine peer/volunteer support programmes, and preferably with a greater focus on men given the positive bias toward women with breast cancer in existing studies. Furthermore, levels of psychosocial adjustment and motivation to seek support should be screened prior to programme participation as patients with low levels may gain limited benefit from such programmes. Finally, different modes of peer/volunteer support (e.g. individual/group face-to-face, group internet, individual telephone) need to be compared to determine the best methods for offering such programmes to cancer patients.

2.2.8 Spirituality, religion and prayer

Spirituality and religion are overlapping concepts that involve a search for the sacred, in which individuals seek to discover, hold on to, and, when necessary, transform whatever they hold sacred in their lives. Spirituality differs from religion in that religion is a search
for significance in ways related to the sacred and, in instances of popular usage, places spirituality within the context of beliefs, values and practices of an organised institution.

Religion and spirituality may be utilised by cancer patients in adjusting to and coping with cancer. They may serve many functions in long-term adjustment to cancer, including maintaining self-esteem; providing hope, psychological comfort and strength; and giving one a sense of meaning and purpose. A systematic review of 7 longitudinal and 10 cross-sectional studies found some evidence for improved adjustment to illness or reduced distress of religious/spiritual coping with cancer, but could not draw any firm conclusions due to serious methodological problems in many studies (e.g. poor conceptualisation and/or measurement of religious/spiritual coping; inadequate control of confounding variables, such as disease site/stage/treatment and perceived social support). A more recent review of 4 longitudinal and 36 cross-sectional studies drew similar conclusions regarding spirituality and emotional well-being in cancer patients. Further sizable longitudinal studies are required that compare spirituality and/or religion (across faiths) as primary endpoints to other coping strategies (e.g. social support) in specific cancer populations, and adequately control for potential confounding variables.

Researchers have argued that prayer can be separated from religion in the same way that related activities such as meditation have (e.g. [Rossiter-Thornton]). Private or personal prayer also needs to be distinguished from intercessory prayer in which a prayer is made on behalf of someone else, either in their presence or from afar and with or without their knowledge and approval. A systematic review of 7 prospective cohort studies, 14 cross-sectional studies and 3 qualitative studies involving hospitalised populations (including cancer patients) found a positive association between private prayer and emotional well-being (anxiety, depression), optimism and functioning, respectively, in patients with religious faith who engage in regular devoted prayer, and some evidence that prayer out of desperation (e.g. in response to pain, poor prognosis or postoperative trauma) in the absence of faith is associated with poorer emotional well-being and functioning. Nevertheless, these observations were based on correlational studies and others (involving mostly Christian samples) that were considerably flawed by the impossibility of including a true control group (i.e. participation in prayer cannot be manipulated); thus, more rigorous studies focusing on a range of religious/non-religious coping strategies including faith-
non-faith-based private prayer across different religions are required in cancer patients and, where possible, must include adequate control for possible confounding variables.

Studies examining the effects of intercessory prayer on well-being in cancer patients are virtually non-existent. A double-blind RCT of 999 cancer patients found that those receiving distant intercessory prayer by a Christian prayer chain showed significantly greater improvement in spiritual and emotional well-being, peace and faith (and, counterintuitively, a significantly greater decline in meaning over time) compared to controls, although effect sizes were small in each case. Again, whilst interesting, such studies are considerably flawed by the impossibility of including a true control group (i.e. intercessors outside the research study cannot be prevented from praying for patients in the control group; nor can control patients be prevented from believing that they have been allocated to the prayer group). Nonetheless, more rigorous studies involving triple-blind designs (i.e. participants themselves being unaware that they are part of a study) and a range of coping strategies including different types of intercessory prayer across faiths (e.g. distant vs non-distant, daily vs less frequent, long vs short duration, group vs individual prayer) are required and, where possible, must include adequate control for potential confounding variables.

More controversial, however, is the research examining the use of religion, spirituality or intercessory prayer to reduce the risk of cancer incidence or mortality, or improve survival. Reviews have revealed little evidence that religion or spirituality positively affect cancer progression or mortality, with the authors in the first review highlighting that any association observed might be confounded by cancer patients being more likely to become spiritual/religious following diagnosis. Additionally, a systematic review of 17 epidemiological studies (including a subgroup analysis of 11 studies adjusted for demographic and lifestyle factors) revealed no significant reduction in cancer risk among members of Christian communities compared to the general population, and concluded that healthy lifestyle was the most important mediating factor in explaining any correlation observed between religious membership and cancer risk. Finally, two meta-analyses of randomised trials involving medical populations (including leukaemia patients) have found insufficient evidence that distant intercessory prayer has beneficial effects on clinical outcomes (health, mortality, hospital re-admission). Whilst seeing no health risks to
patients or others from distant intercessory prayer and not trying to persuade believers to discontinue the practice as part of their faith, the authors in each case questioned the value of further trials in preference to studies examining the effects of prayer that can be conceptualised in scientific terms.

2.3 **Biologically-based practices**

Biologically-based practices involve supplementing a person’s normal diet with additional extracts, nutrients, herbs and/or certain foods. Examples include, but are not restricted to, nutritional supplements, herbal and other plant-based preparations (botanicals), animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics and probiotics (live bacteria often found in whole grains, yoghurt and functional foods), whole diet therapies, functional foods, and other so-called natural therapies (e.g. shark cartilage for cancer treatment).47

2.3.1 **Nutritional supplements (dietary supplements, food supplements)**

Nutritional supplements serve to augment the daily diet with nutrients in instances where people’s daily intake is insufficient, or they consider their diet requires supplementation. Nutrients in these products may include vitamins, minerals, herbs or other plant-based substances (botanicals), amino acids, fatty acids, and substances such as enzymes. Nutritional supplements may take the form of extracts or concentrates and are marketed in many guises, including tablets/capsules, liquids, or powders.

2.3.1.1 **Antioxidants**

Free radicals are unstable molecules produced when the body breaks down food, or is exposed to environmental influences (e.g. tobacco smoke, radiation). While free radicals are essential for various biological functions including the removal of damaged cells, they are also highly reactive and can damage healthy cells via oxidation. Excessive free radicals may play a role in the development and progression of certain diseases, such as cancer, cardiovascular disease and liver disease (e.g. [Ames et al]).48 Antioxidants neutralise free radicals and may protect cells in the body from damage caused by oxidative stress (e.g. [Wilcox et al]).49 Broadly, antioxidants take the form of nutrients [e.g. vitamins C (ascorbic acid) and E (alpha-tocopherol); minerals such as selenium and zinc] and non-nutrients (e.g. phytochemicals such as lycopene, beta-carotene and indole-3-carbinol; zoochemicals in red
meat and fish products). Whilst present in food and beverages, they are commonly taken as nutritional supplements (capsules/tablets, powders). Antioxidant supplements are available individually or in combination with other antioxidants, vitamins, or vitamins and minerals as part of multivitamins.

Cancer patients use antioxidants to relieve treatment side-effects (predominantly from chemotherapy and radiotherapy), for cancer treatment and prevention, and to improve general health and QoL. The benefits and risks of using antioxidants during cancer treatment are controversial. Proponents argue that antioxidants are beneficial to patients undergoing treatment because they enhance the efficacy of chemotherapy, as well as alleviate treatment toxicity and thus allow patients to tolerate full courses of chemotherapy and/or radiotherapy with fewer interruptions and dose reductions.50 Others are concerned that antioxidants may not only reduce the efficacy of some chemotherapy agents and radiotherapy, but may protect cancer cells as well as healthy cells from oxidative damage.51,52

In relation to treatment toxicity, a recent systematic review of 33 RCTs found that concurrent use of antioxidants with chemotherapy resulted in reduced toxicity in the majority of studies, and that patients in 5 studies completed more full doses of chemotherapy or had fewer dose reductions when receiving antioxidants than control patients.53 Similarly, another review suggested that antioxidants may mitigate the adverse effects of radiotherapy,54 while a meta-analysis of 14 RCTs showed that amifostine (synthetic antioxidant) significantly reduced the side-effects of radiotherapy.55 In contrast, however, a systematic review of 22 controlled trials and observational studies involving breast cancer patients found insufficient evidence that individual antioxidant supplements reduced toxicity during conventional breast cancer treatment.56 Other systematic reviews have also revealed insufficient evidence that selenium supplementation alleviates chemotherapy- or radiotherapy-induced toxicity or postoperative side-effects in cancer patients,57 or that selenium or lycopene supplementation relieves symptoms in prostate cancer patients.58,59 Similarly, a systematic review of 6 controlled trials found inconclusive evidence that coenzyme Q10 (synthetic antioxidant) reduced chemotherapy-induced toxicity.60 Poor quality and small samples were problematic with some studies in all the systematic reviews discussed, however, thus large, well-designed RCTs are warranted.
The formation of free radicals is the primary mechanism of radiotherapy and many chemotherapy drugs in destroying cancer cells. Such chemotherapy drugs include anthracyclines (e.g. doxorubicin, epirubicin), alkylating agents (e.g. cyclophosphamide, ifosfamide), platinum-containing complexes (e.g. cisplatin, carboplatin), podophyllotoxin derivatives (e.g. etoposide), camptothecins (e.g. irinotecan), and cytotoxic antibiotics (e.g. bleomycin).\textsuperscript{61,62} Antioxidant supplementation could improve treatment response and survival by helping patients tolerate full doses of these chemotherapy drugs with uninterrupted treatment schedules. However, they could also hinder the cytotoxic mechanisms of chemotherapy by scavenging free radicals produced by the drugs.

One systematic review of 21 randomised trials and 31 observational studies of antioxidants and chemotherapy observed such great diversity across studies (study design, cancer diagnoses, chemotherapy regimens, type/dose/schedule of antioxidant supplementation) that definitive conclusions could not be made about the efficacy and safety of antioxidant supplementation.\textsuperscript{63} Similarly, a systematic review of 22 controlled trials and observational studies could not draw any conclusions regarding the effects of antioxidants during breast cancer treatment (chemotherapy, radiotherapy and/or hormonal therapy) on tumour response, survival or recurrence;\textsuperscript{56} nor could the authors in a systematic review of lycopene supplementation in prostate cancer patients.\textsuperscript{59} Another review of 44 randomised trials, however, went further and concluded that concurrent use of antioxidants with chemotherapy and/or radiotherapy should be discouraged due to the possibility of tumour protection and reduced survival, despite limited evidence of these negative outcomes during radiotherapy and limited evidence that some antioxidant supplements may actually enhance the efficacy of chemotherapy.\textsuperscript{61} In contrast, a systematic review found that the great majority of 19 RCTs demonstrated either statistically significant or non-significantly greater survival and/or treatment response for concurrent use of antioxidants with free radical-generating chemotherapy, in patients with predominantly advanced or recurrent cancer.\textsuperscript{62} Additionally, no evidence was found that antioxidant supplementation reduced the efficacy of chemotherapy. Nevertheless, the authors concluded that the number of small, statistically underpowered studies and diversity of cancer diagnoses and chemotherapy treatments limits any clear conclusions being made about the potential benefits of
antioxidant supplementation during chemotherapy, and recommended that large, well-designed studies be performed.

More unequivocal, though, were the results of three meta-analyses. One meta-analysis of 7 RCTs (with no evidence of heterogeneity) found that amifostine (synthetic antioxidant) had no effect on tumour response in locally advanced non-small cell lung cancer patients treated with radiotherapy ± chemotherapy.64 Another meta-analysis and systematic review of 38 studies found no support that vitamin E or C supplementation helped treat or prevent cancer.65 The third meta-analysis of 10 unblinded RCTs (with no evidence of heterogeneity), however, demonstrated consistent positive effects on 1-year survival across melatonin dose and diagnosis for advanced solid tumour patients receiving melatonin alone or combined with cancer treatment.66

In summary, many of the studies (including the RCTs) examining the effects of antioxidants during cancer treatment on tumour response, survival or recurrence have employed insufficient sample sizes based on estimates of the primary endpoints of toxicity rather than local tumour control. Moreover, variable doses and protocols of antioxidants, chemotherapy and/or radiotherapy have been used and only short-term follow-up has occurred. Large, well-designed RCTs should measure both the benefits and toxicities of specific antioxidants (defined by dose and schedule) used concurrently with different chemotherapy and/or radiotherapy protocols and cancer populations. Furthermore, studies should measure short- and long-term tumour control and toxicities, as well as long-term survival and recurrence rates. Finally, RCTs need to employ multiple arms to evaluate multiple regimens simultaneously, given the large number of antioxidants and combinations thereof.67

Turning to chemoprevention, several recent meta-analytic and systematic reviews have produced disappointing results. A meta-analysis of 22 RCTs indicated that there is no evidence for the primary or secondary prevention of cancer through use of antioxidant supplements.68 Another meta-analytic and systematic review of 12 RCTs (predominantly high quality) revealed that antioxidant supplementation did not significantly reduce total cancer incidence or mortality or any site-specific cancer incidence in primary prevention.69 Similarly, meta-analytic and systematic reviews do not support the supplementation of antioxidants (vitamins A, C, E; selenium; beta-carotene) alone or in combination to prevent
colorectal cancer\textsuperscript{70} or gastrointestinal cancers;\textsuperscript{71} vitamin C or E individually to prevent cancer overall;\textsuperscript{65,69,72,73} or vitamin C or E, folate or beta-carotene individually to prevent lung cancer.\textsuperscript{74,75} Perhaps the only exceptions to these discouraging results are that vitamin E and selenium may have preventative effects for prostate cancer and gastrointestinal cancers or cancer in men, respectively, although confirmation is required in further RCTs.\textsuperscript{69,71,72}

Despite the lack of clinical trial data, antioxidants in foods are generally considered safe and few studies of antioxidant supplements have reported adverse effects. Common minor adverse effects include mild diarrhoea and gastrointestinal upset for vitamin C,\textsuperscript{76} and carotenodermia (yellowish discolouration of the skin) following heavy, chronic intake of beta-carotene.\textsuperscript{71} However, the research does point to some potential concerns. For example, high-dose beta-carotene appears to increase lung cancer incidence and cancer mortality among smokers;\textsuperscript{69,77} antioxidant supplementation may increase the risk of bladder cancer;\textsuperscript{68} and high vitamin E supplementation may increase bleeding in individuals with drug-induced vitamin K deficiency.\textsuperscript{76,78} Possible contraindications therefore include coagulation disorders and surgery, as well as use of anticoagulants (e.g. warfarin) and antiplatelet medications (e.g. aspirin). Given the lack of human clinical trials, particularly those providing long-term safety data, concurrent antioxidant supplementation during cancer treatment is not recommended without the guidance of the oncology treatment team.

2.3.1.2 Omega-3 fatty acids (\textit{n-3 polyunsaturated fatty acids})

Omega-3 fatty acids [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA)] influence many physiological functions, including fertility, cell division, angiogenesis, apoptosis and immune cell function, thus suggesting they may protect against cancer or alter the response to cancer treatment.\textsuperscript{79,80} Omega-3 fatty acids are found naturally in fish, fish oil, vegetable oils (mainly canola and soybean), walnuts, wheat germ, and other foods. They are also available as nutritional supplements in fish oil preparations in both capsule and liquid form. EPA and, to a lesser extent, DHA have demonstrated anti-cancer and anticachectic effects in human studies.\textsuperscript{81-84}

Omega-3 fatty acids have been used to prevent cancer, as well as to decrease weight loss, promote weight gain and increase survival in cancer patients with cachexia.\textsuperscript{84} A meta-analytic and systematic review of 38 studies, involving 20 different prospective cohorts
across 7 countries with different demographics, revealed that data across 11 different types of cancer suggested that nutritional supplementation with omega-3 fatty acids is unlikely to prevent cancer. Additionally, a recent meta-analysis of 5 prospective studies found a weak protective association between high dietary ALA intake (1.5g/day) and prostate cancer risk. In contrast, two other recent meta-analyses of prospective and case-control studies revealed that high intake or blood level of ALA (but not EPA or DHA intake) is weakly associated with an increased risk of prostate cancer. Heterogeneity across identified studies and/or publication bias in these meta-analyses necessitates clarification of these inconsistent results in further in vitro and epidemiological studies.

Many advanced cancer patients develop cachexia and treatment of associated weight loss and other symptoms has proven difficult. More recently, novel approaches have included the use of fish oils containing EPA and DHA. A Cochrane meta-analytic review of 5 RCTs found insufficient data to establish whether oral EPA was better than placebo in improving symptoms associated with cachexia in advanced cancer patients. Similarly, a meta-analytic and systematic review of 19 studies demonstrated no effect of omega-3 fatty acids on weight loss, nutritional status, postoperative complications, mortality or length of hospital stay after surgery for upper gastrointestinal cancers. A more recent systematic review of 17 clinical trials and prospective studies, however, suggested that dietary or supplemental intake of omega-3 fatty acids (EPA and/or DHA; 1.5g/day) for prolonged periods (8 weeks) by advanced cancer patients is associated with improved clinical (nutritional status, tolerance, survival, hospital stays), biological and QoL outcomes. Given the paucity of RCTs and the frequent employment of small samples and supplementation of omega-3 fatty acids with other supportive treatments (e.g. corticosteroids, appetite stimulants such as megestrol acetate), further large RCTs are required to determine whether EPA or DHA supplementation alone or in combination with each other or other supportive treatments is beneficial for cachexia in specific cancer populations.

Generally, omega-3 fatty acids are well-tolerated and cause few adverse effects in low to moderate doses. Gastrointestinal symptoms (e.g. diarrhoea, heartburn, bloating, nausea) are the most common side-effects. In pancreatic cancer patients, the dosage tolerated was limited by a sensation of fullness, cramping abdominal pain, diarrhoea and nausea.
Omega-3 fatty acids are thought to increase the risk of bleeding, but clinical trials have shown that high doses do not affect coagulation and platelet function following major surgery or when concurrently administered with anticoagulant/antiplatelet medications such as warfarin, and aspirin (e.g. [Carayol et al, Simon et al]). Nonetheless, it may be prudent to avoid high-dose fish oil intake or supplementation in patients with coagulation disorders or at high risk to haemorrhagic stroke, and discontinue use 4-7 days prior to surgery. Finally, excessive fish consumption may result in adverse effects due to toxic levels of mercury and other contaminants, although this does not apply to fish oil supplements.

2.3.1.3 Shark cartilage and AE-941 (Neovastat)

Shark cartilage use by cancer patients became popular in the 1980s after several poor quality studies claiming “miracle” cancer cures were reported by the US media, many of which were generated by a single manufacturer (Lane Labs-USA, producer of BeneFin). Use of shark cartilage in cancer patients originally stemmed from and has been perpetuated by the popular belief that sharks do not develop cancer because of the high proportion of cartilage in their body (about 6% by body weight). Scientifically, this has been shown to be untrue (several tumours in sharks have subsequently been detailed in a review article).

Primarily extracted from the backbone and head of the spiny dogfish shark (Squalus acanthias) and hammerhead shark (Sphyrna lewini), shark cartilage is frequently promoted as a nutritional supplement for the alternative treatment of diseases including cancer, arthritis, osteoporosis and pain. The major compounds in shark cartilage are proteoglycans and glycosaminoglycans (large molecules made of protein and carbohydrate), protein and calcium salts. Shark cartilage preparations are administered orally (tablets/capsules, powdered liquid), topically, subcutaneously by injection, or used rectally or intravaginally as an enema/suppository. Shark cartilage preparations are not standardised and there is no generally accepted recommended dosage or duration for administration. Preparations may contain varying amounts of shark cartilage (e.g. liquid shark cartilage preparations reportedly contain over 99% water and less than 1% protein; excessive binding agents and fillers may be added to powdered shark cartilage during processing, including collagen, gelatin, t alc, magnesium stearate and silica), which may not have any biological activity and can affect the safety of their use. The only standardised
source of shark cartilage is Neovastat (AE-941, manufactured by AEterna Zentaris), a matrix metalloproteinase inhibitor that has been specifically developed as a highly purified liquid shark cartilage extract for evaluation in clinical drug trials.

