

Accepted Manuscript

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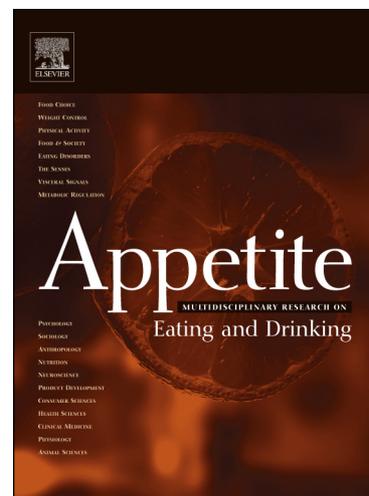
PII: S0195-6663(14)00002-6
DOI: <http://dx.doi.org/10.1016/j.appet.2014.01.001>
Reference: APPET 2019

To appear in: *Appetite*

Received Date: 25 February 2013
Revised Date: 16 December 2013
Accepted Date: 1 January 2014

Please cite this article as: Cohen, J., Laing, D.G., Wilkes, F.J., Chan, A., Gabriel, M., Cohn, R.J., Taste and smell dysfunction in childhood cancer survivors, *Appetite* (2014), doi: <http://dx.doi.org/10.1016/j.appet.2014.01.001>

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Taste and smell dysfunction in childhood cancer survivors

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Text Pages: 21

Tables: 2

Figures: 2

Funding

There was no funding provided for this study and no financial disclosures for each author

Keywords

Taste function; smell function; pediatric oncology; survivorship; food preferences; QoL

Introduction

Reduced or altered taste and smell function may occur as a side-effect of cancer therapy. This can lead to altered nutrient and energy intake. Some studies have suggested that taste and smell dysfunction can persist many years after treatment completion but this has not been previously assessed in survivors of childhood cancer. The aim of this study is to determine if taste and smell dysfunction is present in childhood cancer survivors (CCS). Food preference and Quality of Life was also assessed.

Methods

Fifty-one child cancer survivors (mean age: 19.69 ± 7.09 years), more than five years since treatment completion, (mean: 12.4 years) were recruited from the long term follow-up clinics at two Sydney-based children's hospitals. Taste function was assessed using a 25 sample taste identification test comprising five concentrations each of sweet, salty, sour and bitter tastes and water. Smell function was assessed by determining the ability of participants to identify 16 common odorants. The participants' Quality of Life was assessed using the Functional Assessment of Anorexia Cachexia scale and food preferences were assessed using a 94-item food liking tool.

Results

Taste dysfunction was found in 27.5% of participants (n=14), and smell dysfunction in 3.9% (n=2) of participants. The prevalence of taste dysfunction was higher than that seen in the non-cancer population. The child cancer survivors' appeared to "like" the

less healthy food groups such as flavoured beverages, takeaway and snacks over healthier food groups such as vegetables and salad. No correlation was found between those with a taste dysfunction and their food “likes”

Conclusion

A high level of taste dysfunction was found in CCS though there did not appear to be an issue with smell dysfunction. Further work is also needed to assess whether a taste dysfunction do play a role in the dietary habits of CCS.

Introduction

One potential side-effect of cancer therapy is reduced or altered taste and smell function [1]. Both taste and smell receptor cells rapidly turn over and are produced from dividing basal cells [2-3]. The division mechanism is sensitive to the effects of chemotherapy and/or radiotherapy [4]. The senses of taste and smell are integral in motivating a person’s food preferences [5-6] and both child and adult cancer patients commonly attribute difficulties maintaining food intake to the altered taste developed during treatment [1, 7-8]. Altered taste in cancer patients has also been associated with decreased energy and nutrient intake [9], potentially leading to nutrient deficiencies [10].