While some preclinical studies of shark cartilage and preliminary clinical studies of Neovastat have demonstrated anti-angiogenic and anti-cancer properties, and it has been observed that cartilage lacks blood vessels and that human cancer rarely invades cartilage, no controlled study has demonstrated that crude cartilage extracts are beneficial in the treatment of cancer in humans (or animals). In a double-blind RCT of 83 incurable breast and colorectal carcinoma patients (with good performance status and organ function), no differences in overall survival or QoL were observed between patients receiving standard conventional care (including chemotherapy for some patients) + powdered liquid shark cartilage extract (BeneFin nutritional supplement, 3-4 times daily until unacceptable toxicity developed) versus standard conventional care + placebo. These results mirrored those of a previous uncontrolled phase I/II trial involving 60 advanced cancer patients.

Larger RCTs involving the use of Neovastat in cancer patients have been similarly disappointing. In a double-blind RCT of 305 metastatic renal cell carcinoma patients refractory to immunotherapy, no survival advantage was observed in patients treated with Neovastat versus placebo. More recently, a comprehensive double-blind RCT of 379 locally advanced non-small cell lung cancer patients (newly-diagnosed, unresectable and previously untreated) found no differences in overall survival, tumour response rates, time to disease progression and progression-free survival between patients receiving chemoradiation + Neovastat (120ml orally, twice daily until disease progression or unacceptable toxicity developed) versus chemoradiation + placebo. It was concluded that the results do not support the use of shark cartilage-derived products for lung cancer patients, and has prompted the pharmaceutical manufacturer of Neovastat to cease clinical development. Given the lack of available evidence and the expense associated with shark cartilage products, it is difficult to recommend shark cartilage even as a complementary therapy to conventional anticancer treatments. Certainly, it is not recommended as an alternative therapy to conventional anticancer treatments.
A limited number of published studies suggest that shark cartilage is well-tolerated in most people (including advanced cancer patients) at doses administered in clinical trials, even in the long-term (over 4 years with Neovastat). Additionally, drug interactions with shark cartilage have not been reported. The most common adverse effects reported are gastrointestinal symptoms (nausea, vomiting, stomach upset, constipation, diarrhoea, flatulence) and taste alteration.

Very limited evidence suggests that shark cartilage may result in lower blood sugar levels in diabetics, thus caution is advised in patients with diabetes, hypoglycaemia or liver disease and in those taking medications, herbs, or nutritional supplements that affect blood sugar levels or liver function. Additionally, some shark cartilage products may contain high calcium content; while hypercalcaemia is not contraindicated, use is best avoided with calcium supplements and medications (e.g. calcitriol, thiazide diuretics, antacids) that elevate blood calcium levels. Consistent with warning labels on some products due to the anti-angiogenic effects of shark cartilage, use is also best avoided in surgical patients (potential for slow wound healing) and pregnant or breast-feeding women (potential teratogenic effects). Finally, excessive shark cartilage consumption may result in adverse effects due to toxic levels of mercury, cadmium and other contaminants. In short, the available evidence does not indicate great safety concerns regarding shark cartilage use; however, a systematic long-term safety study of shark cartilage nutritional supplements (as performed for Neovastat) would be advisable given the standardisation and contamination issues reported.

2.3.1.4 Laetrile and amygdalin (Vitamin B17)
Laetrile has been popularly used by cancer patients worldwide since the 1970s in the hope that it might cure or slow the growth of cancer. The term “laetrile” is an amalgam of laevorotatory and mandelonitrile, which is used to describe a purified form of amygdalin (cyanogenic glycoside plant compound). Amygdalin is found in the stones of many fruits (primarily apricots); nuts (e.g. almonds, cashews); many plants belonging to the Rosaceae family, such as Prunus persica (peach), Prunus armeniaca (apricot), Prunus amygdalus (almond) and Prunus amygdalus var. amara (bitter almond); and the bark of Prunus Africana (pygeum; often mistaken as bitter almond). Laetrile may be taken as an oral supplement (dubbed vitamin B17, although not a real vitamin), or injected intravenously,
Laetrile/amygdalin is typically used as an adjunct to conventional anticancer treatments or in combination with other alternative therapies, such as metabolic therapy (e.g. combining diet, enzymes and vitamins), dietary intake of fruit seeds (apricot, peach, bitter almond), diet therapy, nutritional supplements, urine therapy and beta-glucuronidase injections. In vitro studies suggest that amygdalin has anti-cancer properties (e.g. [Fukuda et al, Syrigos et al]), but no RCTs have been performed of amygdalin or laetrile in humans. A limited uncontrolled phase II trial, performed by the US National Cancer Institute in 1982, found that 95 of 178 (53%) mixed, non-metastatic cancer patients experienced disease progression and only 1 patient exhibited a partial tumour response (lasting 10 weeks) following 21 days of intravenous laetrile + oral maintenance therapy combined with metabolic therapy (pancreatic enzymes, high vitamin doses, dietary changes employed by metabolic practitioners). Furthermore, all remaining patients experienced disease progression within 7 months post-treatment, and no significant difference in survival was observed compared to historical controls who had inactive or no treatment.

Better evidence, however, is offered by a systematic review of 36 studies (25 case reports, 6 best case series of case reports, 3 non-consecutive case series, 2 consecutive case series) involving 352 cancer patients treated with laetrile/amygdalin. Despite the likelihood of positive bias in case reports, only 3.1% of patients reportedly had a complete response and 9.4% had a partial response (although some of these patients may have received conventional treatments and no detailed follow-up information was reported for complete response patients), while 36.4% exhibited disease progression; symptomatic benefits were also reported in 22.9% of cases. The authors concluded that the claim that laetrile has beneficial effects for cancer patients is not supported by sound clinical evidence, although well-designed RCTs could be considered given several limitations of the review (i.e. poor quality and methodological/clinical heterogeneity of identified studies, paucity of data).
Possible adverse effects of laetrile/amygdalin are of particular concern, given the belief that cyanide produced when it is broken down is what kills cancer cells. In the aforementioned systematic review, 14.4% of patients experienced adverse reactions consisting mainly of nausea, vomiting, headache, fever and abdominal pain. Other adverse effects include dizziness, acute cognitive disorientation, dermatitis, bluish discolouration of the skin (due to oxygen deprivation in the blood), hypotension, neuropathy, hepatotoxicity, and coma. Adverse events are usually associated with intravenous administration of laetrile, but have been observed in patients receiving laetrile orally, intramuscularly, or as enemas.

The most important concern with toxicity, however, involves several reports of cyanide poisoning (including deaths) from use of laetrile/amygdalin by cancer patients in North America in the 1970s and 80s, which prompted the US to ban its use and other countries (including Australia, UK and other European nations) to require special permission from governing health regulatory agencies to import it from Mexico and other countries. The risk of cyanide poisoning associated with laetrile/amygdalin appears high; it is elevated by concurrent dietary intake of fruit seeds (apricot, bitter almond, peach, apple) and raw almonds (containing beta-glucosidase that combines with laetrile/amygdalin to produce cyanide) or megadoses of vitamin C (reducing body stores of cysteine, an amino acid that facilitates the detoxification of cyanide), as well as in individuals who have a genetically predisposed, diminished capacity to detoxify cyanide. Adverse events could also be related to overdosing or problems relating to product standardisation and labelling. Studies indicate that adulteration, contamination of laetrile/amygdalin preparations (e.g. by bacteria) and mislabelling in Mexico (the world’s largest supplier) are not uncommon. In summary, the evidence that laetrile/amygdalin does more good than harm is weak and it would, therefore, be prudent to advise cancer patients to avoid use outside clinical trial settings.

2.3.2 Chinese herbal medicine

Chinese herbal medicine (CHM) is a key part of TCM and is used to normalise imbalanced energy that runs through invisible meridians in the body. CHM includes any mixture of herbs (mainly plant-based, but may include minerals or animal extracts) and decoction (liquid extraction of boiled herbs), which may take the form of tablets/capsules, powders,
tonics, lotions and pastes. There are a number of issues associated with the safety and quality of CHMs, including herb-drug interactions [via induction or inhibition of enzyme systems (e.g. cytochrome P450) or by affecting efflux proteins (e.g. P-glycoprotein)], resulting in reduced efficacy or increased toxicity of chemotherapy and prescription medications; direct (pharmacological) or indirect (e.g. free radical-mediated) toxicities; allergic responses; contamination with heavy metals, pesticides, micro-organisms or other impurities; deliberate substitution or adulteration with prescription or non-prescription drugs (e.g. corticosteroids, hormones, salicylates, antihistamines, caffeine); and microbial reactivation of virii or disease (e.g. hepatitis B or C, herpes simplex, varicella zoster, tuberculosis). The safety and quality of CHMs are regulated by the Therapeutic Goods Administration (TGA) in Australia, but limitations of The Therapeutic Goods Act 1989 do not subject individual practitioners to the standards that companies selling CHMs are required to meet. Consequently, practitioners can import raw herbs that may not meet the TGA standards and legally dispense them over the counter without registering with the TGA.

2.3.2.1 Astragalus (*Astragalus membranaceus, Astragalus mongolicus, Astragalus propinquus, Radix astragali*)

Astragalus is usually combined with other Chinese herbs, particularly as part of an immune-enhancing herbal regimen known in TCM as Fu Zheng therapy. It is typically administered as a dried root, a powder or in a decoction, although may be given by intraperitoneal injection also. Human and *in vitro* studies have demonstrated the immunostimulatory properties of astragalus polysaccharides and triterpinoid saponins in both healthy individuals and cancer patients (e.g. by stimulating macrophage and natural killer cell activity, and inhibiting T-helper cell type 2 cytokines), as well as anti-cancer activity.

Astragalus is primarily used by cancer patients to boost immunological function, reduce chemotherapy toxicity and increase survival (via use as an adjunct to conventional anticancer treatment). In China, astragalus-based Chinese herbs (e.g. Jin Fu Kang) combined with platinum-based chemotherapy is a standard treatment for non-small cell lung cancer. A meta-analysis of 34 Chinese RCTs found evidence that astragalus-based herbal medicine (oral Jin Fu Kang, Aidi injection, other preparations) may enhance the
treatment outcomes (improved survival, tumour response and performance status) and reduce the toxicity (leukopenia, haemoglobin toxicity) of standard platinum-based chemotherapy for advanced non-small cell lung cancer patients.\(^\text{120}\) Similarly, a more recent meta-analysis and systematic review of 45 RCTs revealed that oral astragalus-based herbal medicine enhanced complete/partial tumour response, survival rates and symptom control (abdominal pain, fatigue, appetite loss), and reduced the risk of disease progression (for astragalus alone also) in unresectable liver cancer patients receiving transcatheter arterial chemoembolization.\(^\text{354}\) Another systematic review of 14 Chinese RCTs suggested that Aidi injection improved the tumour response and QoL of non-small cell lung cancer patients receiving chemotherapy involving vinorelbine and cisplatin injections or cobalt-60 (but not etoposide or paclitaxel combined with cisplatin injections).\(^\text{355}\) Finally, a Cochrane meta-analytic review of 4 RCTs involving colorectal patients suggested that astragalus (huang qi) compound decoctions as an adjunct to chemotherapy may decrease chemotherapy toxicity (nausea and vomiting, leukopenia) and stimulate immunocompetent cells.\(^\text{121}\) The authors in each review, however, concluded that more large, rigorous RCTs were needed to confirm these benefits given the poor quality of the studies examined (e.g. selection bias, small sample size, lack of blinding and use of true randomisation procedures),\(^\text{120,121,354,355}\) not to mention the heterogeneity in astragalus preparations (e.g. single herb vs combined herbal preparations, oral administration vs injection, dosage) and clinical characteristics (e.g. disease stage) also observed across studies.

Astragalus is generally considered safe, with no serious adverse events or drug interactions reported to date in cancer and other populations.\(^\text{120-123,356}\) Attributing specific adverse events or drug interactions to astragalus is difficult, however, given that it is predominantly used in combined herbal preparations. Nevertheless, side-effects of oral astragalus-based preparations have been reported in two phase II studies involving incurable cancer patients receiving standard care (including chemotherapy and/or radiotherapy) and incurable non-small lung cancer patients undergoing adjuvant chemotherapy with paclitaxel, respectively.\(^\text{356,357}\) Most predominant were grade 3 lymphopenia, grade 3/4 hyperglycaemia and grade 1/2 gastrointestinal symptoms (e.g. diarrhoea, dyspepsia).\(^\text{356,357}\) Additionally, direct ingestion of certain toxic astragalus plants (locoweed) containing swainsonine or selenium may cause neurological symptoms, some of which are irreversible.\(^\text{358,359}\) Finally, due to its immunostimulatory properties, possible
contraindications of astragalus include autoimmune diseases (e.g. multiple sclerosis, lupus, rheumatoid arthritis) and organ transplant, and use of medications that suppress the immune system including chemotherapy agents such as cyclophosphamide, immunosuppressants (e.g. cyclosporine, tacrolimus) and corticosteroids. Overall, more rigorous studies are required to investigate the safety of astragalus.

2.3.2.2 Ginseng (Panax ginseng, Panax quinquefolium, Eleutherococcus senticosus, Angelica sinensis)

Ginseng is primarily used by cancer patients to boost immunological function, reduce physical and emotional stress, inhibit cancer growth, and ameliorate fatigue and menopausal symptoms. While the immunostimulatory properties of ginseng (and its ginsenosides) have in recent reviews suggested its use as an adjuvant or immunotherapeutic agent, to enhance immunological function and improve QoL in cancer patients during chemotherapy and radiotherapy, RCTs are yet to be performed to confirm these benefits.

Ginseng is associated with a relatively low incidence of adverse events, with reports being attributed to adulterated or contaminated preparations. Common side-effects of ginseng include insomnia if taken in the evening, and agitation/overstimulation if excessively used. Possible contraindications of Asian ginseng (Panax ginseng) and American ginseng (Panax quinquefolium) include hypertension, diabetes, coagulation disorders and surgery, and use of anticoagulants (e.g. warfarin) or antiplatelet medications (aspirin), phenelzine (monoamine oxidase inhibitor antidepressant), hypoglycaemics, oestrogens, corticosteroids or alcohol. Possible contraindications of Siberian ginseng/eleuthero (Eleutherococcus senticosus) include cardiovascular disease and use of digoxin (heart medication) and antihypertensive medications. Finally, ginseng, particularly dong quai/female ginseng (Angelica sinensis), has oestrogenic effects and may interfere with the treatment of hormone-sensitive conditions, such as breast cancer (e.g. hormonal therapy) and pregnancy.

2.3.2.3 Ginger (Zingiber officinale)

Ginger may be used by cancer patients to alleviate postoperative and chemotherapy-induced nausea and vomiting, as well as gastrointestinal symptoms including diarrhoea. A
A meta-analysis of 5 RCTs demonstrated that a fixed dose of ≥1g of ginger is more effective than placebo in reducing acute postoperative nausea and vomiting. Studies examining the efficacy of ginger for chemotherapy-induced nausea and vomiting, however, have produced mixed results and are still in their infancy. More RCTs comparing ginger to current antiemetics are required.

Ginger causes few adverse effects when taken in small doses. Gastrointestinal symptoms (e.g. heartburn, bloating, flatulence) are the most common side-effects. Additionally, ginger inhibits thromboxane synthase (platelet enzyme) and platelet aggregation, thus the risk of bleeding is increased in individuals taking anticoagulant/antiplatelet medications (e.g. warfarin, aspirin), those with coagulation disorders and surgical patients.

2.3.2.4 Lingzhi/Reishi mushroom (*Ganoderma lucidum, Ganoderma tsugae*)
Lingzhi is a traditional medicinal mushroom that has been used extensively in cancer treatment in Asia. Lingzhi polysaccharides have demonstrated anti-cancer and immunostimulatory properties. Reviews of preliminary clinical data suggest that Lingzhi extracts or powders may have some potential in cancer treatment, but more rigorous RCTs are required to establish its efficacy and safety as an adjuvant or standalone treatment. Adverse effects from medicinal mushrooms are rare. Dry throat and nose and gastrointestinal symptoms are the most common side-effects of Lingzhi. Caution is warranted, however, as Lingzhi causes platelet inhibition, thus the risk of bleeding is increased in individuals taking anticoagulant/antiplatelet drugs (e.g. warfarin, aspirin), those with coagulation disorders and surgical patients. Additionally, Lingzhi can increase antioxidant capacity and may interact with chemotherapy agents that rely on free radicals [i.e. anthracyclines (e.g. doxorubicin, epirubicin), alkylating agents (e.g. cyclophosphamide, ifosfamide), platinum-containing complexes (e.g. cisplatin, carboplatin), podophyllotoxin derivatives (e.g. etoposide), camptothecins (e.g. irinotecan), cytotoxic antiobiotics (e.g. bleomycin)].

2.3.2.5 Green tea (*Camellia sinensis, Thea sinensis*)
Green tea and its extracts have a long history of use as a traditional cancer treatment in Asian cultures. Polyphenols in green tea known as catechins, particularly epigallocatechin gallate (EGCG), have demonstrated anti-cancer, antioxidant and chemopreventive
properties. The US Food and Drug Administration (FDA) in a review of studies concluded that there is no supportive evidence for green tea decreasing the risk of gastric, lung, colorectal, oesophageal, pancreatic, ovarian and combined cancers, but weak evidence for decreased risk in breast and prostate cancer. Similarly, more recent systematic reviews have suggested that green tea may reduce cancer risk and slow or prevent progression in cancer patients, but found the overall evidence to be inconclusive and counselled that use of green tea alone to treat cancer may be ill-advised given its limited cytotoxic effects. Given the paucity of observational studies and RCTs and heterogeneity of existing studies, further large prospective cohort studies and clinical trials are warranted and should involve standardised preparations of green tea in various populations and control for lifestyle factors and other confounding variables.

Green tea is generally safe when consumed in moderate amounts (3-9 cups per day). Excessive consumption (5-6 litres per day) may cause gastrointestinal and central nervous system disturbances (e.g. nausea, insomnia, irritability, frequent urination, cardiac arrhythmia), however, predominantly as a result of the caffeine content rather than the tannin content of green tea. Possible contraindications include known allergy/hypersensitivity to caffeine or tannin (in food such as fruit, nuts and chocolate, and beverages such as coffee, teas, fruit juices, wine and beer), pregnancy, breast-feeding and heart conditions, and use of verapamil (antihypertensive/antiarrhythmic). Additionally, EGCG and other polyphenols in green tea are potent blockers of boronic acid-based proteasome inhibitors and can reduce the efficacy of bortezomib during chemotherapy for multiple myeloma and mantle cell lymphoma.

2.3.2.6 Ginkgo (Ginkgo biloba, EGb 761)
Ginkgo is one of the most popular herbal medicines worldwide; it is used for a wide range of conditions including cardiovascular disease, stress, neurodegenerative diseases such as Alzheimer’s, cognitive impairment including memory loss and psychiatric disorders such as schizophrenia, as well as cancer. Ginkgo is contained in the leaves and seeds of the ginkgo tree and is available as a standardised extract (EGb 761), thus may be taken orally or, in rare cases, intravenously. Amongst others, the flavonoids and the terpenoids (gingkOLIDes, bilobalide) of ginkgo have been reported to have anti-cancer, antioxidant,
cardioprotective, antiplatelet, stress-alleviating, cognitive-improving and sexually-enhancing effects.\textsuperscript{346} RCTs are yet to confirm these benefits in cancer patients, however.

Ginkgo has been associated with adverse effects in recent years. Side-effects of excessive consumption include headache, gastrointestinal disturbances (e.g. nausea, diarrhoea), dizziness, palpitations, convulsions (due to 4-methoxypyridoxine in ginkgo seeds), allergic skin reactions (by handling ginkgo seeds), and anaphylaxis-like reactions (intravenous administration only).\textsuperscript{346} Ginkgo enhances anticoagulant/antiplatelet activity and increases the risk of bleeding, thus possible contraindications include coagulation disorders and surgery and use of anticoagulant/antiplatelet medications (e.g. warfarin, aspirin) and non-steroidal anti-inflammatory drugs (e.g. ibuprofen).\textsuperscript{128,203,346} Other possible contraindications include seizure disorders, and use of anticonvulsants/antiepileptics (e.g. phenytoin, valproic acid) in individuals with seizure disorders and other drugs metabolised by the cytochrome P450 C219 enzyme, such as omeprazole (proton pump inhibitor for gastrointestinal disorders).\textsuperscript{141,203}

\subsection*{2.3.3 Western herbal medicine}

Western herbal medicine (WHM) includes any mixture of herbs that are primarily native to Europe, which may take the form of tablets/capsules, infusions (teas), concentrated liquid extracts (requiring dilution) and lotions. WHMs share the same safety and quality issues associated with TCMs.