Although the taste and smell receptor cells are replaced regularly over several weeks and longer, cancer therapy can potentially lead to long term taste and smell receptor damage. This occurs due to an alteration in the structure of the receptors or a decrease in the number of normal receptor cells [10]. Long-term taste and smell dysfunction has been documented in the adult oncology population [11-12]. Patients who have received radiation therapy for head and neck cancer and those who have undergone a

Hematopoietic Stem Cell Transplant (HSCT) demonstrate taste dysfunction, after their cancer treatment, up to seven and three years respectively. [11, 13]

Survivors of childhood cancer have been shown to have poor dietary habits [14-16] and preferences for high fat foods [17]. In the general population, those with a documented taste or smell dysfunction can alter their food intake, either by compensating for the lack of flavour in foods with an increase in intake, or decreasing their intake due to a lack of enjoyment of the food [18, 9]. Taste dysfunction has also been associated with obesity in both adults and children [19-20] in the general population. The taste and smell function of childhood cancer survivors (CCS) has not been previously assessed. If CCS are found to have a taste or smell dysfunction this may be one factor influencing their food preferences and dietary intake. The aim of this study was to assess smell and taste function in this population and to determine whether this influences food preferences which could in turn influence their dietary intake. To this end, it was hypothesised that the CCS level of taste and smell functioning would be related to food liking scores.

Methods

Participants

Participants were CCS who were at least 5 years since cancer treatment completion and who attended the long-term follow-up clinics for a their yearly review, at Sydney Children's Hospital, Randwick and the Children's Hospital Westmead, Australia, between July and September 2011. Participants were excluded from participation if they were under the age of 12 years, did not speak English or were pregnant. Participants were also excluded if they had known problems with swallowing as the testing required participants to swallow a small amount of the tasting solutions. The study protocol was

approved by The Royal Alexandra Hospital for Children Ethics Committee (Approval No. 11/CHW/24) and informed consent was obtained from all participants

Demographics

Demographic information (Table 1) collected from the medical records of participants included, age, sex, cancer diagnosis, type of treatment received, time since treatment completion and current medications.

Taste Identification

Taste function was assessed by the ability to identify four different tastes – sweet, sour, salty and bitter across five different concentrations, and five samples of water. Each participant was familiarised with the test procedure by sipping a few millilitres of a moderate strength solution. Each child was familiarized with the test by being asked to sip a solution (2–3 ml of a single sample) that was moderately sweet (sucrose, 0.36 M; Sigma, Sydney, Australia), salty (sodium chloride, 0.18 M; BDH, Sydney, Australia), sour (citric acid, 0.009 M; BDH) and bitter (quinine hydrochloride, 0.0001 M; Aldrich, Sydney, Australia), respectively, and water (Nobles Ultra Pure Water, Sydney, Australia). Test tastant concentrations were prepared by dissolving analytical grade sucrose (0.05, 0.08, 0.12, 0.20, 0.32 M, Sigma, Sydney, Australia) citric acid (0.0038, 0.0062, 0.0100, 0.0159, 0.0256M BDH, Sydney, Australia) , sodium chloride (0.07, 0.11, 0.18, 0.28, 0.46 BDH) and quinine hydrochloride (0.00009, 0.00016, 0.00026, 0.00041, 0.00065M, Aldrich, Sydney, Australia) in purified drinking water (Nobles Ultra Pure Water, Sydney). For each of the 25 samples, participants were presented with a small amount of tastant solution and then asked to select one of three labelled photographs which best described the taste they had sampled. The photographs were a pictorial representation of the tastant. The photographs also contained the name of the three tastants represented e.g.

sweet, sour, salty, bitter or water. The assessor read out all three names to the participant [21] before they made their choice. The 25 tastants were presented to each participant in a random order with a 20-30 second break between the assessment of each tastant. Participants were advised to rinse their mouth with pure water between each sample.

For each tastant, participants who identified less than four out of the five concentrations for each individual tastant were considered to have impairment in their ability to detect that taste [21]. This criteria was established from normative data for children (n=232) and adults (n= 56) older than five years, using the same test procedure [21]. The same criteria for taste impairment has been used with participants with cystic fibrosis [22], chronic kidney disease [23] and healthy school children [24].

Smell Identification

Smell function was assessed by determining the ability of participants to identify 16 common odorants including Dettol™ (a common antiseptic product based on chloroxylenol), sour, baby powder, fishy, grassy, paint, flowers, strawberry, cheesy, petrol, spicy, onion, Vicks VapoRub™ (odour of mentholated topical cream), minty, orange and chocolate. The 16 odorants were diluted to a total volume of 20ml with odourless dipropylene glycol (Fluka 99% pure) and placed in individual opaque squeeze bottles which each participant was shown how to squeeze and sniff from the bottle [21]. The participants were then presented with three labelled photographs and asked to pick the one most representative of the smell they had just been presented. The photographs were a pictorial representation of the odorant combined with the name of the odorant. The test was developed not only for adults but for use with children from five years of age [21]. It was developed with children five to nine years old (n=232) and adults (n=56). Early data indicated that children from nine years of age performed similarly to adults [25]. In addition, it has been shown to have a test-retest reliability of 0.98 [24]

indicating a high level of reliability. A score of less than 13 out of a possible 16 (e.g. more than four smells incorrectly identified) was defined as an olfactory impairment [21].