\subsubsection*{2.3.3.1 St. John’s wort (\textit{Hypericum perforatum})}

St. John’s wort (SJW) is well-known for its antidepressant activity. Cancer patients often use SJW to reduce depression and anxiety. While a Cochrane meta-analytic review of 29 RCTs suggests that SJW has similar efficacy to standard prescription antidepressants and fewer side-effects,\textsuperscript{148} multiple herb-drug interactions preclude safe use in cancer patients and other populations. In fact, SJW is the most implicated herbal product in herb-drug interactions reported in the literature to date.\textsuperscript{149} Human studies suggest that SJW can interact with medicines by affecting drug metabolism (via induction of cytochrome P450 enzymes, particularly cytochrome P450 3A4, and P-glycoprotein) or levels of neurotransmitters (primarily serotonin).\textsuperscript{141,203} Consequently, SJW is contraindicated with the use of opioids, anaesthetics (e.g. fentanyl and propofol), benzodiazepines (e.g.
midazolam) and anticoagulants (e.g. warfarin) in surgical patients, and opioid use for cancer pain in (palliative) patients (e.g. morphine, fentanyl).\textsuperscript{128,203}

SJW taken in combination with other antidepressants (e.g. selective serotonin reuptake inhibitors such as sertraline; serotonin and noradrenaline reuptake inhibitors such as venlafaxine; tricyclics such as amitryptiline; monoamine oxidase inhibitors such as phenelzine) by cancer patients may result in reduced efficacy of the antidepressants or serotonin syndrome [cognitive, autonomic and somatic effects ranging from mild symptoms (e.g. hypervigilance, agitation, muscle twitching) to severe symptoms (e.g. tachycardia and hypertension that may lead to shock and death)].\textsuperscript{149,203} Additionally, SJW can reduce the efficacy of imatinib during chemotherapy for chronic myeloid leukaemia, gastrointestinal stromal tumours and other malignancies, while having the same effect accompanied by greater myelosuppression in advanced colorectal and lung cancer patients receiving irinotecan.\textsuperscript{150,203} Finally, other contraindications of SJW include cardiovascular drugs (e.g. digoxin; beta-blockers such as talinilol; antihyperlipidemic drugs, such as simvastatin, for high cholesterol), immunosuppressants (e.g. cyclosporine, tacrolimus), anxiolytics (e.g. buspirone), anticonvulsants (e.g. mephenytoin), antimigraine drugs (e.g. triptans such as eletriptan), antiretrovirals (e.g. protease inhibitors such as indinavir; non-nucleoside reverse transcriptase inhibitors such as nevirapine), anti-addiction medications (e.g. buproprion for smoking cessation), muscle relaxants (e.g. chlorzoxazole), respiratory drugs (e.g. antihistamines such as fexofenadine), hypoglycaemics (e.g. gliclazide), antimicrobial drugs (e.g. antibiotics such as erythromycin), drugs acting on the GI tract (e.g. antidiarrhoeal drugs such as loperamide, antacids such as omeprazole), and oral contraceptives (e.g. ethinyl estradiol/norethindrone).\textsuperscript{149,151,203}

2.3.3.2 Garlic (\textit{Allium sativum})

Garlic has had a long history of use worldwide for general health, as well as a variety of conditions including infections and cancer. Garlic can be eaten raw or cooked, may be dried or powdered and used in tablets/capsules, or take the form of oils and liquid extracts. Amongst others, garlic has been reported to have antimicrobial, antithrombotic, immune-enhancing, and anti-cancer/chemopreventive effects.\textsuperscript{152-155} A meta-analysis of 18 observational studies suggested that high consumption of raw and/or cooked garlic (but not garlic supplements) may be associated with reduced risk of colorectal and gastric cancers,
although a review of intervention studies was recommended given that many of the studies identified did not control for dietary differences.\textsuperscript{156} A more recent meta-analysis of 2 small RCTs and 8 observational studies also found an inverse relationship between high garlic intake and colorectal cancer risk despite great heterogeneity of measures of intake and lack of control for dietary differences in the studies examined.\textsuperscript{157} Additionally, a recent large RCT found that long-term garlic supplementation has no beneficial effects on the incidence of gastric cancer or the prevalence of precancerous gastric lesions.\textsuperscript{158} Given the paucity of RCTs and the heterogeneity and small samples of existing studies, further large prospective cohort studies and RCTs are needed and should determine the minimum intake of garlic necessary to exert protective effects for different cancers and control for lifestyle factors and other confounding variables.

Garlic appears to be generally safe, but may cause mild to severe gastrointestinal symptoms (stomach upset, heartburn, bloating) and allergic reactions (e.g. contact dermatitis, garlic burns and anaphylaxis resulting in possible death with topical or oral use).\textsuperscript{159} Consequently, oral garlic should be avoided by patients with stomach and duodenal ulcers. Human clinical trials using well-established probe drugs have demonstrated that oral garlic inhibits cytochrome P450 2E1 enzymes (but not 1A2, 3A4 or 2D6 enzymes),\textsuperscript{160,161} which may reduce the efficacy of chemotherapy involving dacarbazine (metastatic melanoma, Hodgkin’s lymphoma and other malignancies) and that of certain other drugs (e.g. anaesthetics, paracetamol).\textsuperscript{168,203} Garlic may also reduce the efficacy of antiretrovirals (e.g. saquinavir, ritonavir).\textsuperscript{162} Finally, due to its anticoagulant properties, garlic should be avoided by patients undergoing surgery and should be used with caution by those taking anticoagulant/antiplatelet medications (e.g. warfarin, fluindione, aspirin).\textsuperscript{163}

2.3.3.3 Kava (\textit{Piper methysticum})

Kava, a psychoactive substance, is derived from the pepper plant and has been traditionally consumed as a beverage in cultural practices of Pacific countries. It has gained popularity in Western countries in recent years as a medicinal herb because of its anxiolytic, stress-relieving and sedative properties.\textsuperscript{164} The roots and rhizomes of kava are used to prepare beverages, extracts, tablets/capsules, and topical solutions. Complementary medicine practitioners commonly prescribe kava for anxiety, sleep disorders and menopausal symptoms. A recent Cochrane meta-analytic review of 7 RCTs suggests that kava extract is
a safe, effective treatment for anxiety in the short-term (1-24 weeks) compared to placebo, but more rigorous studies are required to clarify uncertainties about long-term efficacy and safety.\textsuperscript{165}

Possible adverse effects of kava are of concern. Chronic and/or heavy use (300-400g per week) may cause appetite loss leading to malnutrition and weight loss, shortness of breath, skin conditions (e.g. dry, scaly skin; yellow or white ulcer-like lesions known as kani or kava dermopathy), blood and metabolic abnormalities, loss of muscle control (ataxia/dystonia), and pulmonary hypertension.\textsuperscript{166} The most important concern with toxicity, however, involves several reports of hepatotoxicity (including those resulting in death and liver transplants) from use of concentrated kava extracts (but not beverages) in Europe and North America, which prompted several European countries to ban its use in 2002 and other countries (including Australia and the US) to issue health warnings to healthcare professionals and consumers. Although a highly probable causal association was established in few reported cases \textit{per se},\textsuperscript{167} use of kava extracts are best avoided in cancer patients with (a history of) liver disease, or those receiving hepatotoxic drugs including chemotherapy agents such as cyclophosphamide, camptothecins (e.g. irinotecan), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vinorelbine) and EGFR-TK inhibitors (e.g. erlotinib for non-small cell lung, pancreatic and other cancers).\textsuperscript{168} Additionally, due to the possibility that kava may potentiate the sedative effect of anasthetics, benzodiazepines (e.g. alprazolam) and barbiturates [via gamma-aminobutyric acid (GABA) neurotransmission], it is recommended that patients discontinue use at least 24 hours prior to surgery.\textsuperscript{128} Finally, human studies have shown that kava extract may inhibit cytochrome P450 2E1 and 1A2 (but not 3A4) enzymes,\textsuperscript{169-171} and thus precipitate herb-drug interactions with substances metabolised by those enzymes (e.g. anaesthetics, antidepressants, antipsychotics, anticoagulants, alcohol).\textsuperscript{203} Similar inhibitory effects have also been observed on dopamine, thus reducing the efficacy of medications such as levodopa (anti-Parkinsonian drug).\textsuperscript{203}

\section*{2.3.3.4 Valerian (\textit{Valeriana officinalis})}
Valerian, although native to Europe and Asia, grows in most parts of the world and has a long history of use as a sedative for sleep disturbance. The roots and rhizomes of valerian can be prepared to make supplements including capsules/tablets and liquid extracts, as well as infusions (teas). Short-term use (\textless{} 4-6 weeks) of valerian in recommended doses is
generally well-tolerated. Common side-effects include central nervous system (e.g. headache, nervousness, dizziness) and gastrointestinal symptoms (notably diarrhoea, but also nausea, heartburn and epigastric pain). As with conventional sleep medications, chronic use of valerian (≥ 2-4 months) may result in insomnia, as well as withdrawal effects (e.g. delirium, tachycardia) if also used heavily.

Valerian is associated with few serious adverse effects. Studies suggest the absence of adverse interactions with alcohol. Human studies have not found any effects of valerian on cytochrome P450 enzymes involved in drug metabolism either, thus clinically-relevant interactions with chemotherapy drugs (and many other medications) are unlikely. Like kava, however, the effects of valerian are mediated through GABA neurotransmission, thus concomitant use of sedatives (benzodiazepines and barbiturates), hypnotics, anxiolytics and anaesthetics are contraindicated due to possible potentiation effects. Additionally, cancer patients planned for surgery should taper use over a period of weeks rather than cease use abruptly to avoid possible withdrawal symptoms.

Valerian is often used for the treatment of insomnia, fatigue and anxiety/stress, which are common symptoms experienced by cancer patients. A Cochrane review found only one small RCT evaluating the treatment of anxiety disorders using valerian and recommended that more, larger RCTs be performed before drawing any conclusions about its efficacy for anxiety. Evidence for the treatment of insomnia using valerian, however, is mixed. One systematic review of 29 controlled trials found no significant differences between valerian pills and placebo, overall, in healthy individuals or individuals with general sleep disturbance or insomnia. A more recent meta-analysis of 18 RCTs, however, found that valerian resulted in significant improvement on subjective measures of sleep quality, but the effect was not mirrored in objective sleep measures. This not only confirmed observations made in an earlier meta-analysis, but outcomes were maintained in subgroup analysis of more recent, higher quality RCTs that contained less methodological heterogeneity and, importantly, controlled for differences in odour between valerian and placebo. More RCTs assessing different doses of standardised preparations of valerian in individuals with sleep disturbance and using both subjective and objective measures are required, as well as studies evaluating the efficacy of valerian in liquid form for sleep disturbance, none of which exist. Nevertheless, despite the different conclusions regarding
efficacy, the reviews were unanimous in finding that valerian is generally safe and rarely associated with adverse events. Consequently, short-term use of valerian could be considered for some cancer patients (e.g. non-surgical patients who prefer not to take conventional sleep medications), particularly given there is no evidence of potential interactions with chemotherapy agents.

### 2.3.3.5 Evening primrose oil (*Oenothera biennis*)

Evening primrose, although native to North America, grows in Europe and parts of the southern hemisphere. Flowers and seeds are pressed to make evening primrose oil (EPO) that contains gamma-linolenic acid (GLA), an omega-6 essential fatty acid believed to be the active ingredient. EPO is commercially available in capsule or liquid form and widely used to treat menopausal symptoms, premenstrual syndrome and chronic mastalgia (breast pain associated with menstruation), as well as other problems such as atopic eczema and rheumatoid arthritis.¹⁸¹

Breast cancer patients may experience symptoms of (premature) menopause (e.g. hot flashes, night sweats, vaginal dryness) as a result of chemotherapy, which may be exacerbated by 5 year follow-up hormonal therapy with tamoxifen in patients with hormone-receptor positive (HR+) tumours.¹⁸² Non-hormonal therapies in the form of herbal medicines such as EPO have become a popular alternative for women (including breast cancer survivors) for the treatment of menopausal symptoms, particularly since health risks were cast over prolonged use (> 5 years) of hormone replacement therapy by the Women’s Health Intervention study published in 2002.¹⁸³ The menopausal benefits of EPO, however, have yet to be confirmed in RCTs involving postmenopausal women or breast cancer patients.¹⁸⁴,¹⁸⁵ Few studies examining the safety of EPO have been conducted either. Common adverse effects include headache and gastrointestinal symptoms (e.g. stomach upset, nausea, mild diarrhoea).¹⁸⁶ Limited evidence suggests that EPO may lower the seizure threshold and increase the risk of seizures in individuals taking phenothiazines (e.g. fluphenazine).¹⁸¹ Finally, despite the absence of reported herb-drug interactions of EPO, it may be prudent to monitor use by patients receiving chemotherapy.¹⁶⁸
2.3.3.6 Black cohosh (*Actaea racemosa, Cimicifuga racemosa*)

Black cohosh, a member of the buttercup family, was traditionally used by the North American Indians and in 19th-century America for a variety of conditions ranging from gynaecological disorders to rheumatism, but has more recently been adopted for use in Europe and Western countries for the treatment of menopausal symptoms and dysmenorrhoea. The roots and rhizomes of black cohosh are commonly used fresh or dried to make infusions (strong teas), capsules, solid extracts used in pills, or liquid extracts.

Like evening primrose oil, black cohosh is used by breast cancer survivors for the treatment of menopausal symptoms. Alternatively, prostate cancer patients may use black cohosh to control hot flushes after surgical or medical castration (e.g. hormonal ablation). Systematic reviews of RCTs, however, have found inconclusive evidence to support the use of black cohosh for menopausal symptom relief in peri-/post-menopausal women and breast cancer patients. Given the general poor quality of existing studies, more rigorous RCTs of longer duration (> 6 months) are required and should involve standardised preparations and uniform outcome measures, as well as prostate cancer patients.

Black cohosh appears to be relatively safe despite reports that it may be associated with hepatotoxicity. Approximately 50 cases of hepatotoxicity associated with black cohosh use have been reported since 2002, including 16 in Australia (of which three required liver transplants). While this has prompted the application of health warning labels to black cohosh sold in Australia and the US, recent expert panel reviews failed to establish a causal link and suggested that the risk of liver damage with black cohosh use is very low. Nevertheless, use is best avoided by patients with (a history of) liver disease and caution is warranted in those receiving hepatotoxic drugs, including chemotherapy agents such as cyclophosphamide, camptothecins (e.g. irinotecan), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vinorelbine) and EGFR-TK inhibitors (e.g. erlotinib for non-small cell lung, pancreatic and other cancers).

The most important safety concern with black cohosh, however, is the fear that it has oestrogenic effects and may promote breast or uterine cancer in women. Early studies suggested an oestrogenic mechanism of action for black cohosh, but this may have been due to phyto-oestrogen contamination. More recent *in vitro* and human studies of
unadulterated black cohosh extracts, though, have demonstrated no oestrogenic activity.\(^{190,191}\) Nevertheless, women with oestrogen-dependent cancers may want to avoid black cohosh until its long-term effects on breast or uterine tissue are more clearly established in epidemiological studies. Finally, no herb-drug interactions have been reported for black cohosh,\(^ {195}\) nor does it inhibit the cytochrome P450 3A4 enzyme or P-glycoprotein in human studies.\(^ {141}\) In summary, while the efficacy of black cohosh for treatment of menopausal symptoms is inconclusive, short-term use (< 6 months) is relatively safe and may include minor side-effects (e.g. gastrointestinal symptoms such as stomach upset; headaches, dizziness). Further studies examining the efficacy and safety of black cohosh in breast, uterine and prostate patients in the longer-term are required.

### 2.3.3.7 Echinacea (Echinacea purpurea, Echinacea angustifolia, Echinacea pallida)

Echinacea is an immunostimulant that is commonly used by cancer patients to boost their immune system and prevent or treat upper respiratory tract infections. RCTs are yet to confirm these benefits in cancer patients, however.\(^ {122}\) Safety of echinacea has recently been reviewed. Short-term use of echinacea is relatively safe, although there is some concern about allergic reactions including rashes, increased asthma and, in rare cases, anaphylaxis.\(^ {122,196}\) Individuals with asthma or atopy (a genetic tendency towards allergic reactions) may be more likely to have an allergic reaction when taking echinacea, thus use is contraindicated.\(^ {122}\)

Currently, there are no verifiable reports of herb-drug interactions for any echinacea products,\(^ {197,198}\) despite probe studies indicating a low potential for herb-drug interactions with substances metabolised by the cytochrome P450 1A2 and 3A4 enzymes.\(^ {199,200}\) Nevertheless, marked differences in the quality of echinacea preparations could alter the potential for interactions and is of major concern.\(^ {168,201,202}\) Possible contraindications of echinacea, therefore, include use with chemotherapy agents producing cytochrome P450 3A4 substrates [e.g. cyclophosphamide, camptothecins (e.g. irinotecan), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vinorelbine), EGFR-TK inhibitors (e.g. erlotinib for non-small cell lung, pancreatic and other cancers)], antipsychotics (e.g. clozapine, olanzipine), tricyclic antidepressants (e.g. amitriptyline), benzodiazepines (e.g. midazolam), immunosuppressants (e.g. corticosteroids, cyclosporine), antihypertensives/antiarrhythmics (e.g. verapamil), antihyperlipidemic drugs to reduce high cholesterol (e.g. simvastatin),
antimicrobial drugs (e.g. antibiotics such as erythromycin), oral contraceptives (e.g. ethinyl estradiol/norethindrone) and caffeine.\textsuperscript{168,199,203}

\subsection*{2.3.3.8 Milk thistle (\textit{Silybum marianum, Carduus marianum})}

Milk thistle is one of the most popular herbal medicines worldwide and is commonly used for liver disorders. The principal constituent of milk thistle is silymarin, which is a mixture of flavonolignans (silychristin, silydianin, silybin and others) isolated mainly from the seeds (fruit) of the plant. The seeds are used to prepare capsules, extracts, and infusions (strong teas). Evidence suggests that milk thistle has hepatoprotective, anti-cancer, tissue-regenerative, hypoglycaemic and cardioprotective properties.\textsuperscript{204,205} Milk thistle is being increasingly used by cancer patients for liver protection during chemotherapy (e.g. involving hepatotoxic agents, including docetaxel, gemcitabine, methotrexate, oxaliplatin, daictinomycin, daunorubicin and imatinib)\textsuperscript{206} and detoxification between chemotherapy cycles or after chemotherapy, as well as an adjuvant treatment and chemopreventive agent. A Cochrane meta-analytic review of 13 RCTs involving alcoholic and/or hepatitis B or C liver disease patients found significant benefits of milk thistle on mortality or hepatic complications across low quality trials alone, but not across all trials or high quality trials alone.\textsuperscript{207} High quality RCTs on milk thistle in liver disease are required, and should include patients with chemotherapy-induced hepatotoxicity given the absence of adult studies.

Reviews of preclinical studies suggest that milk thistle extract may have some potential in protecting the liver against toxins and stimulate the transcription and activity of phase II detoxification enzymes, but no clinical trials have assessed the detoxification effects of milk thistle.\textsuperscript{205,208} Similarly, reviews of preclinical studies and preliminary clinical trials suggests that milk thistle extract may potentiate the antitumour action of certain chemotherapy drugs (e.g. doxorubicin, cisplatin) and radiotherapy\textsuperscript{208} and have chemopreventive potential (e.g. skin cancer, colorectal cancer),\textsuperscript{208,209} but rigorous RCTs are required to establish its efficacy and safety as an adjuvant or chemopreventive treatment.