Quality of Life (QoL)

The Functional Assessment of Anorexia/Cachexia Treatment QoL scale (FAACT) was used for participants greater than 18 years of age and the Pediatric Functional Assessment of Anorexia Cachexia (Peds-FAACT) used for participants less than 18 years of age. These tools are validated in this population to measure health related quality of life [26-27] and contain an additional items section on issues relating to anorexia/cachexia. This tool was used as a subjective measure of the severity of food-related symptoms such as taste change and poor appetite.

Food Liking

A 94-item food liking questionnaire was used to elicit participant's food preferences [28-29]. The questionnaire required participants to rate their attitudes towards a range of common foods on a scale of 0 to 5, with 0 = not having tried a food, 1 = hating a food, up to 5 = loving the food. The responses were then sorted according to 10 food groups; meat/fish, vegetarian foods other than vegetables, bakery goods, breakfast foods, convenience foods/takeaways, dairy foods, fruit, snacks, green vegetables/salad and other vegetables. The mean liking scores for each of the 10 categories were calculated. The higher the mean score, the more likely the food group was "liked". This data was then analysed to illustrate trends in participant's food likes.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 19 (IBM Corp., Armonk, New York). Previous research in clinical and non-clinical populations using the same taste and smell tests utilised here indicate that the majority of people score towards the high-functioning end of the scale on both of these tests [24, 30, 22]. Since the underlying distribution of these smell and taste tests are non-normal, and the comparisons between treatment groups involved small and uneven group sizes, non-parametric statistics were considered the most appropriate method of analyses for the current data [31]. Differences and associations were considered significant at $p < .05$ (2-tailed). Bonferroni corrections were applied to alpha for all subsequent post-hoc tests to reduce the chance of type I error [31]. The specific analyses used to examine each of the variables are described in the respective results sections. Where Bonferroni corrections have been applied, the relevant adjusted alpha level is indicated alongside the reported results and significance values.

Results

Demographics

Fifty-five childhood cancer survivors were approached to participate in the study of which 51 (93%) were recruited. The mean age of the participants was 19.69 (± 7.09) years and a mean of 12.4 (± 6.87) years had passed since completion of their treatment (Table 1).

Taste

Taste dysfunction was found in 14 of the 51 participants (27.5%). Of those with a taste dysfunction, five (9.8%), eight (15.7%), four (7.8%) and six (11.8%) had a sweet, sour, salty or bitter dysfunction, respectively. Seven participants had a dysfunction involving one tastant only, five had a dysfunction involving two tastants and two had a dysfunction involving three tastants. No patient had a dysfunction involving all four tastants. A Friedman's ANOVA test indicated the total scores for sweet (4.47 ± 0.67), sour ($4.45 \pm$

0.86), salty (4.61 ± 0.70), bitter (4.47 ± 0.92) and water (4.45 ± 1.12) were not significantly different ($p=0.490$).

A series of Spearman's correlation tests found no significant relationship between taste scores and the age at diagnosis ($\rho = -0.078$; $p = 0.585$) or years since treatment completion ($\rho = -0.101$; $p = 0.481$). When these variables were correlated with individual tastant scores there was a significant negative correlation between age and bitter score ($\rho = -.357$; $p = 0.01$) suggesting that as age increased participants were less able to identify a bitter taste. No other significant results were found. When the participants were separated into three treatment types (chemotherapy ($n=27$), chemotherapy + radiotherapy ($n=17$), HSCT ($n=7$)) a Kruskal-Wallis test indicated that there were no significant differences in total taste scores between the treatment types. It should be noted that the power to find differences between treatment types was limited by small group sizes, for analyses between the three treatment types the power ranged between 0.18 and 0.34.