Reviews have established that chronic use ($\leq$ 41 months) of milk thistle is generally safe and well-tolerated in recommended doses (oral form standardised to contain 70-80\% silymarin, 420mg daily).\textsuperscript{207,210,211} Gastrointestinal problems are the most common complaint, but are infrequent.\textsuperscript{212} Allergic reactions, ranging from itchiness to eczema and
anaphylaxis, are rare. Large doses (> 1.5g/day) may cause diarrhoea, and very high doses (10-20g/day) can result in asymptomatic hepatotoxicity (hyperbilirubinaemia) in cancer patients.\textsuperscript{213} Drug interactions do not appear to be problematic either. Silymarin and silybin have been shown to inhibit cytochrome P450 enzyme activity.\textsuperscript{214,215} A review of several recent \textit{in vitro} and human studies, however, reported no clinically-relevant effects with chemotherapy agents (e.g. irinotecan, vincristine) or other drugs (e.g. midazolam, caffeine) metabolised by the cytochrome P450 and UGT1A1 enzymes, or interference with P-glycoprotein modulation.\textsuperscript{204} Nonetheless, these effects may be dose-responsive and require further study at higher doses.\textsuperscript{216} It would, therefore, be prudent to monitor milk thistle use by cancer patients receiving chemotherapy.

\textbf{2.3.3.9 European mistletoe (\textit{Viscum album} L.)}

Mistletoe has a long tradition of folk remedy use in Europe, but has been used extensively in recent years in adjuvant cancer treatment or as a standalone alternative therapy, by and large, in German-speaking countries (Switzerland, Austria, Germany). Its use in cancer treatment stems from anthroposophic medicine developed in the early 1900s, which approaches disease as an imbalance in the biological organism and utilises treatment strategies designed to restore this balance. Anthroposophic doctors believe that regular injections of mistletoe will inhibit or stop tumour growth and improve QoL in cancer patients.\textsuperscript{217} Mistletoe preparations undergo a standardised manufacturing process, but may also be standardised to include specific amounts of a particular component (e.g. mistletoe lectin). The stem and leaves of the semi-parasitic mistletoe plant are used to make commercial preparations (e.g. extracts, pressed sap) that are often administered by subcutaneous injection (near or directly into the tumour), but may be taken orally, intravenously or intrapleurally. Currently, there is no generally accepted protocol for administering mistletoe preparations, but studies indicate that injections given 2-3 times per week for varying lengths of time are most common with dosage depending on the response and disease stage of cancer patients.\textsuperscript{218,219}

\textit{In vitro} studies indicate that mistletoe or its main constituents (lectins, viscotoxins, polysaccharides, alkaloids) have anti-angiogenic, anti-cancer and immunostimulatory properties.\textsuperscript{220} Several systematic reviews over the last decade have examined the efficacy of mistletoe use in cancer patients with varying results. In 2003, a systematic review of 10
RCTs found some benefits of mistletoe extract as adjuvant or standalone treatment for cancer patients, particularly in relation to QoL, across low quality trials alone; however, no benefits in terms of QoL, survival and other outcomes were demonstrated in higher quality trials. In contrast, another systematic review in 2003 involving 16 RCTs and 7 quasi-/non-randomised controlled trials of mistletoe preparations revealed that 12 studies exhibited significantly positive results on at least one clinically-relevant outcome measure, 7 studies indicated a positive trend on at least one measure, 3 showed no significant results and 1 demonstrated a negative trend. The authors concluded that whilst all studies exhibited methodological weaknesses, further research was warranted given that a small number of relatively high quality trials produced positive outcomes. In 2007, a systematic review of 16 RCTs and 9 non-RCTs involving mistletoe use as adjuvant or standalone treatment found arguable benefits for cancer survival, but better evidence for the efficacy of anthroposophic mistletoe preparations in improving QoL and reducing toxicity of conventional treatments. Despite similar observations, a 2008 Cochrane meta-analytic review of 21 RCTs found weak evidence to support that mistletoe extract improves survival and QoL or reduces the adverse effects of chemotherapy and radiotherapy, although the conclusions for QoL were qualified by stating that a small number of higher quality trials suggested possible benefits for breast cancer patients during chemotherapy.

Interestingly, the conclusions concerning the efficacy of mistletoe use in cancer patients drawn from systematic reviews limited to RCTs were more negative. This may reflect the dubious nature of blinding in RCTs on mistletoe (i.e. some patients may be able to identify whether they are receiving mistletoe or placebo according to the presence/absence of local reactions to mistletoe injections) and the recruitment problems related to randomisation in such clinical trials, as well as the heterogeneity observed across the systematic reviews (e.g. varying inclusion criteria and study quality ratings; different mistletoe species, forms of extraction, and route, schedule and dosage of administration). A more recent systematic review of 18 RCTs and observational studies sought to minimise these problems. The authors found inconsistent evidence for the efficacy of mistletoe preparations as adjuvant or standalone treatment in increasing cancer survival and tolerance to chemotherapy and radiotherapy, but concluded that there was clear evidence for enhanced QoL and that these benefits were not limited to specific mistletoe preparations or cancer populations. The latest systematic review (26 RCTs, 10 non-RCTs) has further
confirmed the QoL benefits also. Nevertheless, given that the majority of existing studies have significant problems in methodology and/or reporting, further high quality prospective trials (e.g. involving different dosages, preparations, schedules, cancer sites and disease stages, treatment durations) are needed to consolidate the efficacy of mistletoe preparations as a supportive treatment enhancing QoL in cancer patients.

In terms of safety, recent reviews predominantly involving RCTs indicate that mistletoe preparations are usually well-tolerated and that serious adverse effects are rare (cf. mistletoe plants and berries, which are poisonous) when used as directed under the supervision of health professionals. Depending on the dose, local reactions (e.g. pruritis, erythema or induration at the injection site) have been observed in 0.9-43% of cancer patients and systemic reactions (e.g. headaches, fever, influenza-like symptoms) in up to 10% of patients. Allergic reactions (e.g. breathing difficulties, anaphylaxis) have been reported, but are rare (< 1%). Also, long-term use of mistletoe extracts may reduce T-cell function in cancer patients without local reactions, thus use should be suspended periodically to allow T-cell reactivity to recover. Finally, preclinical and human studies examining possible herb-drug interactions with mistletoe have been lacking, with the existence of only one human study examining interactions with chemotherapy agents (concomitant use of mistletoe and gemcitabine in advanced cancer patients produced no clinically-relevant effects). Human clinical trials using well-established probe drugs are required, as well as phase I studies examining possible interactions between mistletoe and other chemotherapy agents, hormone therapies and immunotherapies, respectively. It would, therefore, be prudent to monitor mistletoe use by cancer patients receiving chemotherapy and other treatments.

2.4 Manipulative and body-based practices

Manipulative and body-based practices focus primarily on body structures and systems including bones and joints, soft tissue, and the circulatory and lymphatic systems. They involve manipulation or movement of one or more parts of the body in order to heal the body and achieve good health. Examples include massage, acupuncture/acupressure, chiropractic and osteopathic manipulation, tui na, reflexology, and Bowen therapy. There is considerable variation in the level of formal training and approaches taken by practitioners both across and within modalities (e.g. chiropractic and osteopathic manipulation primarily
involve rapid movements, whereas massage therapy involves slower application of force. Despite this heterogeneity, manipulative and body-based practices share some common principles (e.g. the human body is self-regulating, parts of the body are interdependent) and features (e.g. therapies tend to be tailored to the specific needs of patients).

2.4.1 Massage therapy

Massage therapy involves the systematic manipulation of soft tissues of the body. There are many types of therapeutical massage, with most cultures having developed their own variations (e.g. Swedish massage, aromatherapy, shiatsu, reflexology, acupressure). The common goal of most massage techniques is to promote relaxation and general well-being. Overall, therapeutic massage administered by trained practitioners is very safe. Two reviews, one focusing on cancer patients, found few reported adverse events. Most adverse effects involved massage administered by laypeople and techniques other than Swedish massage (e.g. bleeding ranging from minor bruising to internal haemorrhaging in patients with coagulation disorders and/or those using anticoagulant/antiplatelet medications; bone fractures in at-risk patients including those with osteoporosis and metastatic cancer in the bones; increased pain and infection in surgical patients with open wounds and patients with skin afflictions, such as radiation dermatitis, or prosthetic devices such as colostomy bags; oxidation, bacterial contamination or accidental overdose of aromatherapy essential oils due to incorrect storage and handling). While there is no evidence that massage therapy can spread cancer, applying direct pressure over known tumours is best avoided. Reduced pressure and/or avoidance of direct or deep tissue massage is also advisable for cancer patients with coagulation disorders (and those using anticoagulant/antiplatelet medications, such as warfarin and aspirin), bone metastases or severe osteoporosis, open wounds or radiation dermatitis, and prosthetic devices (e.g. infusaport, colostomy bag, stents). Finally, caution is advised with use of aromatherapy essential oils in cancer patients with renal or liver disorders, and direct application should be avoided in those with wounds, skin conditions or allergies to essential oils.

Cancer patients have increasingly employed massage therapy for symptom control. A Cochrane meta-analytic review of 8 RCTs found limited evidence for short-term benefits of massage/aromatherapy on anxiety in cancer patients, but inconclusive results for other symptoms. More recent systematic reviews of RCTs and observational studies have also
suggested that massage may alleviate anxiety, as well as other symptoms such as pain, nausea, depression and stress.\textsuperscript{233,235-237} However, in light of the methodological limitations of the studies examined, the authors of these reviews collectively recommended that larger RCTs involving more clinically homogeneous samples, standardised massage doses and protocols, and more appropriate measurement intervals including longer follow-up periods be performed to develop a consensus on the most suitable type of massage therapy to offer different cancer patients. Nevertheless, massage therapy should be supported for use by patients in the interim, given the promising evidence for symptom control and that it is associated with few adverse effects.

2.4.2 Acupuncture

Acupuncture, a key aspect of TCM, is a family of procedures that involves the application of needles, pressure, heat and other treatments to the skin at particular sites called acupuncture points for therapeutic purposes. Acupuncture performed by competent and experienced practitioners is safe. Large studies have shown that major adverse events such as pneumothorax are extremely rare, and that local bleeding and needling pain, the most common minor adverse effects, occur in a very small minority of individuals (< 0.1% overall).\textsuperscript{238-240}

Acupuncture is predominantly used in supportive and palliative care for cancer patients, and has been utilised in the management of a diverse range of symptoms. Clinical trials have produced mixed results, however. Systematic reviews revealed that there is no convincing evidence that acupuncture alleviates cancer pain\textsuperscript{241,242} or hot flushes in breast and prostate cancer patients,\textsuperscript{243,244} although further randomised controlled trials (RCTs) were recommended given the paucity of rigorous controlled studies in the cancer literature. In contrast, a Cochrane meta-analytic review of 11 RCTs concluded that acupuncture-point stimulation (manual acupuncture, electroacupuncture, self-/practitioner-administered acupressure) in combination with antiemetics demonstrated benefit for acute chemotherapy-induced nausea and/or vomiting and complemented the positive evidence for postoperative nausea and vomiting.\textsuperscript{245} Additionally, an exploratory meta-analysis of 11 Chinese non-randomised clinical trials of poor quality found that acupuncture was associated with an increase in leukocytes during chemotherapy and chemoradiation, suggesting that acupuncture may be effective in reducing leukopenia in patients.
undertaking such treatments. Finally, several pilot studies suggest that acupuncture may improve radiation-induced xerostomia in head and neck cancer patients, although RCTs are needed to further confirm these encouraging results.

### 2.4.3 Exercise interventions

There are two broad categories of exercise. Aerobic or cardiorespiratory exercise involves large muscle groups performing continuous or intermittent physical activity over an extended period of time, while anabolic or resistance exercise involves performing sets of repetitive movements against a resistance during which neuromuscular fatigue occurs within 6-12 repetitions. Exercise may be home-based or take the form of highly structured, supervised interventions. Cancer survivors and patients undergoing treatment are generally prescribed aerobic and/or resistance exercise of low to moderate intensity and regular frequency (3-5 times per week) for at least 20 minutes per session.

Aerobic and resistance exercise appear to be relatively safe in cancer patients during treatment or survivorship, even in home-based programmes and older or advanced cancer patients. Recent meta-analytic and systematic reviews have found that serious adverse events (e.g. back injury; falls; development or exacerbation of lymphoedema, anaemia or cachexia) are rare, and that the most common minor adverse effects (e.g. hip/calf pain, pulled hamstring, shoulder tendonitis) of exercise interventions were no more frequent compared to control interventions in RCTs. Some researchers have suggested that anaemia, lymphoedema and cachexia are contraindications to exercise during cancer treatment. However, exercise intervention studies that have used these outcomes as primary endpoints have demonstrated no safety risks, with risk of exacerbated lymphoedema even being reduced in one study. Additionally, it has been proposed that values above $20 \times 10^9/L$ for platelet counts and $1.5 \times 10^9/L$ for leukocyte counts are safe for patients to engage in vigorous activity. Nevertheless, individuals must be aware of their physical limitations with any form of exercise, thus exercise interventions should be used with caution or avoided in patients with severe osteoporosis, joint problems, acute back pain, sprains or fractures, or whose physical functioning otherwise precludes certain exercises. Additionally, straining downward or holding low postures is contraindicated in patients with inguinal hernia; artificial joints or prosthetic devices (e.g. infusion port, colostomy bag, stents); pregnancy; or those recovering from abdominal surgery. Finally, larger studies are
required to examine the long-term safety of exercise interventions in cancer patients and survivors.

Recent attention has focused on the use of physical exercise by cancer patients to ameliorate fatigue and other symptoms (e.g. cachexia, mood) related to cancer and its treatment, and improve QoL during treatment and survivorship. A meta-analysis and systematic review of exercise-based and psychological interventions revealed in a subgroup analysis of 17 RCTs that there were no significant decreases in cancer-related fatigue (CRF) during treatment or survivorship for predominantly non-metastatic cancer patients who completed various exercise-based interventions. In contrast, a Cochrane meta-analytic review of 28 RCTs found a small beneficial effect of exercise in reducing symptoms of CRF during treatment or survivorship in patients (predominantly diagnosed with breast cancer) who completed various exercise-based interventions compared to control interventions. The authors recommended that exercise be considered for inclusion as part of comprehensive multifaceted interventions for CRF. Unfortunately, while the authors acknowledged several problems with the studies identified (e.g. small sample sizes, fatigue was not a primary endpoint in many studies and therefore was not assessed as part of eligibility criteria; clinical heterogeneity in terms of disease site/stage; type of cancer treatment received; time elapsed in survivorship; and form, mode, intensity, frequency and duration of exercise), they failed to state what impact they had on their findings and conclusions.

In an effort to address some of these shortcomings, a more recent meta-analysis of 18 RCTs examined the effects of different exercise parameters on CRF symptoms experienced during cancer treatment. Overall, exercise produced small significant reductions in CRF for breast cancer patients and moderate significant reductions in prostate cancer patients. Supervised aerobic exercise interventions proved more effective in reducing CRF during breast cancer treatment than home-based programmes, which did not significantly decrease CRF. Neither home-based programmes or supervised aerobic and resistance exercise interventions, however, significantly reduced CRF among prostate cancer patients, although statistical power may have been lacking due to small samples. Insufficient data, heterogeneity and/or poor reporting prevented evaluation of the long-term effects of exercise on CRF, the effects of exercise in metastatic cancer patients, and the determination
of the most effective parameters for exercise frequency, duration and intensity. Consequently, more large RCTs are required comparing the different forms of exercise interventions (aerobic and/or resistance) across settings (home-based, supervised) to other non-pharmacological interventions for CRF. Clearly defined cancer populations (e.g. early-stage vs advanced cancer, older vs younger, treated patients vs survivors) extending beyond breast cancer patients and assessed to have CRF must be targeted and the most effective exercise prescription parameters (mode, intensity, frequency, duration) must be determined.

Exercise interventions have been examined in relation to clinical and QoL outcomes in cancer patients extending beyond CRF. A meta-analysis of 16 randomised and 14 non-randomised trials found that exercise interventions resulted in small positive effects on clinical and QoL outcomes (physical functioning, symptoms other than fatigue, body composition, fatigue, mood, overall QoL) during cancer treatment, although larger effects were generally contributed by poorer quality studies. Similarly, a systematic review of 3 RCTs and 5 non-randomised trials found positive effects on QoL and physical outcomes in metastatic cancer patients, although heterogeneity was problematic and limited the generalisability of results. Also, a Cochrane meta-analytic review of 9 RCTs revealed a moderate positive effect of exercise interventions on physical functioning during adjuvant breast cancer treatment (and insufficient evidence for other outcomes, such as fatigue, mood disturbance, immune function and weight gain), although heterogeneity again was problematic. A more recent meta-analysis of exercise and behavioural interventions revealed in a subgroup analysis of 17 RCTs that physical exercise produced small positive effects on fatigue, depression, body image and QoL in breast cancer survivors or patients receiving treatment.

Finally, in the most comprehensive evaluation to date, a meta-analysis and systematic review of 74 RCTs and 8 non-randomised trials (including 66 judged to be of high quality) showed a large beneficial effect of exercise interventions for cancer survivors on lower and upper body strength and moderate effects on fatigue and breast cancer-specific concerns. Small to moderate positive effects in cancer patients undergoing treatment were observed for physical activity level, aerobic fitness, muscular strength, functional QoL, anxiety and self-esteem. Nevertheless, as with the CRF studies above, these positive preliminary results are compromised by the marked heterogeneity seen in exercise intervention studies.
involving cancer patients and survivors, as well as other major methodological problems (i.e. study participants were not recruited based on their need for improvement on the clinical/QoL outcomes measured, such as impaired physical functioning and poor overall QoL; few studies compared supervised interventions and home-based programmes or included populations outside breast cancer). Further large RCTs as prescribed above for CRF should extend to exercise intervention studies involving other targeted clinical and QoL outcomes and, perhaps most importantly, focus on cancer patients and survivors in greatest need for improvement on these targeted outcomes.

2.5 Energy therapies

Energy therapies involve the use of two types of energy fields. Veritable energy fields, which can be measured, employ mechanical vibrations (e.g. sound) and electromagnetic forces including visible light, magnetism, monochromatic radiation (e.g. laser beams), and rays from other parts of the electromagnetic spectrum. Specific, measurable wavelengths and frequencies are used to treat individuals.\(^{272}\) In contrast, putative energy fields or biofields are theorised to surround the body and have yet to be scientifically measured. Biofield therapies are based on the concept that humans are infused with a subtle form of energy or life force (termed differently in different cultures; for example, qi in TCM, ki in the Japanese Kampo system, doshas in Ayurvedic medicine, and elsewhere as prana, etheric energy and other names) that can be manipulated to effect changes in the physical body and influence health.\(^{273,274}\)

2.5.1 Biofield therapies

Biofield therapies refer to techniques which use energy fields that purportedly surround the human body to stimulate one’s own healing (internal practices; e.g. internal Qigong) or healing in others (external practices; e.g. external Qigong, therapeutic touch, healing touch, Reiki, Johrei, polarity therapy). Energy fields are sometimes manoeuvred by manipulating the body using light touch or placing the hands above the body. The broad goal of biofield therapies is to heal mental or physical disorders by rebalancing the energy fields in the body or by drawing upon spiritual energies for such healing. Cancer patients may use them to improve general well-being and QoL (e.g. pain relief), particularly in palliative and supportive care settings. Biofield therapies are generally safe when administered by trained practitioners. Although few (if any) adverse events have been reported for touch therapies
(healing touch, therapeutic touch, Reiki), use of Reiki is not advised for individuals with (a history of) psychosis, personality disorders or bipolar disorder.

6.5.1.1 Qigong
Qigong is the most studied biofield therapy among cancer patients and refers to a whole host of different meditative exercises (sometimes combined with breathing techniques, imagery and/or vocalisation of sounds) from traditional Chinese medicine used to prevent or slow disease and maintain health. Medical Qigong, however, has been specifically developed for the treatment and cure of disease (e.g. hypertension, arthritis, cancer, HIV), and may be used as an adjunct to conventional medical treatments. Given its utilisation of meditation, imagery and breathing techniques and dependence on regular practice, Qigong has many parallels to Western behavioural medicine.

Qigong is generally safe for most individuals when instructed by qualified practitioners and practiced correctly according to standard moderate principles [i.e. individuals should master the basic skills and progress gradually, step-by-step; practice with moderation, patience and intuition; demonstrate dedication and perseverance, but avoid over-meditation (e.g. 3 hour sessions) and preoccupation with Qigong; and, most importantly, lead a balanced life with moderation and not neglect the pleasures of life]. Abnormal psychosomatic responses and culture-bound psychiatric disorders (specific to individuals of Chinese or other Asian ethnicities, even when living in Western countries) may be induced, however, when Qigong is practiced inappropriately, excessively and/or unguided, particularly by psychologically vulnerable individuals. Serious adverse events are rare, but Qigong-induced psychiatric disorders are becoming more prevalent in China. An estimated 5% of people in China practice Qigong and 5% of these individuals develop psychiatric sequelae, albeit briefly (episodes lasting 1-2 months) and never coming to medical attention in most cases. Adverse effects range from mild to severe and may include sensory or somatic disturbances (e.g. headache, dizziness, chest tightness, tachycardia, breathlessness); motor disturbances (e.g. muscle twitching, tremors, odd limb movements, uncontrolled motor activity); cognitive impairment (e.g. memory, attention); psychological symptoms (e.g. anxiety, irritability, hypochondriasis, obsessive thoughts or images, delusions, visual/auditory hallucinations, disorganised speech, dissociation, altered consciousness, disorientation, mania, depression, suicidal or bizarre behaviour); and allergic skin
Consequently, Qigong (particularly in the absence of a qualified practitioner) should be used with caution or is best avoided in cancer patients with neurotic traits or (a history of) psychosis, personality disorders or other psychiatric disorders, and those who are suggestible or otherwise psychologically vulnerable, or whose physical functioning precludes certain exercises. Additionally, patients from Chinese and other Asian backgrounds should be more closely monitored, given the culture-specific nature of the Qigong-induced psychiatric disorders reported.

In relation to efficacy, an exploratory review of 21 Chinese studies (mostly controlled) revealed that cancer patients predominantly treated with internal Qigong and conventional medical treatment exhibited a consistent tendency for greater improvement on biological indicators and/or longer survival time than those who received conventional treatment alone, but concluded that there was much need for replication and improved methodological quality in future studies. A more recent systematic review of 9 controlled studies involving palliative/supportive care cancer patients, however, was less positive and concluded that the efficacy of internal Qigong (alone or combined with conventional medical treatment) in cancer care is not yet supported due to the poor methodological quality of existing studies, and recommended that large-scale RCTs be performed along with studies investigating possible scientific mechanisms. Finally, a systematic review of 66 RCTs and observational studies examining a variety of practitioner-administered biofield therapies (external Qigong, therapeutic touch, Reiki, spiritual healing, healing touch and others) in different medical populations found moderate (level 2) evidence for their efficacy in reducing acute pain in cancer patients and postoperative and hospitalised patients, but mixed (level 4) evidence for chronic pain, fatigue, physiological arousal (heart/respiratory rate, blood pressure) and QoL in cancer patients. Again, larger high-quality studies were advised, and must adequately assess the efficacy and dose-response effect of particular biofield therapies for symptom control in cancer using disease-specific measures.

### 2.5.2 Bioelectromagnetic-based therapies

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as magnetic, pulsed or alternating-/direct-current fields. Examples include magnetic, millimetre wave, sound energy (vibrational or frequency), and light therapy.
2.5.2.1 Microwave (UHF radiowave)/Tronado therapy

Microwave or ultra high frequency (UHF) therapy is designed to treat cancer via exposure of tumorous tissue to electromagnetic radiation delivered using frequencies ranging 300MHz-3GHz (although super high and extra high frequencies ranging up to 300GHz have reportedly been utilised also). UHF frequencies commonly used include 200-300MHz, 434MHz, 915MHz and 2450MHz. Microwave therapy is generally thought to exert therapeutic effects via direct or indirect heating of cancer cells, thus thermometry is typically undertaken at the time of treatment to measure intra-tumour temperature. Microwave therapy is usually combined with conventional radiotherapy or uncommonly with infusions of glucose-blocking agents (e.g. cyclophosphamide, cystine disulphide or penicillamine disulphide), and is often administered 5 days per week over a period of weeks.

A systematic review of 58 controlled and uncontrolled studies (mostly poor quality due to the absence of single or double-blind RCTs and inadequate patient follow-up, and exhibiting significant clinical heterogeneity), largely comparing microwave therapy and radiotherapy combined to microwave therapy alone in relation to tumour response and overall survival, found minimal evidence to support the routine use of microwave therapy for cancer treatment. Additionally, in the same review, a limited clinical audit of the medical records of 179 cancer patients treated in Western Australia suggested that microwave therapy + radiotherapy resulted in greater toxicity than radiotherapy alone or microwave therapy + glucose-blocking agents for patients with bladder or other invasive cancers. Some of the more common adverse effects associated with microwave therapy appear to be pain, erythema, fibrosis, necrosis, ulcerations, blisters and thermal burns. Third degree burns, arterial rupture and development of fistulae have been reported on occasions, as have deaths (often related to inadvertent heating of blood vessels or infections following invasive thermometry). Finally, microwave therapy is contraindicated in individuals with thalassaemia (an inherited autosomal recessive blood disorder that results in abnormal production of haemoglobin molecules, thus causing anaemia).

3. Summary Conclusions

Complementary and alternative therapies or CAM, as they are commonly referred to by patients and clinicians, are much sought after by Australian cancer patients as a means of
coping with the physical and emotional impact of their disease and/or treatment. Irrespective of whether doctors like them or believe in them, patients will use them. If physicians in the medical profession are to provide cancer patients with the best care and best advice possible, then they cannot ignore this sign of the times.

The complementary and alternative therapies used by cancer patients are diverse in their origin, premise (including proposed or actual mechanisms of action), practice, efficacy and safety. In Australia, complementary and alternative medicines may be categorised by the TGA as registered (prescribed or non-prescribed medications which meet Australian standards of quality, safety and efficacy) or listed (low risk products that are not routinely evaluated with respect to a manufacturer’s claims before marketing, but are subject to a random audit after listing).\(^{362}\) Listed medicines consist almost entirely of complementary and alternative medicines, which implies that they are produced according to appropriate standards for quality and safety but guarantees nothing in regard to their efficacy. Cancer patients and other members of the public are mostly unaware of such distinctions and may believe that a CAM listed by the TGA has been assessed as both effective and safe and approved for such use by the Federal Government. Additionally, many complementary and alternative therapies have long histories as components of ancient traditional medical practices, but have only been subjected to rigorous scientific investigation in the last 10-20 years. More research is required to evaluate or confirm the efficacy and safety of many of these therapies.

Currently, however, there is evidence from high quality clinical trials that some complementary therapies, used as adjuncts to conventional medical treatments, are beneficial in reducing disease or treatment symptoms and improving QoL and psychological functioning (e.g. relaxation). There is evidence of potential harm also. Nutritional supplements, herbal preparations, and other natural therapies among the biologically-based practices may pose direct safety risks because of their potential adverse effects or interactions with conventional anticancer treatments (chemotherapy, radiotherapy, surgery, hormonal therapies) and other medications. Some should not be used under any circumstances in cancer patients irrespective of potential benefit (e.g. St. John’s wort), while others may be beneficial when patients are not undergoing these treatments and have no other contraindications (e.g. valerian for short-term amelioration of sleep
problems in non-surgical cancer patients). Alternative therapies promoted as “cures” in place of conventional treatments (e.g. shark cartilage) have the potential to cause patients (and their loved ones) the most harm, however, when they forego evidence-based cancer treatments that are likely to be more effective.

It is therefore imperative that those involved in the medical care of cancer patients are equipped with the skills and knowledge to help patients appropriately evaluate complementary and alternative therapies, in order to receive benefit while avoiding harm. Additionally, as a consequence of the safety risks associated with CAM use, clinicians are strongly encouraged to routinely ask patients about complementary and alternative therapy use.

In conclusion, whether termed complementary medicine or integrative oncology, cancer physicians in Australia should strongly consider offering evidence-based complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services. Conceivably, this will influence patients to continue with mainstream care and help them avoid any potential harm that may occur with autonomous CAM use. In this way, optimal holistic care will be ensured for cancer patients by clinicians providing conventional oncology treatment and care.

4. Summary Recommendations
Refer to Tables 2 through 13 that follow for a summary of recommendations regarding the evidence for the efficacy and safety of popular CAM approaches (mind-body techniques, biologically-based practices consisting broadly of nutritional supplements and Chinese/Western herbal medicine, manipulative and body-based practices, energy therapies) used by cancer patients in Australia and elsewhere.

5. Acknowledgements
I would like to thank Professor Ian Olver (editor), Professor Peter Drummond and Mr Paul Katris for their comments on early drafts of this chapter. Finally, I would like to thank my loved ones for the patience they showed during the writing of this chapter.
### Table 1. Classification of complementary and alternative therapies

<table>
<thead>
<tr>
<th>Therapeutic Approaches</th>
<th>Definition</th>
<th>Examples of therapies used for cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole medical systems</td>
<td>Encompass complete systems of diagnosis and practice, which have some overlap with the other four therapeutic approaches</td>
<td>Traditional Chinese medicine, homeopathy, naturopathy, Ayurveda</td>
</tr>
<tr>
<td>Mind-body techniques</td>
<td>Techniques designed to increase the mind’s capacity and behavioural repertoire of active coping strategies to heal or manage physical and/or psychological symptoms of disease and promote general health and well-being</td>
<td>Practitioner-administered therapies e.g. hypnotherapy, mindfulness-based stress reduction, support groups</td>
</tr>
<tr>
<td>Biologically-based practices</td>
<td>Involve supplementing normal dietary intake with additional extracts, nutrients, herbs and/or certain foods</td>
<td>Self-help strategies e.g. relaxation, guided imagery/visualisation, meditation, music therapy, art therapy, support groups, yoga, tai chi, spiritual/religious coping, prayer</td>
</tr>
<tr>
<td>Manipulative and body-based practices</td>
<td>Involve manipulation or movement of one or more parts of the body in order to heal the body and achieve good health</td>
<td>Herbal medicines and other plant-based preparations (botanicals), animal-derived extracts, nutritional supplements, vitamins, minerals, antioxidants, fatty/amino acids, enzymes, proteins, antineoplastons, whole diet therapy (e.g. macrobiotic diet), prebiotics/probiotics, functional foods, metabolic therapy (e.g. Gerson diet), other “natural” therapies (e.g. shark cartilage)</td>
</tr>
<tr>
<td>Energy therapies</td>
<td>Involve the unconventional use of <em>putative energy fields or biofields</em>, which purportedly surround the human body and have yet to be scientifically measured; and <em>veritable energy fields</em>, which employ mechanical vibrations (e.g. sound) and electromagnetic fields (e.g. magnetic, pulsed or alternating/direct-current fields)</td>
<td>Biofield therapies e.g. Qigong, therapeutic touch, healing touch, Reiki, Johrei, polarity therapy</td>
</tr>
</tbody>
</table>

*Bioelectromagnetic-based therapies* e.g. microwave/UHF/Tronado therapy, magnetic therapy, light therapy, sound energy therapy
Table 2. Evidence supporting benefit in using whole medical system approaches to prevent/ameliorate cancer symptoms and treatment side-effects

Whole Medical Systems: Recommendations for each intervention approach across types of outcome based on meta-analysis and/or systematic review

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Homeopathy</th>
<th>Naturopathy*</th>
<th>Traditional Chinese Medicine†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Treatment/Survival Outcomes</strong></td>
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<tr>
<td>Survival</td>
<td></td>
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<td>√?</td>
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<tr>
<td><strong>Side-Effect/Symptom Outcomes</strong></td>
<td></td>
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<tr>
<td>Chemo Toxicity</td>
<td>√?</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Radiotherapy Toxicity</td>
<td>√?</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chemo-Induced</td>
<td>√?</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Stomatitis</td>
<td>√?</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Radiation-Induced Dermatitis</td>
<td>√?</td>
<td>–</td>
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</tr>
<tr>
<td><strong>Quality of Life and Psychosocial Outcomes</strong></td>
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<tr>
<td>(Overall) QoL</td>
<td></td>
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<td>√?</td>
</tr>
</tbody>
</table>

Chemo = chemotherapy; CAM = complementary and alternative medicine; QoL = quality of life
√ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ?? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; X = decisively advise against, no evidence for beneficial effects

* Naturopathy encompasses a wide variety of treatment modalities including dietary and lifestyle changes (e.g. eating more whole and unprocessed foods, abstaining from alcohol and sugar, stress reduction); vitamins, minerals and nutritional supplements; herbal medicine; homeopathy; mind-body techniques (e.g. meditation, yoga, counselling); and manipulative and body-based therapies (e.g. hydrotherapy, physical exercise). Given the overlap of naturopathic remedies with other categories of CAM, recommendations for various individual modalities are made in the tables that follow.

† Given the overlap of traditional Chinese medicine with other categories of CAM (e.g. Chinese herbal medicine as part of biologically-based practices, acupuncture as part of energy therapies), recommendations for various individual modalities are made in the tables that follow.
<table>
<thead>
<tr>
<th>Whole Medical System</th>
<th>Indication</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
</table>
| **Homeopathy**       | Chemotherapy or radiotherapy toxicity, chemo-induced stomatitis, radiotherapy-induced dermatitis | Homeopathic medicines prescribed by trained practitioners in low concentrations are probably safe and unlikely to cause serious adverse events, with the main risks being indirect and stemming from inexperienced practitioners (e.g. misdiagnosis)  
* ► Monitor use in all cancer patients receiving chemotherapy and other treatments |
| **Naturopathy***     | Various (see individual modalities in the tables that follow) | Naturopathy encompasses a wide variety of treatment modalities including dietary and lifestyle changes (e.g. eating more whole and unprocessed foods, abstaining from alcohol and sugar, stress reduction); vitamins, minerals and nutritional supplements; herbal medicine; homeopathy; mind-body techniques (e.g. meditation, yoga, counselling); and manipulative and body-based therapies (e.g. hydrotherapy, physical exercise). Given the overlap of naturopathic remedies with other categories of CAM, refer to the adverse effects and contraindications for various individual modalities made in the tables that follow.  
* ► Monitor use in all cancer patients receiving chemotherapy and other treatments  
* ► Refer to safety recommendations for various individual modalities made in the tables that follow |
| **Traditional Chinese Medicine** | Various (see individual modalities in the tables that follow) | Given the overlap of traditional Chinese medicine with other categories of CAM (e.g. Chinese herbal medicine as part of biologically-based practices, acupuncture as part of energy therapies), refer to the adverse effects and contraindications for various individual modalities made in the tables that follow  
* ► Monitor use in all cancer patients receiving chemotherapy and other treatments  
* ► Refer to safety recommendations for various individual modalities made in the tables that follow |
Table 4. Evidence supporting benefit in using mind-body interventions to prevent/ameliorate cancer symptoms and treatment side-effects

Mind-Body Interventions: Recommendations for each intervention strategy across types of outcome based on meta-analysis and/or systematic review

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Relaxation</th>
<th>Meditation (MBSR)</th>
<th>Hypnotherapy</th>
<th>Yoga</th>
<th>Tai Chi</th>
<th>Music Therapy</th>
<th>Professional-led Support Groups</th>
<th>Peer/Volunteer Support Groups</th>
<th>Religious/Spiritual Coping</th>
<th>Private/Personal Prayer</th>
<th>Intercessory Prayer</th>
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<tbody>
<tr>
<td>Quality of Life and Psychosocial Outcomes</td>
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<tr>
<td>(Overall) QoL</td>
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<td>✓?</td>
<td>✓?</td>
<td>X?*</td>
<td>✓?</td>
<td>✓?</td>
<td>✓?</td>
<td>✓? or X**</td>
<td>✓? or X**</td>
<td>✓?</td>
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<tr>
<td>Cancer Survival/Risk Outcomes</td>
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<td>Cancer Risk</td>
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<td>Side-Effect/Symptom Outcomes</td>
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</tbody>
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### Table 4. (Continued)

Mind-Body Interventions: Recommendations for each intervention strategy across types of outcome based on meta-analysis and/or systematic review

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Relaxation</th>
<th>Meditation (MBSR)</th>
<th>Hypnotherapy</th>
<th>Tai Chi</th>
<th>Music Therapy</th>
<th>Professional-led Support Groups</th>
<th>Peer/ Volunteer Support Groups</th>
<th>Religious/ Spiritual Coping</th>
<th>Private/ Personal Prayer</th>
<th>Intercessory Prayer</th>
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<tr>
<td>Pain</td>
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<td>Fatigue</td>
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<td>Sleep Disturbance</td>
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<tr>
<td>Physical Health/Functioning</td>
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<td>Physiological Arousal (BP, heart rate)</td>
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<td>Overall Side-Effects/Syptoms</td>
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<td>Conditioned Nausea</td>
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<td>Conditioned Vomiting</td>
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<tr>
<td>Acute Procedural Pain</td>
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<tr>
<td>Acute Procedural Distress</td>
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</table>

*BP = blood pressure; MBSR = mindfulness-based stress reduction or mindfulness meditation; Psych. = psychological; QoL = quality of life; √ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ?? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; X = decisively advise against, no evidence for beneficial effects; * breast cancer; † regular personal/private prayer as part of religious faith; ‡ personal/private prayer out of desperation in the absence of religious faith; § Christian religion members per se; || distant intercessory prayer per se*
<table>
<thead>
<tr>
<th>Mind-Body Technique</th>
<th>Indication</th>
<th>Adverse Effects  and Contraindications</th>
</tr>
</thead>
</table>
| Relaxation          | Anxiety, depression, hostility, nausea, vomiting, cancer pain, physiological arousal (BP, heart rate), anticipatory/conditioned nausea or vomiting | Relaxation-induced anxiety, intrusive thoughts, sense of losing control, sensory disturbances, muscle cramps and spasms, abreaction and others  
► *Use relaxation with caution or avoid in patients with (a history of) psychosis or PTSD*  
Heart rate and BP fluctuations (via the Valsalva response due to muscle tensing)  
► *Avoid autogenic training and PMR in patients with poorly-controlled cardiovascular disease* |
| Meditation          | Psychological adjustment to illness, anxiety, general mood, stress/distress, fatigue | Relaxation-induced anxiety, panic, restlessness, frustration, derealisation, depersonalisation, paradoxical tension, antisocial behaviour, flattened affect and others  
► *Use meditation (esp. transcendental or Vipassana meditation) with caution or avoid in patients with (a history of) psychosis, schizoid or schizotypal personality disorder, bipolar disorder, dissociative states, or hypochondrial and somatisation disorders*  
► *Contraindicated in patients experiencing physical exhaustion caused by fasting and sleep reduction during longer-term, unguided and intensive meditation* |
| Hypnotherapy        | Cancer pain, acute procedural pain/distress | Headaches, drowsiness, confusion, dizziness, nausea, anxiety, panic, abreaction and others  
► *Use with caution or avoid in patients with (a history of) psychosis, personality disorders or organic psychiatric conditions* |
| Music Therapy       | Cancer pain, anxiety, general mood, nausea, vomiting, QoL, acute procedural pain/distress | No adverse effects have been reported in the health literature (as far as can be ascertained)  
► *No obvious contraindications* |
<table>
<thead>
<tr>
<th>Mind-Body Technique</th>
<th>Indication</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoga</td>
<td>General mood, stress/distress, sleep disturbance, overall QoL</td>
<td>▶ Avoid or use in a gentler, modified form under guided instruction in patients with balance problems; uncontrolled hypertension, symptomatic anaemia, postural hypotension or lightheadedness/dizziness; fever, systemic infection or significant thrombocytopenia; certain eye conditions, including glaucoma and retinal detachment; severe osteoporosis, vertebral damage or cervical spondylosis; fragile or atherosclerotic neck arteries or a risk of blood clots; artificial joints or prosthetic devices (e.g. infusaport, colostomy bag, stents); pregnancy; and psychosis</td>
</tr>
<tr>
<td>Tai Chi</td>
<td>Psychological outcomes, cancer pain</td>
<td>▶ Tai chi is considered to be a relatively safe, moderate physical activity, although adverse effects (albeit rare) can occur (e.g. sore muscles, sprains) ▶ Use with caution or avoid in patients with severe osteoporosis, joint problems, acute back pain, sprains or fractures, or whose physical functioning otherwise precludes certain exercises ▶ Straining downward or holding low postures should be avoided by patients with inguinal hernia, artificial joints or prosthetic devices (e.g. infusaport, colostomy bag, stents), pregnancy, or those recovering from abdominal surgery</td>
</tr>
<tr>
<td>Professional-led Support Groups</td>
<td>Anxiety, depression, general mood, psychological adjustment to illness, QoL, (psycho)social functioning, marital satisfaction</td>
<td>Acute feelings of discomfort, vulnerability or distress may occur in group internet forms of professional-led support groups in instances of technological unfamiliarity (e.g. of computers or online mediums) or technical failure (e.g. disconnection) ▶ No obvious contraindications (provided contingency plans are put in place should technical problems arise; e.g. using telephones as a back-up if disconnected)</td>
</tr>
</tbody>
</table>
Table 5. (Continued)