Smell

Of the 51 participants, six participants (11.8%) were identified as having some degree of a smell dysfunction. Two (3.9%) identified only nine of the 16 odors and were classified as hyposmic (i.e. significant loss of smell function). Four of the participants were slightly hyposmic with scores of 11 and 12 out of 16 respectively. Sour and flower odorants were the least identified odorants while Vicks VapoRub™, minty and paint were identified by all the participants (Figure 1).

A series of Spearman's correlation tests found no significant relationship between smell scores and age of participants ($\rho = -0.223$; $p = 0.116$), time since treatment completion ($\rho = -0.178$; $p = 0.211$), or age at diagnosis ($\rho = -0.165$; $p = 0.248$). A comparison of

the smell scores between the three treatment groups (chemotherapy (n=27), chemotherapy + radiotherapy (n=17), HSCT (n=7)) using a Kruskal-Wallis test found a significant difference ($p=0.013$). Post-hoc Mann-Whitney tests indicated the odour identification scores for the chemotherapy-only group were significantly higher than for the HSCT group [$p=0.004$; Bonferroni adjusted $\alpha=0.0167$]. Again, it should be noted that the small group sizes limited power to find significant differences between treatment types (power ranged 0.18 to 0.34). Of the six participants with hyposmia, four of these received a HSCT transplant of whom two received total body irradiation (TBI) as part of their treatment. No other significant differences were found when comparing the treatment groups.

Food Liking

The final mean score for each food category was out of five with the higher the score, the more likely the food was "liked" (Figure 2). The data showed that the most "liked" foods were non-dairy liquids (4.0), followed by takeaway (3.84) and snacks (3.8). The least "liked" food groups were the salads and greens (3) followed by breakfast cereal (3.03), vegetarian food (3.14) and then vegetables (3.3).

Spearman's correlations indicated a significant negative correlation between smell score and liking for snacks ($\rho=-0.294$, $p=0.036$). Thus, as the smell score decreased the liking for snacks increased. In contrast, a significant positive correlation was found between smell score and salad/greens, ($\rho=0.404$, $p=0.003$), suggesting that as the smell score increased liking of salad/greens also increased. Mann-Whitney tests comparing the food liking scores between those with and without a smell dysfunction found significantly higher mean food liking scores (possible score out of five) for those without a smell dysfunction for dairy foods (2.90 vs. 3.56; $p=0.027$), fruit (2.14 vs. 3.92; $p=0.001$) and salad/greens (1.61 vs. 3.19; $p=0.0001$). No significant differences or correlations were found between the food groupings and the taste scores. The

treatment group numbers were small, therefore results should be interpreted with caution. The results of this study indicate that the differences in food liking for those with and without a smell dysfunction along with the above significant correlations provide partial support for the hypothesis that smell function is related to CCS food liking.

Quality of Life

Results from the additional concerns section of the QoL tool indicated that the participants had no significant food related concerns (Table 2). For example, the mean score for the section on "food tasting bad" was rated low. Correlation tests showed there were no significant relationships between smell and taste function (total scores) and any food-related QoL measure. Mann-Whitney tests comparing the individual QoL domains between those with a taste dysfunction and those who did not, found a significantly higher QoL score for those with a taste dysfunction in response to "My general health is improving" (3.46 vs. 2.29 $p=0.016$). There were no QoL associations found when comparing those with and without a smell dysfunction.

Discussion

The results of this study in CCS demonstrate that 27.5% ($n=14$) had some degree of taste dysfunction and 4% ($n=2$) had a significant smell dysfunction. There was an absence of relationships between taste, food liking and QoL and the modest relationship between smell dysfunction and liking for healthy foods.

The prevalence of a taste dysfunction in adult oncology patients during chemotherapy has been reported to be as high as 40% [9] using objective measures or 86% using subjective measures such as self-report [18]. In the paediatric oncology population, prevalence rates of a taste dysfunction do not exist though it has been reported to be an

issue during cancer therapy [32, 7]. A taste dysfunction during the more intensive pediatric HSCT have been reported to be around 40% [30].