<table>
<thead>
<tr>
<th>Mind-Body Technique</th>
<th>Indication</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
</table>
| Peer/Volunteer Support Groups | Psychosocial functioning | Acute feelings of discomfort, vulnerability or distress may occur in group internet forms of peer/volunteer support programmes in instances of technological unfamiliarity or technical failure  
► No obvious contraindications (provided contingency plans are put in place should technical problems arise; e.g. using telephones as a back-up if disconnected) |
| Religious/Spiritual Coping | Stress/distress, psychological adjustment to illness | No adverse effects have been reported in the health literature (as far as can be ascertained)  
► No obvious contraindications |
| Private/Personal Prayer | Anxiety, depression, psychological adjustment to illness, functional outcomes | Poorer emotional well-being and functioning if prayer is turned to out of desperation in the absence of pre-existing religious faith  
► Use prayer with caution or avoid in patients devoid of religious faith prior to diagnosis |
| Intercessory Prayer | None | No adverse effects have been reported in the health literature (as far as can be ascertained)  
► No obvious contraindications |

BP = blood pressure; esp. = especially; QoL = quality of life
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<tr>
<td><strong>Cancer Treatment/Survival/Risk Outcomes</strong></td>
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<td>Tumour Response</td>
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<td>Survival Length</td>
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<td>Progression-Free Survival Length</td>
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<td>Mortality</td>
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<td>Recurrence</td>
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<td>X†,‡ or X†‡</td>
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<td>Cancer Risk</td>
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<td><strong>Side-Effect/Symptom Outcomes</strong></td>
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<tr>
<td>Chemo Toxicity (Overall)</td>
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<tr>
<td>Radiotherapy Toxicity</td>
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<td>Postoperative Side-Effects (Overall)</td>
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Table 6. (Continued)

**Nutritional Supplements: Recommendations for each supplement across types of outcome based on meta-analysis and/or systematic review**

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Anti-oxidants (Overall)</th>
<th>Selenium (AO)</th>
<th>Lycopene (AO)</th>
<th>Coenzyme Q10 (AO)*</th>
<th>Amifostine (AO)*</th>
<th>Vit. A (AO)</th>
<th>Vit. C (AO)</th>
<th>Vit. E (AO)</th>
<th>Beta-Carotene (AO)</th>
<th>Folate (AO)</th>
<th>Omega-3 Fatty Acids</th>
<th>Shark Cartilage</th>
<th>AE-941 (Neovastat)*</th>
<th>Laetrile/Amygdalin</th>
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<td><strong>Side-Effect/Symptom Outcomes</strong></td>
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<td>Pain</td>
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<td>Urinary Tract Symptoms</td>
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<td><strong>Quality of Life and Psychosocial Outcomes</strong></td>
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</tr>
</tbody>
</table>

AO = antioxidant; Chemo = chemotherapy; QoL = quality of life; Vit. = vitamin

√ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ?? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; X = decisively advise against, no evidence for beneficial effects

* synthetic nutritional supplement; † prostate cancer; ‡ (upper) gastrointestinal cancer; § locally advanced non-small cell lung cancer; || colorectal cancer; ¶ lung cancer;

# advanced cancer; ** metastatic renal cell carcinoma
<table>
<thead>
<tr>
<th>Nutritional Supplement</th>
<th>Indication</th>
<th>Adverse Effects, Drug Interactions and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidants</strong></td>
<td>Radiotherapy toxicity overall (general antioxidants, amifostine alone); pain, urinary tract symptoms and cancer progression in prostate cancer (lycopene only); cancer prevention in prostate or GI cancer (selenium or vitamin E only)</td>
<td>Mild diarrhoea and GI upset (vitamin C); yellowish discolouration of the skin (heavy, chronic beta-carotene intake); increased risk of bleeding in individuals with drug-induced vitamin K deficiency (high vitamin E intake); increased lung cancer incidence and cancer mortality in general among smokers (high-dose beta-carotene); possible increased risk of bladder cancer (antioxidant supplementation in general)</td>
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<td>► Avoid in all surgical patients, patients undergoing chemotherapy and other cancer treatments (except under the guidance of the treatment team), and those with coagulation disorders</td>
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<td>► Avoid use with anticoagulants (e.g. warfarin) and antiplatelet medications (e.g. aspirin)</td>
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<td>► Avoid high-dose fish oil or supplementation in all surgical patients, cancer patients with coagulation disorders, and those at high risk to haemorrhagic stroke</td>
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<td></td>
<td>Cachexia, nutritional status, survival, other clinical outcomes (tolerance, hospital stays) and QoL in advanced cancer</td>
<td>Adverse effects related to toxic levels of mercury and other contaminants in fish (excessive fish consumption only)</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong></td>
<td></td>
<td>► Use high dietary intake of fish with caution in all cancer patients</td>
</tr>
<tr>
<td>Nutritional Supplement</td>
<td>Indication</td>
<td>Adverse Effects, Drug Interactions and Contraindications</td>
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</tbody>
</table>
| Laetrile/Amygdalin     | None       | Nausea, vomiting, headache, fever, abdominal pain, dizziness, acute cognitive disorientation, dermatitis, bluish discoloration of the skin (due to oxygen deprivation in the blood), hypotension, neuropathy, hepatotoxicity, coma, infection or disease (e.g. hepatitis B or C, herpes simplex, varicella zoster, tuberculosis) [due to contamination by bacteria and other impurities], cyanide poisoning, death  
► Avoid in all cancer patients (except in clinical trials of laetrile/amygdalin)  
► Avoid in patients who have a genetically predisposed, diminished capacity to detoxify cyanide  
► Avoid use with dietary intake of fruit seeds (apricot, bitter almond, peach apple) and raw almonds, or megadoses of vitamin C (due to elevated risk of cyanide poisoning and related death) |
| Shark Cartilage and AE-941 (Neovastat) | None       | GI symptoms (e.g. nausea, vomiting, stomach upset, constipation, diarrhoea, flatulence); taste alterations; increased blood calcium levels (due to the high calcium content of some shark cartilage preparations); potential for slow wound healing and teratogenic effects (due to the anti-angiogenic effects of shark cartilage)  
► Avoid in all surgical patients and pregnant or breast-feeding women  
► Avoid use with calcium supplements and medications (e.g. calcitriol, thiazide diuretics, antacids) |

GI = gastrointestinal; QoL = quality of life
Table 8. Evidence supporting benefit in using Chinese or Western herbal medicines to prevent/ameliorate cancer symptoms and treatment side-effects

<table>
<thead>
<tr>
<th>Herbal Medicines: Recommendations for each herbal medicine across types of outcome based on meta-analysis and/or systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Outcome</td>
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<tr>
<td>Tumour Response</td>
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<tr>
<td>Cancer Progression</td>
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<td>Survival Length</td>
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<td>Cancer Risk</td>
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<tr>
<td>Chemo Toxicity (Overall)</td>
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<tr>
<td>Radiotherapy Toxicity (Overall)</td>
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<tr>
<td>Clinical Outcomes</td>
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<tr>
<td>Performance Status</td>
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<td>Type of Outcome</td>
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<tr>
<td>Acute Postoperative Nausea</td>
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<td>Acute Postoperative Vomiting</td>
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<td>Chemo-Induced Nausea</td>
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<td>Chemo-Induced Vomiting</td>
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<td>Appetite Loss</td>
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<td>Pain</td>
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<td>Fatigue</td>
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<td>Sleep Disturbance</td>
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<tr>
<td>Cognitive Functioning</td>
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<tr>
<td>Sexual Functioning</td>
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</table>
Table 8. (Continued)

Herbal Medicines: Recommendations for each herbal medicine across types of outcome based on meta-analysis and/or systematic review

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Astragalus*</th>
<th>Ginseng*</th>
<th>Ginger*</th>
<th>Ling-zhi/ Reishi Mushroom*</th>
<th>Green Tea*</th>
<th>Ginkgo*</th>
<th>St. John’s Wort†</th>
<th>Garlic‡</th>
<th>Kava†</th>
<th>Valerian†</th>
<th>EPO†</th>
<th>Black Cohosh†</th>
<th>Echinacea†</th>
<th>Milk Thistle†</th>
<th>European Mistletoe</th>
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<td>Side-Effect/Symptom Outcomes</td>
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<td>Immunological Function</td>
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Chemo = chemotherapy; QoL = quality of life; URTI = upper respiratory tract infections
√ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; √ = decisively advise against, no evidence for beneficial effects
* Chinese herbal medicines; † Western herbal medicines; ‡ non-small cell lung cancer patients receiving platinum-based chemotherapy combined with astragalus-based Chinese herbal medicine; § colorectal cancer; ¶ gastric cancer; ¶¶ lung cancer; # oesophageal cancer; ** pancreatic cancer; †† ovarian cancer; ††† breast cancer; §§ prostate cancer; ‖‖ as adjuvant or standalone treatment; ¶¶¶ = unresectable liver cancer patients receiving transcatheter arterial chemoembolization combined with astragalus-based Chinese herbal medicine
<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
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</thead>
<tbody>
<tr>
<td>Astragalus*</td>
<td>Chemo toxicity, QoL, immune function, tumour response, survival (all as an adjunct to chemo for CRC or advanced NSCLC)</td>
<td>No significant interactions reported for astragalus alone, although more safety studies are required</td>
<td>Lymphopenia, hyperglycaemia, GI symptoms (e.g. diarrhoea, dyspepsia) [astragalus-based herbal preparations only] Potentially irreversible neurological symptoms from direct ingestion of certain toxic astragalus plants (locoweed) containing swainsonine or selenium</td>
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<td>Astragalus-based preparations: immunosuppressive chemo (e.g. cyclophosphamide) and medications (e.g. immunosuppressants, corticosteroids)</td>
<td>► Avoid in all surgical patients and cancer patients receiving chemotherapy using immunosuppressive agents such as cyclophosphamide ► Avoid or use with caution in cancer patients with autoimmune disease (e.g. rheumatoid arthritis), and those at risk to haemorrhagic stroke or have had a recent organ transplant ► Avoid or use with caution with medications that suppress the immune system such as cyclophosphamide, immunosuppressants (e.g. cyclosporine) and corticosteroids</td>
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<tr>
<td>Ginseng*</td>
<td>None</td>
<td>Asian/American Ginseng: anticoagulants or antiplatelet drugs (e.g. warfarin, aspirin), phenelzine (MAOI), hypoglycaemics, oestrogens, corticosteroids, alcohol Siberian Ginseng/Eleuthero: digoxin, antihypertensives Female Ginseng/Dong Quai: oestrogens</td>
<td>Insomnia (after evening intake), agitation/overstimulation (high intake)</td>
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<td>► Avoid use of ginseng or use with caution in hormone-sensitive cancers (e.g. breast and endometrial cancer) and conditions (e.g. pregnancy) [due to potential stimulation of tumour growth via oestrogenic effects] ► Avoid use of ginseng (esp. female ginseng/dong quai) with oestrogens ► Avoid use of Asian or American ginseng in all surgical patients, cancer patients with coagulation disorders, hypertension or diabetes, and those at risk to haemorrhagic stroke ► Avoid use of Asian or American ginseng with anticoagulant/antiplatelet drugs (e.g. warfarin), phenelzine (MAOI), hypoglycaemics, oestrogens, corticosteroids and alcohol ► Avoid use of Siberian ginseng/eleuthero in cancer patients with cardiovascular disease ► Avoid use of Siberian ginseng/eleuthero with digoxin (cardiac drug) and antihypertensive medications (e.g. verapamil, nifedipine) ► Avoid use of female ginseng/dong quai in hormone-sensitive cancers (e.g. breast and endometrial cancer) and conditions (e.g. pregnancy), or with oestrogens</td>
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Table 9. (Continued)

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<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
</table>
| Ginger*         | Acute postoperative nausea and/or vomiting | Anticoagulants or antiplatelet medications (e.g. warfarin, aspirin) | GI symptoms (e.g. heartburn, bloating, flatulence), increased risk of bleeding  
|                 |            |                        | ► Avoid in all surgical patients, cancer patients with coagulation disorders, and those at risk to haemorrhagic stroke  
|                 |            |                        | ► Avoid use with anticoagulants (e.g. warfarin, heparin) or antiplatelet drugs (e.g. aspirin) |
| Ginkgo*         | None       | All drugs metabolised by the cytochrome P450 2C19 enzyme (CYP2C19 induction) | Headache, GI symptoms (e.g. GI upset, nausea, diarrhoea), dizziness, palpitations, convulsions, allergic skin reactions, anaphylaxis-like reactions (iv admin. only), increased risk of bleeding  
|                 |            | e.g. anticonvulsants/ antiepileptics, omeprazole | Reduced efficacy of drugs metabolised by the CYP2C19 enzyme (e.g. increased risk of seizures and possible death with antiepileptics)  
|                 |            | NSAIDs, anticoagulants or antiplatelet drugs | ► Avoid in all surgical patients, cancer patients with coagulation or seizure disorders, and those at risk to haemorrhagic stroke  
|                 |            |                        | ► Avoid use with all drugs metabolised by the cytochrome P450 2C19 enzyme, including anticonvulsants (e.g. phenytoin, valproic acid) and omeprazole (proton pump inhibitor)  
|                 |            |                        | ► Avoid use with anticoagulant/antiplatelet drugs (e.g. warfarin) and NSAIDs (e.g. ibuprofen) |
| Lingzhi/ Reishi Mushroom* | None | Chemo agents that rely on free radicals including: anthracyclines (e.g. doxorubicin); alkylating agents (e.g. cyclophosphamide); platinum-containing complexes (e.g. cisplatin); podophyllotoxin derivatives (e.g. etoposide); camptothecins (e.g. irinotecan); cytotoxic antibiotics (e.g. bleomycin) | Dry throat and nose, GI symptoms (e.g. heartburn, bloating, flatulence), increased risk of bleeding  
|                 |            |                        | ► Avoid in all surgical patients  
|                 |            |                        | ► Avoid in all cancer patients receiving chemotherapy and other treatments (except under the guidance of the treatment team), and those with coagulation disorders  
<p>|                 |            |                        | ► Avoid use with anticoagulants (e.g. warfarin, heparin) and antiplatelet medications (e.g. aspirin) |</p>
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<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
</table>
| Green Tea*      | Breast or prostate cancer risk | Boronic acid-based proteasome inhibitors (e.g. bortezomib in chemo for multiple myeloma or mantle cell lymphoma); verapamil; caffeine; tannin (in food such as fruit and nuts, drinks such as coffee, teas, fruit juices, wine/beer) | GI and CNS disturbances (e.g. nausea, insomnia, irritability, frequent urination, cardiac arrhythmia) [high intake of 5-6 litres per day]  
Reduced efficacy of boronic acid-based proteasome inhibitors (e.g. increased risk of suboptimal tumour response and survival in chemotherapy with bortezomib)  
► Avoid in cancer patients receiving chemotherapy using bortezomib (e.g. for multiple myeloma and mantle cell lymphoma), cancer patients with known allergy/hypersensitivity to caffeine or tannin and heart conditions, and pregnant or breast-feeding women  
► Avoid use with boronic acid-based proteasome inhibitors (e.g. bortezomib), verapamil (antihypertensive/antiarrhythmic), caffeine and tannin (in food and drinks incl. wine/beer) |
| Garlic†         | Colorectal or gastric cancer risk | All drugs metabolised by the cytochrome P450 2E1 enzyme (CYP2E1 inhibition)  
e.g. dacarbazine in chemo (metastatic melanoma, Hodgkin’s lymphoma, other cancers), anaesthetics, paracetamol  
Antiretrovirals (e.g. saquinavir), anticoagulants or antiplatelet drugs | Mild to severe GI symptoms (e.g. stomach upset, heartburn, bloating) and allergic reactions (e.g. contact dermatitis, garlic burns and anaphylaxis resulting in possible death with topical or oral use); increased risk of bleeding  
Reduced efficacy of chemotherapy with dacarbazine and other drugs metabolised by the CYP2E1 enzyme, and antiretrovirals  
► Avoid in all surgical patients  
► Avoid in cancer patients receiving chemotherapy using dacarbazine (e.g. metastatic melanoma and Hodgkin’s lymphoma patients)  
► Avoid use with all drugs metabolised by the cytochrome P450 2E1 enzyme (e.g. dacarbazine, anaesthetics, paracetamol) and antiretrovirals (e.g. saquinavir)  
► Use with caution when combined with anticoagulants (e.g. warfarin, heparin) or antiplatelet medications (e.g. aspirin) |
<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort ¹</td>
<td>Depression, anxiety</td>
<td>All drugs metabolised by cytochrome P450 enzymes and P-glycoprotein (CYP3A4, CYP2E1, CYP2C19 and P-glycoprotein induction) e.g. chemo agents (e.g. imatinib, irinotecan), opioids, anaesthetics, benzodiazepines, anticoagulants, CV/GI tract/respiratory drugs, antiretrovirals, immunosuppressants, anticonvulsants, muscle relaxants, anti-addiction drugs, hypoglycaemics, antimicrobials, oral contraceptives</td>
<td>Headache, nausea, GI discomfort, diarrhoea, dizziness, palpitations, allergic skin reactions, intermenstrual bleeding, pregnancy, serotonin syndrome [cognitive, autonomic and somatic effects – mild (e.g. hypervigilance, agitation, muscle twitching) to severe symptoms (e.g. tachycardia and hypertension that may lead to shock and death)]; increased risk of bleeding; potentiation or reduced efficacy of medications in drug interactions</td>
</tr>
</tbody>
</table>

- **Avoid in all surgical patients**
- **Avoid in all cancer patients receiving chemotherapy** (esp. imatinib for chronic myeloid leukaemia, GI stromal tumours and other malignancies; and irinotecan for advanced colorectal and lung cancer patients), and those with coagulation disorders

- **Avoid use with all drugs metabolised by the CYP450 enzyme, including opioids (esp. in palliative patients with cancer pain), anaesthetics (e.g. fentanyl, propofol), benzodiazepines (e.g. midazolam), antidepressants (e.g. SSRIs such as sertraline; SNRIs such as venlafaxine; tricyclics such as amitryptiline; MAOIs such as phenelzine), anticoagulants or antiplatelet drugs (e.g. warfarin, aspirin), cardiovascular drugs (e.g. simvastatin for high cholesterol; verapamil for hypertension and arrhythmias; beta-blockers such as talinolol; antianginals such as ivabradine; cardiac inotropic drugs such as digoxin for heart failure), immunosuppressants (e.g. cyclosporine, tacrolimus), antiretrovirals (e.g. protease inhibitors, such as indinavir, and non-nucleoside reverse transcriptase inhibitors, such as nevirapine, widely used for HIV/AIDS), antimigraine drugs (e.g. triptans such as eletriptan), anxiolytics (e.g. buspirone), anticonvulsants (e.g. mephentoin), anti-addiction medications (e.g. bupropion for smoking cessation), muscle relaxants (e.g. chlorzoxazone), respiratory drugs (e.g. antihistamines such as fexofenadine), hypoglycaemics (e.g. gliclazide), antimicrobial drugs (e.g. antibiotics such as erythromycin), drugs acting on the GI tract (e.g. antidiarrhoeal drugs such as loperamide, omeprazole), and oral contraceptives (e.g. ethinyl estradiol/norethindrone)**
<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kava†</td>
<td>Short-term anxiety (1-24 weeks)</td>
<td>All drugs metabolised by cytochrome P450 2E1 and 1A2 enzymes (CYP2E1 and CYP1A2 inhibition) e.g. dacarbazine (chemo drug), anaesthetics, muscle relaxants, antidepressants, antipsychotics, anticoagulants, paracetamol, alcohol</td>
<td>Appetite loss, malnutrition, weight loss, shortness of breath, skin conditions (e.g. kava dermopathy; dry, scaly skin), blood and metabolic abnormalities, ataxia, dystonia, pulmonary hypertension [all with chronic and/or high intake of 300-400g per week]; sedative effects; possible hepatotoxicity, liver transplantation and death; increased risk of bleeding; potentiation or reduced efficacy of medications in drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All drugs mediated via GABA neurotransmission (additive effects) e.g. sedatives (benzodiazepines, barbiturates), anaesthetics</td>
<td>► Avoid in all surgical patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially all hepatotoxic drugs, including chemo agents such as dacarbazine, cyclophosphamide, camptothecins, taxanes, vinca alkaloids and EGFR-TK inhibitors</td>
<td>► Avoid in cancer patients with (a history of) liver disease or coagulation disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially all dopaminergic drugs (inhibitory effects) e.g. levodopa</td>
<td>► Avoid use with all drugs metabolised by the cytochrome P450 2E1 and 1A2 enzymes, including dacarbazine (chemo drug), anaesthetics (e.g. fentanyl and propofol), muscle relaxants (e.g. chlorzoxazone), antidepressants, antipsychotics (e.g. paroxetine), anticoagulant/antiplatelet medications (e.g. warfarin, aspirin), paracetamol and alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>► Avoid use with all drugs mediated via GABA neurotransmission (e.g. anaesthetics, benzodiazepines such as alprazolam, barbiturates, hypnotics, anxiolytics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>► Avoid use or use with caution with all hepatotoxic drugs unrelated to cancer treatment, all drugs that enhance GABA neurotransmission (e.g. anaesthetics; sedatives including benzodiazepines such as alprazolam and barbiturates; hypnotics; anxiolytics), and all dopaminergic drugs (e.g. anti-Parkinsonian drug levodopa)</td>
</tr>
<tr>
<td>Herbal Medicine</td>
<td>Indication</td>
<td>Herb-Drug Interactions</td>
<td>Adverse Effects and Contraindications</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Valerian†</td>
<td>Sleep disturbance</td>
<td>All drugs mediated via GABA neurotransmission (additive effects) e.g. sedatives, analgesics, hypnotics, anxiolytics</td>
<td>CNS symptoms (e.g. headache, nervousness, dizziness), GI symptoms (e.g. diarrhoea, nausea, heartburn, epigastric pain), insomnia (chronic use ≥ 2-4 months), withdrawal effects (e.g. delirium, tachycardia) [high intake] Potentiation effects of medications involved in drug interactions (e.g. excessive sedation)</td>
</tr>
<tr>
<td>Evening Primrose Oil†</td>
<td>None</td>
<td>Anticonvulsants (e.g. phenothiazines such as fluphenazine)</td>
<td>Headache, GI symptoms (e.g. stomach upset, nausea, mild diarrhoea), small increased risk of seizures</td>
</tr>
<tr>
<td>Black Cohosh†</td>
<td>None</td>
<td>Potentially all hepatotoxic drugs, including chemo agents such as dacarbazine, cyclophosphamide, camptothecins, taxanes, vinca alkaloids and EGFR-TK inhibitors</td>
<td>Headache, dizziness, GI symptoms (e.g. stomach upset, nausea), small increased risk of hepatotoxicity</td>
</tr>
</tbody>
</table>

- **Avoid in all surgical patients**
- **Avoid use with all drugs mediated via GABA neurotransmission (e.g. anaesthetics, benzodiazepines such as alprazolam, barbiturates, hypnotics, anxiolytics)**
- **Monitor use in all cancer patients receiving chemotherapy and other treatments**
- **Use with caution in cancer patients with seizure disorders**
- **Use with caution when combined with anticonvulsants (e.g. phenothiazines such as fluphenazine)**
- **Avoid in cancer patients receiving hepatotoxic chemotherapy, including cyclophosphamide, camptothecins (e.g. irinotecan), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vinorelbine) and EGFR-TK inhibitors (e.g. erlotinib for non-small cell lung, pancreatic and other cancers)**
- **Avoid in cancer patients with (a history of) liver disease, and women with oestrogen-dependent cancers (e.g. breast or uterine cancer)**
- **Use with caution with all hepatotoxic drugs unrelated to cancer treatment**
<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea†</td>
<td>None</td>
<td>Potentially all drugs metabolised by cytochrome P450 1A2 and 3A4 enzymes (weak CYP1A2 and CYP3A4 inhibition/induction) e.g. tricyclic antidepressants, antipsychotics, benzodiazepines, CV drugs (antihypertensives, antiarrhythmics, antihyperlipidemics), antimicrobials, immunosuppressants, oral contraceptives, caffeine</td>
<td>Rashes, increased asthmatic episodes, anaphylaxis and related death (rare) Possible potentiation or reduced efficacy of medications in drug interactions  ► Avoid in cancer patients receiving chemotherapy metabolised by cytochrome P450 1A2 and 3A4 enzymes, including cyclophosphamide, camptothecins (e.g. irinotecan), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vinorelbine) and EGFR-TK inhibitors (e.g. erlotinib for non-small cell lung, pancreatic and other cancers)  ► Avoid in cancer patients with asthma or atopy (genetic tendency towards allergic reactions)  ► Avoid use or use with caution all drugs metabolised by the cytochrome P4501A2 and 3A4 enzymes, including tricyclic antidepressants (e.g. amitryptiline), antipsychotics (e.g. clozapine, olanzpine), benzodiazepines (e.g. midazolam), immunosuppressants (e.g. corticosteroids, cyclosporine), antihypertensives/antiarrhythmics (e.g. verapamil), antihyperlipidemic drugs to reduce high cholesterol (e.g. simvastatin), antimicrobial drugs (e.g. antibiotics such as erythromycin), oral contraceptives (e.g. ethinyl estradiol/norethindrone) and caffeine</td>
</tr>
<tr>
<td>Milk Thistle†</td>
<td>None</td>
<td>No significant interactions reported, but effects may be dose-responsive (i.e. require high doses)</td>
<td>GI symptoms (e.g. stomach upset, nausea); allergic reactions ranging from itchiness to eczema and anaphylaxis (rare) Diarrhoea (high intake &gt; 1.5g/day) and asymptomatic hepatotoxicity (hyperbilirubinaemia, very high intake of 10-20g/day) in cancer patients per se  ► Monitor use in all cancer patients receiving chemotherapy and other treatments</td>
</tr>
</tbody>
</table>
Table 9. (Continued)

<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Indication</th>
<th>Herb-Drug Interactions</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Mistletoe†</td>
<td>Chemotherapy and radiotherapy toxicity, QoL</td>
<td>No significant interactions reported, but studies are lacking</td>
<td>Local reactions (e.g. pruritis, erythema or induration at the injection site), systemic reactions (e.g. headaches, fever, influenza-like symptoms), allergic reactions (e.g. breathing difficulties, anaphylaxis) [rare] Reduced T-cell function in cancer patients without local reactions (chronic use)</td>
</tr>
</tbody>
</table>

* Monitor use in all cancer patients receiving chemotherapy and other treatments

Chemo = chemotherapy; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CRC = colorectal cancer; CV = cardiovascular; CYP = cytochrome P450; EGFR-TK = epidermal growth factor receptor tyrosine-kinase; esp. = especially; GABA = gamma-aminobutyric acid; GI = gastrointestinal; incl. = including, MAOIs = monoamine oxidase inhibitors; NSAIDs = non-steroidal anti-inflammatory drugs; NSCLC = non-small cell lung cancer; QoL = quality of life; SNRIs = serotonin and noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

* Chinese herbal medicines; † Western herbal medicines
Table 10. Evidence supporting benefit in using manipulative and body-based interventions to prevent/ameliorate cancer symptoms and treatment side-effects

**Manipulative and Body-based Interventions**: Recommendations for each intervention strategy across types of outcome based on meta-analysis and/or systematic review

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Massage Therapy</th>
<th>Acupuncture</th>
<th>Exercise Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side-Effect/Symptom Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Outcomes</td>
<td>??‡‡</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>—</td>
<td>—</td>
<td>√? or ψ*,#</td>
</tr>
<tr>
<td>Physical Activity Level and Aerobic Fitness</td>
<td>—</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Body Composition</td>
<td>—</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Body/Muscle Strength</td>
<td>—</td>
<td>—</td>
<td>√? or ψ**</td>
</tr>
<tr>
<td>Acute Postoperative Nausea</td>
<td>—</td>
<td>√?</td>
<td>—</td>
</tr>
<tr>
<td>Acute Postoperative Vomiting</td>
<td>—</td>
<td>√?</td>
<td>—</td>
</tr>
<tr>
<td>Acute Chemo-Induced Nausea</td>
<td>—</td>
<td>√?‡‡</td>
<td>—</td>
</tr>
<tr>
<td>Acute Chemo-Induced Vomiting</td>
<td>—</td>
<td>√?‡‡</td>
<td>—</td>
</tr>
<tr>
<td>Nausea (Overall)</td>
<td>√?</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pain</td>
<td>√?</td>
<td>X?</td>
<td>—</td>
</tr>
<tr>
<td>Fatigue</td>
<td>??</td>
<td>—</td>
<td>X?*—‖—¶ or ψ**,††</td>
</tr>
<tr>
<td>Immunological Function</td>
<td>—</td>
<td>√?</td>
<td>??*</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>—</td>
<td>??</td>
<td>—</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>—</td>
<td>—</td>
<td>??*</td>
</tr>
<tr>
<td>Body Image</td>
<td>—</td>
<td>—</td>
<td>√*††</td>
</tr>
<tr>
<td>Hot Flushes</td>
<td>—</td>
<td>X?*‡‡</td>
<td>—</td>
</tr>
<tr>
<td>Radiation-Induced Xerostomia</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Quality of Life and Psychosocial Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Overall) QoL</td>
<td>??</td>
<td>—</td>
<td>√? or ψ**,††</td>
</tr>
<tr>
<td>Anxiety</td>
<td>√? or ψ††</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Depression</td>
<td>√?</td>
<td>—</td>
<td>√*††</td>
</tr>
<tr>
<td>General Mood</td>
<td>??‡‡</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Stress/Distress</td>
<td>√?</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anger</td>
<td>??</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Self-Esteem</td>
<td>—</td>
<td>—</td>
<td>√?</td>
</tr>
<tr>
<td>Cancer-Specific Concerns</td>
<td>—</td>
<td>—</td>
<td>√*††</td>
</tr>
</tbody>
</table>

BP = blood pressure; chemo = chemotherapy; CRF = cancer-related fatigue; QoL = quality of life

√ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ?? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; X = decisively advise against, no evidence for beneficial effects

* breast cancer; † prostate cancer; ‡ acupuncture-point stimulation (manual acupuncture, electroacupuncture, self-/practitioner-administered acupressure) + antiemetics; § head and neck cancer; ‖ prostate cancer; ¶ supervised + home-based aerobic/resistance interventions overall reduced CRF in breast and prostate patients, but neither supervised intervention alone did so in prostate patients and only supervised aerobic exercise per se did so in breast patients;

# metastatic cancer; ** cancer survivors; †† breast cancer survivors †‡‡ aromatherapy per se
### Table 11. Potential adverse effects and contraindications of manipulative and body-based interventions in cancer patients

<table>
<thead>
<tr>
<th>Manipulative and Body-Based Practice</th>
<th>Indication</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massage Therapy</td>
<td>Anxiety, stress/distress, depression, nausea, cancer pain</td>
<td>Bleeding (ranging from minor bruising to internal haemorrhaging), bone fractures, increased pain, infection, and adverse events (e.g. allergic reactions, infection, accidental overdose) due to incorrect storage and handling of aromatherapy essential oils [all rare]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Reduce pressure and/or avoid direct or deep tissue massage in all surgical patients, esp. those with open wounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Avoid direct pressure over known tumours in cancer patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Reduce pressure and/or avoid direct or deep tissue massage in cancer patients with bone metastases, radiation dermatitis or prosthetic devices (e.g. infusaport, colostomy bag, stents), and in those with coagulation disorders or severe osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Reduce pressure and/or avoid direct or deep tissue massage with patients using anticoagulants (e.g. warfarin, heparin) or antiplatelet drugs (e.g. aspirin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Avoid direct application of aromatherapy essential oils in cancer patients with known allergy/hypersensitivity, wounds or skin conditions, and use with caution in those with renal or liver disease</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Acute postoperative or chemo-induced nausea/vomiting, nausea (in general), immunological function, radiation-induced xerostomia</td>
<td>Local bleeding and needling pain (rare), pneumothorax (extremely rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Monitor use in all cancer patients receiving chemotherapy and other treatments</td>
</tr>
<tr>
<td>Manipulative and Body-Based Practice</td>
<td>Indication</td>
<td>Adverse Effects and Contraindications</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Exercise Interventions</td>
<td>Physical functioning, physical activity level, aerobic fitness, body composition, body/muscle strength (incl. survivors), fatigue (survivors only), clinical outcomes, QoL (incl. breast cancer survivors); depression, body image and cancer-specific concerns (breast cancer patients and survivors only)</td>
<td>Pain (e.g. hip/calf), pulled muscles (e.g. hamstring), (shoulder) tendonitis; serious adverse events such as back injury, falls and development or exacerbation of lymphoedema, anaemia or cachexia (rare)</td>
</tr>
</tbody>
</table>

- Use with caution or avoid in patients with severe osteoporosis, joint problems, acute back pain, sprains or fractures, or whose physical functioning otherwise precludes certain exercises

- Straining downward or holding low postures should be avoided by patients with inguinal hernia, artificial joints or prosthetic devices (e.g. infusaport, colostomy bag, stents), pregnancy, or those recovering from abdominal surgery

Chemo = chemotherapy; esp. = especially; incl. = including; QoL = quality of life
Table 12. Evidence supporting benefit in using energy therapies to prevent/ameliorate cancer symptoms and treatment side-effects

*Energy Therapies: Recommendations for each therapeutic strategy across types of outcome based on meta-analysis and/or systematic review*

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Biofield Therapies*</th>
<th>Qigong†</th>
<th>Microwave (UHF Radiowave)/Tronado Therapy‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Treatment/Survival/Risk Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour Response</td>
<td>—</td>
<td>—</td>
<td>X? ¶</td>
</tr>
<tr>
<td>Survival Length</td>
<td>—</td>
<td>√?§ or ??║</td>
<td>X?¶</td>
</tr>
<tr>
<td><strong>Side-Effect/Symptom Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Toxicity</td>
<td>—</td>
<td>—</td>
<td>X¶,#</td>
</tr>
<tr>
<td>Clinical Outcomes</td>
<td>—</td>
<td>??║</td>
<td>—</td>
</tr>
<tr>
<td>Physiological Arousal (BP, heart/respiratory rate)</td>
<td>??</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Biological Indicators</td>
<td>—</td>
<td>√?§</td>
<td>—</td>
</tr>
<tr>
<td>Acute Cancer Pain</td>
<td>√?</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chronic Cancer Pain</td>
<td>??</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acute Postoperative Pain</td>
<td>√?</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fatigue</td>
<td>??</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Quality of Life and Psychosocial Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Overall) QoL</td>
<td>??</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

UHF = ultra-high frequency frequency; QoL = quality of life
√ = highly recommended, strong evidence for beneficial effects; √? = tentatively recommended, mixed evidence for beneficial effects; ?? = neither recommend nor advise against, inconclusive evidence for beneficial effects; X? = tentatively advise against, little evidence for beneficial effects; X = decisively advise against, no evidence for beneficial effects
* practitioner-administered biofield therapies (external Qigong, therapeutic touch, Reiki, spiritual healing, healing touch and others); † type of biofield therapy; ‡ type of bioelectromagnetic-based therapy; § predominantly internal Qigong + conventional medical treatment; ║ internal Qigong ± chemotherapy or herbal medicine in palliative/supportive cancer care; ¶ largely microwave therapy + radiotherapy; # bladder or other invasive cancers
Table 13. Potential adverse effects and contraindications of energy therapies in cancer patients

<table>
<thead>
<tr>
<th>Energy Therapy</th>
<th>Indication</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
</table>
| Biofield Therapies*       | Acute cancer or postoperative pain  | Few (if any) adverse events have been reported in the health literature for touch therapies (healing touch, therapeutic touch, Reiki) and other external practices (as far as can be ascertained), but appear more likely for internal practices such as internal Qigong (see below)  
  ► Avoid or use Reiki with caution in patients with (a history of) psychosis, personality disorders or bipolar disorder |
| Qigong†                   | Biological indicators and survival  | Mild to severe adverse effects including sensory or somatic disturbances (e.g. headache, dizziness, chest tightness, tachycardia, breathlessness); motor disturbances (e.g. muscle twitching, tremors, odd limb movements, uncontrolled motor activity); cognitive impairment (e.g. memory, attention); psychological symptoms (e.g. anxiety, irritability, hypochondriasis, obsessive thoughts or images, delusions, visual/auditory hallucinations, disorganised speech, dissociation, altered consciousness, disorientation, mania, depression, suicidal or bizarre behaviour); and allergic skin reactions  
  Qigong-induced, culture-bound psychiatric disorders (specific to individuals of Chinese or other Asian ethnicities, even when living in Western countries) [rare]  
  ► Use with caution or avoid (esp. in the absence of a qualified practitioner) in cancer patients with neurotic traits or (a history of) psychosis, personality disorders or other psychiatric disorders, and those who are suggestible or otherwise psychologically vulnerable, or whose physical functioning precludes certain exercises  
  ► Monitor use in cancer patients from Chinese and other Asian backgrounds, given the culture-specific nature of the Qigong-induced psychiatric disorders reported |
| Microwave (UHF Radiowave)/Tronado Therapy‡ | None                                | Pain, erythema, fibrosis, necrosis, ulcerations, blisters, thermal burns (all more common); third degree burns, arterial rupture, development of fistulae, death (often related to inadvertent heating of blood vessels or infections following invasive thermometry) [all occasional or rare]  
  ► Avoid in cancer patients with thalassaemia (genetic blood disorder causing anaemia)§ |

Esp. = especially; UHF = ultra-high frequency frequency; QoL = quality of life  
* biofield therapies (e.g. Qigong, therapeutic touch, Reiki, spiritual healing, healing touch, Johrei, polarity therapy); † internal qigong, a type of biofield therapy; ‡ type of bioelectromagnetic-based therapy; § an inherited autosomal recessive blood disorder that results in abnormal production of haemoglobin molecules, thus causing anaemia.
6. References


132. S. Sontakke, V. Thawani and M. S. Naik, Ginger as an antiemetic in nausea and vomiting induced by chemotherapy: a randomized, cross-over, double blind study, Indian J Pharmacol. 35: 32-36 (2003).


Appendix D: Complementary and Alternative Medicine Used by Patients with Cancer—Evidence for Efficacy and Safety (Methodology, Study 2)

Appendix D also contains a detailed methodology of study 2 written using the gold standard Cochrane review framework, which provides more detail regarding the process that underpinned the systematic review performed.
OBJECTIVES
The primary objective of this systematic review was to evaluate the efficacy and safety of a range of popular complementary and alternative medicines (CAMs) used by adult cancer patients in Australia and elsewhere, utilising evidence, where possible, from Cochrane and other meta-analytic/systematic reviews. Secondary objectives examined whether specific CAMs can be used with clinical efficacy and safety that is comparable to standard or other existing interventions (medical or otherwise) for particular symptoms or problems, and whether some groups of patients benefit or are more prone to harm in response to particular CAM interventions.

METHODS

Criteria for considering studies for this review

Types of studies
Meta-analytic/systematic ± narrative reviews of randomised controlled trials (RCTs), quasi-RCTs, epidemiological/population/observational/cohort/case-control studies, and case series/report studies were utilised where possible. In their absence, individual RCTs of efficacy were evaluated while all types of studies were considered with respect to potential safety concerns. Primary research studies, however, were otherwise excluded to prevent duplication and to ensure that the literature search and review were manageable given the resources available, unless recent RCTs presented new findings different from those of the reviews utilised. If recent RCTs using the same dataset appeared in more than one publication, the results were reported only once.