The findings in this study show a high prevalence rate of taste dysfunction in survivors of childhood cancer. Some studies have suggested that taste dysfunction continues well after treatment completion [11-12] but this is the first study to assess this in a cohort of survivors of childhood cancer. There are wide variations in the prevalence rates of taste dysfunction in the general population. Taste disorders have been reported to range from 0.85% [34] to 20% [35]. The prevalence rates have been found using a wide variety of methodology for taste assessment and make it difficult to adequately compare findings. A relevant comparison of our prevalence rate of a taste dysfunction of 27% (n=14) in the CCS, is with a group of healthy, nine to 12 year old Australian children (n=432). The group of healthy Australian children exhibited a taste loss prevalence of 10% using the same taste test as used with the CCS and with the same criterion for defining taste loss [25].

Accordingly, the prevalence of taste loss of CCS is higher than the general population and is a potential undesirable outcome as a result of the cancer itself or the treatment received. The mechanism(s) for taste loss in the present group of cancer patients is unknown. Possible explanations include a reduction in the number of taste and smell receptors as a result of the cytotoxic effects of treatment; changes in the rate of turnover of receptor cells, changes induced in the structure of receptors affecting the delivery of taste and smell molecules to taste and smell receptors, or abnormalities in the reestablishment of synaptic connections at the end of cancer treatment [6].

The incidence of smell dysfunction in the present study (3.9%; (n=2)) is slightly higher than the a 1.9% found using the present 16-odour identification test with a cohort of nine to 12 year old Australian children [25]. Although the numbers are small in this study there is the suggestion that the smell dysfunction can be influenced by the type of treatment received. Four of the six participants who had a smell dysfunction underwent a HSCT of whom two received TBI. This may reflect greater and more lasting damage to the olfactory system with the more intensive treatment. Further work investigating taste function may be warranted with this group.

The results from this study indicate childhood cancer survivors appear to “like” less healthy food groups such as flavoured beverages, takeaway and snacks over healthier food groups such as vegetables and salad. These results are consistent with previous research findings with childhood cancer survivors who displayed unhealthy eating habits, such as a poor vegetable intake and a high fat and sugar intake [16, 14-15]. Despite these findings there did not appear to be any association with food likes and taste function. In partial support of the hypothesis, there did appear to be some association with a smell dysfunction and a reduced liking of dairy, fruit and salad/greens. Further work is needed to confirm whether taste or smell dysfunction is affecting CCS’s food choices.

Whilst taste and smell function does not appear to have a key role in the long term food likes of CCS, research suggests that treatment for malignancies may still have an influence on food preferences through the development of food aversions. It has been reported that the likelihood of an individual selecting a food for a second time is related to their prior experiences [33]. This may be relevant to the development of food aversions in the setting of cancer treatment as taste and smell alterations during the period of the disease and subsequent treatments coupled with symptoms of nausea and vomiting may have resulted in negative experiences during feeding [34, 10]. The effect

of food aversions may be even more pronounced in those receiving treatment for cancer at very young ages as food preferences are thought to be largely established through experiences with food in the first 3 years of life [35].

The results from the QoL tool indicate that this cohort have an acceptable QoL as demonstrated by the ratings of participants which corresponded to low levels of concern about weight and appetite. Participants did not report that "food tasted bad" despite 27.5% (n=14) of this cohort displaying some form of taste dysfunction. Furthermore, there was no association found between QoL scores and taste and smell scores. Previous studies suggest that QoL is influenced by perceived level of olfactory dysfunction rather than actual degree of dysfunction [36-37]. It may be that a similar phenomenon occurs with taste dysfunction.

Conclusion

It is concluded that taste dysfunction occurs in pediatric long term cancer survivors although no relationships were found between taste function and food likes, and taste function and QoL. It does not appear that a smell dysfunction were as prevalent though the incidence may be slightly higher than the general population. It is known that CCS have undesirable food habits therefore larger prospective longitudinal studies are needed to further understand the reasons for these poor dietary habits. Further work is also needed to assess whether taste dysfunction plays a role in these dietary habits.

Acknowledgements

The authors would like to thank Sinead Malloy and Lucy Mudge from Children's Hospital Westmead and Karen Jones from Sydney Children's Hospital for their help in recruiting the participants for this study.

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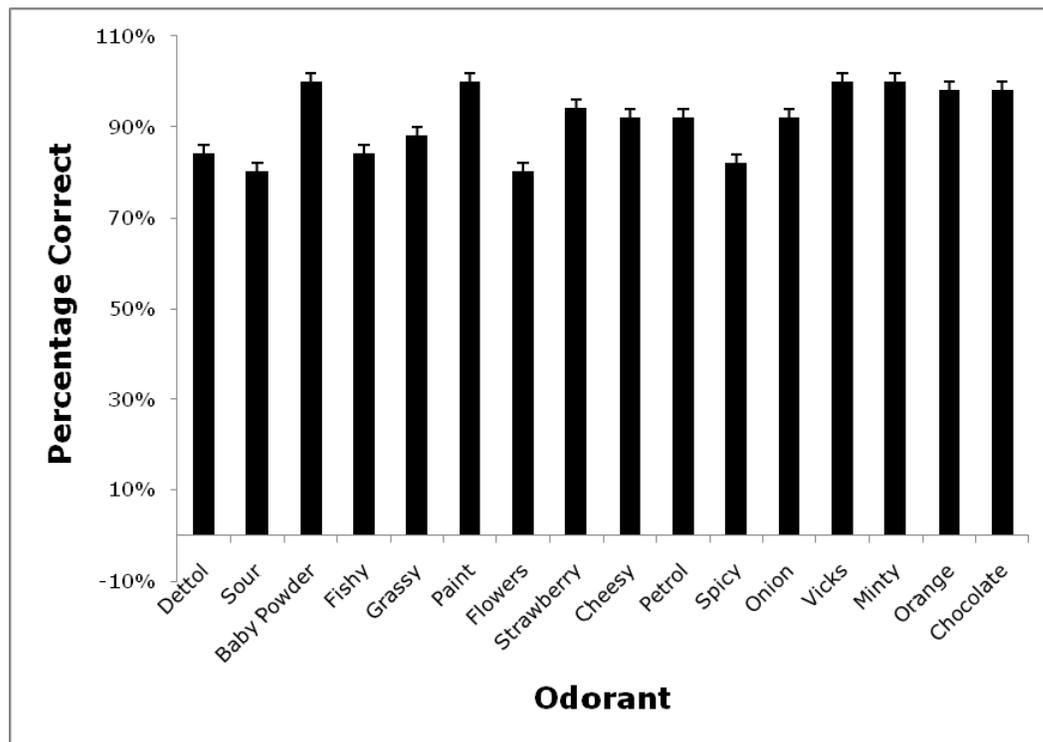
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Figure Legends

Figure 1. Percentage of participants who correctly identified each odorant

Figure 2. Mean liking scores for each food category (0 = not having tried a food, 1 = hating a food, up to 5 = loving the food).