Types of participants
Studies considered included adult cancer patients (18 years and over) using CAM in different phases of their cancer experience or trajectory (upon diagnosis, during conventional treatment, in response to disease progression or recurrence, or during remission/survivorship), irrespective of gender, diagnosis, histological tumour type, cancer
stage, and the intent and type of anticancer treatment received (if undergoing active conventional treatment). The only other populations considered were healthy volunteers and non-oncological medical patients in studies examining cancer prevention or safety. Paediatric, animal and in vitro studies were excluded.

Types of interventions
Pharmacological and non-pharmacological interventions of interest corresponded to the US National Center for Complementary and Alternative Medicine (NCCAM) / Australian National Institute of Complementary Medicine (NICM) classifications of CAM, which fall into 5 categories, whole medical systems, mind-body techniques, biologically-based practices, manipulative and body-based practices, and energy therapies (Table D1; NCCAM, 2009; NICM, 2010). Interventions included for review (Table D1) were guided by those reported by cancer patients in earlier studies in Australia and elsewhere (e.g. Oh et al., 2010; Pirri, Katris, Trotter, Bayliss, Bennett, & Drummond, 2008; Molassiotis et al., 2005), as well as those presented in previous comprehensive evidence-based systematic reviews similar to the one undertaken (e.g. Deng et al., 2009, 2010).

Types of outcome measures
Due to the wide-ranging nature of the present systematic review and the inclusion of patients in different phases of their cancer experience or trajectory, the review was not limited to any particular outcome (clinical or otherwise; see Appendix C, Tables 2-13, pp. 312-338 for an indication of the range of outcomes). For purposes of the review, efficacy was defined as a statistically significant improvement in a clinically-relevant outcome (cf. NHMRC, 2013). Clinically-relevant outcomes varied depending on the CAM being considered and the phase of cancer trajectory of study patients. Safety was defined as any form of direct or indirect harm related to the use of a specific CAM in human studies (see Pirri, 2011, Tables 3 and 4, pp. 196-200). Risk of direct harm was predominantly concerned with clinically-relevant outcomes and effects.
### Table D1. Classification of complementary and alternative therapies evaluated for efficacy and safety

<table>
<thead>
<tr>
<th>Therapeutic Approaches</th>
<th>Definition</th>
<th>Therapies used by cancer patients evaluated for efficacy and/or safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole medical systems</td>
<td>Encompass complete systems of diagnosis and practice, which have some overlap with the other four therapeutic approaches below</td>
<td>Homeopathy, naturopathy, traditional Chinese medicine</td>
</tr>
<tr>
<td>Mind-body techniques</td>
<td>Techniques designed to increase the mind’s capacity and behavioural repertoire of active coping strategies to heal or manage physical and/or psychological symptoms of disease and promote general health and well-being</td>
<td>Practitioner-administered therapies: Hypnotherapy, mindfullness-based stress reduction, music therapy, support groups</td>
</tr>
<tr>
<td>Biologically-based practices</td>
<td>Involve supplementing normal dietary intake with additional extracts, nutrients, herbs and/or certain foods</td>
<td>Dietary supplements: Antioxidants (vitamins A, C, E; alpha/beta-carotene carotenoids, lycopene, selenium, melatonin, amifostine, coenzyme Q10), omega-3 fatty acids (EPA, DHA, ALA), shark cartilage, laetrile/amygdalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese herbal medicines: Astragalus and astragalus-based herbs, ginseng and ginseng-based herbs, ginger, Lingzhi/reishi mushroom, green tea, gingko</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Western herbal medicines: St. John’s wort, garlic, kava, valerian, evening primrose oil, black cohosh, echinacea, milk thistle, European mistletoe</td>
</tr>
<tr>
<td>Manipulative and body-based practices</td>
<td>Involve manipulation or movement of one or more parts of the body in order to heal the body and achieve good health</td>
<td>Massage therapy: therapeutic massage, aromatherapy (isopropyl alcohol, peppermint oil, lavender, orange essential oils)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acupuncture and acupuncture-point stimulation (simple acupuncture needle insertion, manual acupuncture, electroacupuncture, acupuncture injection with herbs, acupoint plaster application, moxibustion, self/practitioner-administered acupressure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exercise interventions (aerobic and/or resistance, unsupervised home-based vs supervised institution-based, individual vs group programmes)</td>
</tr>
<tr>
<td>Energy therapies</td>
<td>Involve the unconventional use of putative energy fields or biofields, which purportedly surround the human body and have yet to be scientifically measured; and veritable energy fields, which employ mechanical vibrations (e.g. sound) and electromagnetic fields (e.g. magnetic, pulsed or alternating/ direct-current fields)</td>
<td>Biofield therapies: Qigong, healing/therapeutic touch, Reiki, Bioelectromagnetic-based therapies: Microwave/Tronado therapy</td>
</tr>
</tbody>
</table>
Search methods for identification of studies

Electronic searches
The following databases were searched: MEDLINE and EMBASE (via EMBASE.com), PubMed, PubMed Health, CAM on PubMed, the Cochrane Library, PsycINFO (via ProQuest), CINAHL (via EBSCOhost), Database of Abstracts of Reviews of Effectiveness (DARE), and Theses and Dissertations (via ProQuest). Search dates for reviews of efficacy were limited from January 1997 to October 2010 (and from January 2000 to August 2014 in the post-publication update, in case any relevant reviews were inadvertently overlooked in the original systematic review). However, search dates were not limited for safety per se, or primary research studies of efficacy in the instance where no reviews were found.

A search strategy for each CAM was devised for use with PubMed and adapted for other databases searched. For example, a search of PubMed for homeopathy (the first CAM in the present review) used the following search terms (and was extrapolated to PubMed searches for other CAMs):

1. (“systematic review” OR meta analysis OR “review” OR “pooled analysis” OR “synthesis” OR “narrative”[Title/Abstract]) AND (homeopath* AND cancer[Title/Abstract]) for the efficacy of homeopathy among cancer patients

2. (homeopath* AND safe*[Title/Abstract]) OR (homeopath* AND harm*[Title/Abstract]) OR (homeopath* AND adverse[Title/Abstract]) OR (homeopath* AND risk*[Title/Abstract]) for the safety of homeopathy

Searches were restricted by date as appropriate, but no search filters were applied to language (i.e. non-English studies were excluded manually).

Searching other resources
Further publications were manually identified using the bibliographies of articles retrieved via the electronic searches, and the “cited by other publications” facility of Google Scholar
when titles of retrieved articles were entered. Relevant publications were also searched for on specific websites:

1. CAM-Cancer (http://www.cam-cancer.org/)
4. The Society for Integrative Oncology (https://integrativeonc.org/)
7. National Health and Medical Research Council (NHMRC) (http://www.nhmrc.gov.au/)
11. U.S. Food and Drug Administration (http://www.fda.gov/)
13. U.S. National Institutes of Health: Office Of Dietary Supplements – Consumer Fact Sheets (http://ods.od.nih.gov/factsheets/list-all/)
Data collection and analysis

Selection of studies

All citations identified in the literature search were initially screened by the review author based on the publication title and abstract. Relevant publications were obtained in full-text and subsequently assessed by two reviewers (CP, PK; see page overleaf).

Consistent with the objectives and criteria outlined for the present systematic review, the following *a priori* exclusion criteria were applied to the citations amassed in the literature search:

1. Duplicate citation.
2. Wrong publication type. CAM efficacy studies that were not reviews (or, as appropriate, RCTs) were excluded. Paediatric/animal/*in vitro* studies editorials, comments, correspondence, and news items relating to efficacy or safety were excluded. Studies were also excluded if they were not fully-reported (e.g. Cochrane review, meta-analytic/systematic review or study protocols, conference proceedings, articles published in abstract form).
3. Wrong intervention. Efficacy studies that did not investigate the effect of the relevant CAM were excluded, as were those that evaluated complex intervention packages that happened to include the relevant CAM.
4. Wrong outcomes. Studies that did not include outcomes relevant to the primary objective of the review were excluded.
5. Study not published in the English language.

Data extraction

Information relevant to the present systematic review of the efficacy and safety of specific CAMs was routinely collated in accordance with NHMRC standards and levels of evidence (NHMRC, 2007, 2009). Extracted information included:

1. General study details (citation, review type/study design, level of evidence, country and setting).
2. Affiliations/sources of funds for each of the included studies.
3. Internal and external validity considerations.
4. Number and methodology of studies reviewed, or sample size of study.
5. Participant details, including key demographic and clinical characteristics.
6. Type of intervention/control.
7. Primary, secondary and other outcome variables, objective/subjective measures used, and study outcome results.
8. Length of any follow-up periods and their outcomes.
9. Limitations noted by the authors or otherwise.

Data was extracted by the review author (CP) and independently verified by a second reviewer (PK, author 2 of study 1, p.31) working in cancer research and education, with a special interest in CAM. Any disagreements were resolved by discussion between the review author and the second reviewer.

Assessment of methodological quality of included reviews and primary studies
Publications were assessed for quality using the brief 10-12 item Critical Appraisal Skills Programme (CASP) checklists for evaluating reviews and primary studies (RCTs, case-control studies), which were developed from guides produced by the Evidence Based Medicine Working Group published in the Journal of the American Medical Association (Public Health Resource Unit, 2006a, b, c, d). The CASP checklists examine 3 broad questions: (i) “Is the study/review valid?”, (ii) “What are the results?”, and (iii) “Are the results relevant and helpful to clinical practice locally?” (National Collaborating Centre for Methods and Tools, 2011). Quality assessments were performed by the review author and checked by the second reviewer.

References


Appendix E: Embracing Complementary and Alternative Medicine (CAM) for All the Right Reasons (Commentary Article Based on Study 2 – MJA InSight Online Publication)

Appendix E contains the published work of the manuscript in chapter 3, as it appears in publication online.
Carlo Pirri: Embracing CAM
(linside/2013/5/carlo-pirri-embracing-cam)
Patients should be encouraged to talk about alternative medicines ...

Lack of e-health standards "unacceptable" (/inside/2013/5/\lack-e-health-standards-unacceptable)
Electronic health records still don't have compulsory basic standards, hampering attempts to improve patient care ...

Spirometry access vital for COPD (/inside/2013/5/spirometry-access-vital-copd)
New research has highlighted underdiagnosis of COPD and the need for better access to spirometry in general practice ...

Jane McCredie: Marking patients (/inside/2013/5/jane-mccredie-marking-patients)
Can patients be identified as potential ingrates?

Steve Hambleton: Intrinsic candour (/inside/2013/5/steve-hambleton-intrinsic-candour)
Australian doctors don't need legislation to be candid with patients ...

Carlo Pirri: Embracing CAM

Monday, 25 February, 2013

Regardless of whether doctors like it or believe in it, complementary and alternative medicine is used by more than half of all Australians each year.

Update among chronically ill patients is often greater, with up to 60% of Australian cancer patients using complementary and alternative medicine (CAM) to complement standard treatments rather than as an alternative to conventional treatments.

What's worrying though, is that many patients do not talk about their CAM use with doctors — only one-third of primary care patients consult their GP and as few as 20% of cancer patients discuss it with their specialists.

There are many stunning books for patients in talking about CAM with doctors. They range from the very real prospect of receiving a negative or indifferent response, to doctors simply not asking about CAM through to the worrying belief of many patients that CAM is entirely 'natural' and safe alongside conventional treatment.

Doctors need to nurture an environment where patients can talk about their use of CAM to doctors without fear of disapproval, if for no reason other than that the prospect of their use may cause serious drug interactions with conventional treatments or adverse side-effects on their own.

A recent systematic review that I carried out sheds more light on the safety risks of CAM use in cancer patients.

The safety and efficacy of over 130 individual complementary and alternative therapies were evaluated across more than 330 meta-analytic and systematic reviews. Weighing up risk versus benefit, the top 10 therapies that cancer patients should be discouraged from using are St John's Wort, selenium, saw palmetto, vitamin D, kava, ginkgo biloba (TRO), black cohosh, shark cartilage and garlic.

Generally, herbal agents pose the greatest risk or harm to cancer patients. In particular, their use as proven alternative therapies (e.g. Celestamine) in place of conventional medicine should be strongly discouraged.

Some herbal medicines, dietary supplements, and other 'natural' therapies have toxic and potentially life-threatening effects (e.g. berberine in St John's Wort can cause vomiting and death), kava and black cohosh may cause liver problems, cannabis interacts with chemotherapy and prescription drugs (e.g. St John's Wort) potentially interacts with 75%-80% of all prescription medicines, and reduces the effectiveness of some chemotherapy drugs. Some cause complications during radiotherapy and surgery (e.g. garlic, ginkgo biloba and gingko may increase bleeding).

That said, we shouldn't dismiss all CAM interventions with the same brush as there is substantial evidence to support the safe and effective use of some interventions. Clinical trials have shown that some therapies, when used in support of conventional treatments, are beneficial in reducing symptoms or emotional distress and improving the quality of life of cancer patients.

Weighing up risk versus benefit once again, the top 10 most effective and safe therapies from my review for people with cancer are relaxation techniques, support groups led by health professionals, physical activity programs, music therapy, meditation (including mindfulness), acupuncture, massage, omega-3 fatty acids, yoga and ginger (combined with prescription antiemetics).

Generally, mind-body and manipulative-body-based therapies have the greatest potential for benefit among cancer patients. Relaxation techniques, for example, are the most effective non-pharmacological approach for the relief and prevention of depression and anxiety in patients undergoing cancer treatment.

Relaxation can also reduce nausea/vomiting, cancer-related pain and fatigue and, in respiratory cancer patients, breathing difficulties. Physical activity programs involving aerobic or resistance exercise can also be particularly beneficial for physical/emotional wellbeing and fatigue, even in metastatic cancer patients.

Patients may seek guidance about CAM therapies and medical practitioners are in the prime position to provide this. Therefore, doctors ought to be educated about CAM.

Medical schools and hospitals should integrate teaching about CAM into medical training. Doctors need to become familiar with websites and online databases that provide information about the wide range of therapies available. The Cancer Council Australia and Australasian Integrative Medicine Association are good starting points.

Cancer specialists should consider offering access to safe and effective complementary therapies (or at least safe forms of them) alongside conventional treatments through their own cancer services.

As long as complementary therapies used by cancer patients are safe and under medical supervision, where is the harm? Hippocrates once said: “As to diseases, make a habit of two things — to help, or at least, to do no harm.”

When patients don’t feel that they can talk about CAM with their doctors for fear of disapproval and doctors don’t routinely take the time to ask, is that likely to help or harm the patient with cancer? It’s certainly a question every doctor should ponder.

Carlo Rini is a research psychologist/consultant and PhD candidate based at Murdoch University, Perth. He is a working party member of the Complementary and Integrated Therapies Interest Group established by the Clinical Oncological Society of Australia.

Posted 15 February 2013
Appendix F: Cancer Patients’ Complementary/Alternative Therapy Use in Relation to Demographics & Clinical Factors (An Alternative Analysis Correcting for Multiple Comparisons using the Benjamini-Hochberg Procedure – Table A2, Study 1)

Appendix F presents an alternative version of Table 1 contained in the study 1 manuscript (chapter 2, p39). Table A2 summarises statistical outcomes for the same variables originally reported in Table 1, but uses a more complex type of statistical analysis that corrects for the large number of statistical tests (more specifically, chi-square tests) performed and the potential elevated risk of chance findings (i.e. $p$-values less than .05 indicating statistically significant outcomes that are not genuine, but rather are the product of chance).

The more complex statistical analysis (i.e. the Benjamini-Hochberg procedure correcting for multiple comparisons; Benjamini & Hochberg, 1995) was originally performed to account for these concerns, but was not reported since it produced outcomes that were no different to the simplified statistical analysis presented in study 1 (pp.37-39). Consequently, outcomes of the simplified analysis per se were reported to avoid any unnecessary confusion among the journal’s wider readership. Nevertheless, the results of the more complex analysis, using the Benjamini-Hochberg procedure correcting for multiple comparisons, are now summarised in Table A2 overleaf.

The Benjamini-Hochberg (B-H) procedure corrects for multiple comparisons by adjusting the false discovery rate. It is an approach similar to the Bonferroni correction for familywise error, but more powerful (McDonald, 2014). Briefly explained in reference to Table A2, the $p$-values derived from the chi-square tests performed for the 15 outcome variables were assigned a rank (i) from smallest to largest (i.e. 1 to 15, with the smallest $p$-value assigned a rank of $i = 1$, the next smallest a rank of $i = 2$, and so on). The $p$-value derived for each outcome variable was then compared to its B-H critical value, $(i/m)Q$, where $i$ is the assigned rank, $m$ is the total number of chi-square tests ($m = 15$), and $Q$ is the false discovery rate selected ($Q = 0.1$, a moderately high false discovery rate, was chosen as the cost of missing a false negative – i.e. missing a statistically significant outcome – was considered high; McDonald, 2014).
The largest $p$-value among the chi-square tests performed for which $p < \text{B-H critical value}$, $(i/m)Q$, is true was deemed significant (i.e. comorbid medical history, $p = .023$). Additionally, all of the $p$-values smaller than it were also deemed significant, irrespective of whether they exceeded their B-H critical value (i.e. education, $p = .016$; age, $p = .004$; treatment duration, $p = .004$).

References
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<th>CAT Users (n=59)</th>
<th>Non-Users (n=141)</th>
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<th>Rank (i)</th>
<th>B-H critical value = (i/m)Q</th>
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<td>20 (39.2)</td>
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<td>48 (28.4)</td>
<td>121 (71.6)</td>
<td>.562</td>
<td>9</td>
<td>0.06</td>
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<tr>
<td>Yes</td>
<td>11 (35.5)</td>
<td>20 (64.5)</td>
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<tr>
<td><strong>Disease Extent</strong></td>
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<tr>
<td>Localised Disease</td>
<td>5 (26.3)</td>
<td>14 (73.7)</td>
<td>.478</td>
<td>8</td>
<td>0.053</td>
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<tr>
<td>Locally Advanced</td>
<td>29 (26.6)</td>
<td>80 (73.4)</td>
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<tr>
<td>Metastatic</td>
<td>25 (34.7)</td>
<td>47 (65.3)</td>
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<tr>
<td><strong>Treatment Goal</strong></td>
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<tr>
<td>Curative</td>
<td>5 (21.7)</td>
<td>18 (78.3)</td>
<td>.686</td>
<td>12</td>
<td>0.08</td>
</tr>
<tr>
<td>Adjuvant / Neoadjuvant</td>
<td>31 (30.7)</td>
<td>71 (69.3)</td>
<td></td>
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</tr>
<tr>
<td>Palliative</td>
<td>23 (30.4)</td>
<td>52 (69.6)</td>
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<tr>
<td><strong>Treatment Received</strong></td>
<td></td>
<td></td>
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<tr>
<td>Chemotherapy + Surgery</td>
<td>21 (31.8)</td>
<td>45 (68.2)</td>
<td>.629</td>
<td>11</td>
<td>0.073</td>
</tr>
<tr>
<td>Chemoradiation + Surgery</td>
<td>17 (32.1)</td>
<td>36 (67.9)</td>
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<tr>
<td>Chemotherapy</td>
<td>10 (21.7)</td>
<td>36 (78.3)</td>
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<tr>
<td>Chemoradiation</td>
<td>11 (31.4)</td>
<td>24 (68.6)</td>
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<tr>
<td><strong>Treatment Duration</strong></td>
<td></td>
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<tr>
<td>G-6 months**</td>
<td>33 (23.7)</td>
<td>106 (76.3)</td>
<td>.004**</td>
<td>1</td>
<td>0.068</td>
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<tr>
<td>6-12 months**</td>
<td>17 (44.7)</td>
<td>21 (55.3)</td>
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<tr>
<td>&gt; 12 months**</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
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</table>

*Summary of a more complex statistical analysis of Table 1 in study 1 using the Benjamini-Hochberg (B-H) procedure. *Patient numbers do not always equal row/column total due to missing data. *Treatment duration excludes any initial surgery received prior to medical oncology presentation. **i = rank of p-value.

m = total no. of chi-square tests (15), Q = false discovery rate (0.1). *p<.05, **p<.01 by chi-square analysis of CAT users vs non-users via the B-H procedure.

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