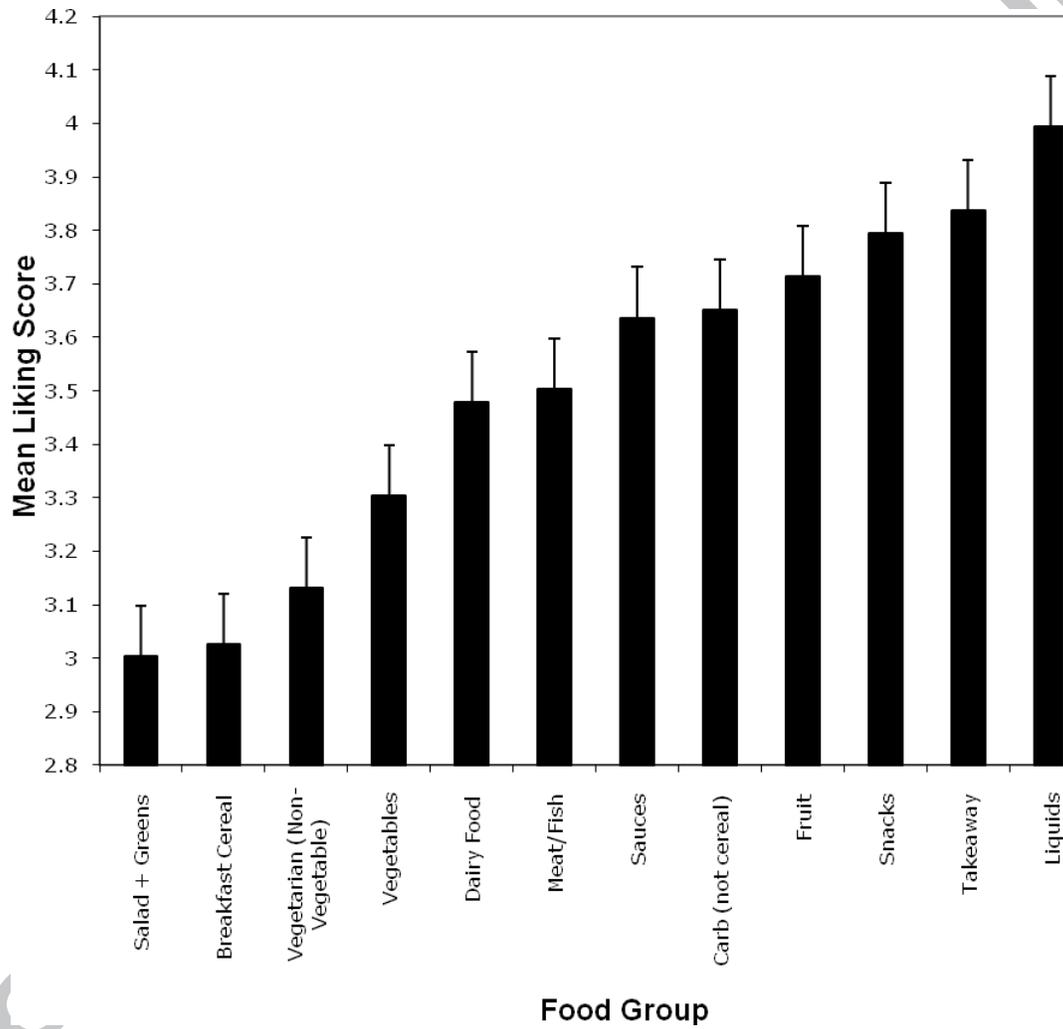


Table 1. Demographics of childhood cancer survivors

Characteristic	
Sex (male:female)	24:27
Age at assessment,	
Mean (SD)(range): Years	19.69 (7.09)(12-40)
Age at diagnosis,	
Mean (SD)(range): Years	5.27 (4.05)(0-17)
Time since treatment completion	
Mean (SD)(range): Years	12.40 (6.87)(5-38)
Cancer diagnosis (n)	
ALL*	18
AML**	1
Neuroblastoma	4
Wilms tumour	4
Rhabdomyosarcoma	3
Lymphoma	4
Medulloblastoma	2
Ewing's Sarcoma	2
Osteosarcoma	3
Other	10
Treatment (n)	
Chemotherapy	27
Chemotherapy + Radiotherapy	17
<i>Cranial Radiotherapy</i>	6

<i>Abdominal Radiotherapy</i>	2
<i>Head and Neck Radiotherapy</i>	1
<i>Other sites</i>	8
HCST#	7
<i>Total Body Irradiation</i>	4

* ALL: Acute Lymphoblastic Leukemia ** AML: Acute Myeloid Leukemia # HSCT: Haematopoietic stem cell transplant (HSCT)

Table 2. Mean score for questions in additional concerns section of the Functional Assessment of Anorexia/Cachexia Treatment QoL scale FAACT (Possible values 0 = Not at all; 1 = A little bit; 2 = somewhat; 3 = Quite a bit; 4 = very much)

FAACT Question	Mean \pm SD	Range
I have a good appetite	2.80 \pm 1.34	0-4
The amount I eat is sufficient to meet my needs	2.92 \pm 1.13	0-4
I am worried about my weight	1.33 \pm 1.43	0-4
Most food tastes unpleasant to me	0.35 \pm 0.86	0-3
I am concerned about how thin I look	0.37 \pm 0.78	0-3
My interest in food drops as soon as I try to eat	0.29 \pm 0.74	0-4
I have difficulty eating rich or "heavy" foods	0.35 \pm 0.93	0-4
My family or friends are pressuring me to eat	0.33 \pm 0.83	0-4
I have been vomiting	0.12 \pm 0.39	0-2
When I eat, I seem to get full quickly	0.80 \pm 1.32	0-4
I have pain in my stomach area	0.29 \pm 0.65	0-2
My general health is improving	2.80 \pm 1.39	0-4

Highlights

- Reduced or altered taste and smell function is a side-effect of cancer therapy
- This is the first study to assess the taste and smell function in survivors of childhood cancer
- Higher than expected levels of taste dysfunction was found in this population
- Smell dysfunction appears to influence food likes for dairy, fruit and salad/greens.