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Towards optimising nutritional intake in the spectrum of childhood cancer treatment and survival

Jennifer Esther Cohen
University of Wollongong

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**UNIVERSITY OF
WOLLONGONG**



School of Medicine

**Towards Optimising Nutritional Intake in the Spectrum of Childhood Cancer
Treatment and Survival**

**Jennifer Esther Cohen
Bachelor of Science (Nutrition)
Masters of Nutrition & Dietetics**

This thesis is presented as part of the requirement for the

**Award of the Degree of Doctor of Philosophy
of the
University of Wollongong**

December 2015

CERTIFICATION

I, Jennifer Esther Cohen declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the School of Medicine, University of Wollongong, is my own work unless otherwise reference of acknowledged. This document has not been submitted in whole, or in part, for qualifications at any other academic institution.

Jennifer Esther Cohen

December 2015

DEDICATION

To my wonderful family and to the amazing patients and families at the Kids Cancer
Centre, Sydney Children's Hospital

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To my primary supervisor, Professor Linda Tapsell, you have been inspiring me for most of my research career. You taught me my first research methods subject as an undergraduate and you have been guiding and supporting me as I complete my PhD. You are an amazing advocate for dietetic researchers and I thank you for encouraging me to be a clinician researcher.

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PUBLICATIONS

Peer reviewed journal articles in support of this thesis

Cohen J, Wakefield CE, Fleming CAK, Tapsell LC, Walton K, Cohn RJ. Exploring the views of parents regarding the dietary habits of their young cancer-surviving children. *Supportive Care in Cancer*. 2015;23(3);463-471

Fleming CAK, **Cohen J**, Murphy AJ, Wakefield CE, Cohn RJ, Naumann FL. Parent feeding interactions and practices during childhood cancer treatment: a qualitative investigation. *Appetite*. Published online January 2015

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Cohen J, Wakefield CE, Bartle J, Cohn RJ. Nutritional interventions in childhood cancer survivors. *Cochrane Database of Systematic Reviews (Protocol)*. 2012.

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Cohen J, Wakefield CE, Cohn RJ. A systematic review of interventions for childhood cancer survivors. *Pediatric Blood and Cancer*. 2013; 60(S3); 163

Cohen J, Wakefield, CE, Fleming CAK, Cohn RJ. Consequences of treatment on food preferences and dietary habits of childhood cancer survivors. *Pediatric Blood and Cancer*. 2011; 57(5); 827

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Cohen J, Wakefield CE, Cohn RJ. A systematic review of interventions for childhood cancer survivors. 45th Congress of the International Society for Pediatric Oncology, Hong King, China. 2013. (Poster Presentation)

Cohen J, Wakefield, CE, Fleming CAK, Cohn RJ. Enteral nutrition in a clinical setting: misconceptions and views. 16th International Congress of Dietetics. Sydney, Australia. 2012. (Poster Presentation)

Cohen J, Wakefield, CE, Fleming CAK, Cohn RJ. Dietary habits of child cancer survivors. 16th International Congress of Dietetics, Sydney, Australia. 2012. (Oral Presentation)

Cohen J, Wakefield, CE, Fleming CAK, Cohn RJ. Consequences of treatment on food preferences and dietary habits of childhood cancer survivors. Australasian Society for Health and Behavioural Medicine ASM. 2012. (Oral Presentation)

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Cohen J, Wakefield CE, Fleming CAK, Cohn RJ. What do parents of childhood cancer patients actually think about enteral nutrition. 43rd Congress of the International Society for Pediatric Oncology, Auckland, New Zealand. 2011. (Poster Presentation)

Cohen J, Wakefield CE, Fleming CAK, Cohn RJ. Parent attitudes to nutrition and physical activity after completion of their child's cancer treatment. Australia and New Zealand Children's Oncology Group ASM, Sydney, Australia. 2010. (Poster Presentation)

Cohen J, Wakefield CE, Fleming CAK, Cohn RJ. Parent attitudes to nutrition and physical activity after completion of their child's cancer treatment. Australia and New Zealand Children's Oncology Group Long-Term Follow-up Symposium, Sydney, Australia. 2010. (Oral Presentation)

Cohen J, Wakefield C.E, Fleming CAK, Cohn RJ. A qualitative study of parent attitudes to nutrition after completion of their child's cancer treatment. Clinical Oncological Society of Australia Annual Scientific Meeting, Melbourne, Australia. 2010 (Poster Presentation).

Cohen J, Goodenough B, Cohn RJ. Parental attitudes to their child's nutrition at completion of cancer treatment. 41st Congress of the International Society for Pediatric Oncology, Sao Paulo, Brazil. 2009 (Poster Presentation)

ABSTRACT

Childhood cancer is the second leading cause of death in Australian children, aged 1-14y. As medical advances improve, outcomes for childhood cancer patients also improve. For children with cancer, treatment occurs at an important period of growth and development, and this can affect their health as adults. In fact chronic disease such as obesity and cardiovascular disease are recognised long term problems for adult survivors of childhood cancer. With the changing landscape in paediatric oncology, the focus of nutritional therapy for paediatric oncology patients may need to shift. Decisions on nutritional management during therapy have the potential to influence nutritional management in the long term. The broad aim of this thesis was to explore the implications for Nutrition and Dietetics care in managing the needs of child cancer patients during therapy and following survival. The research was grounded in clinical practice, using an in depth case study of a specialist paediatric oncology clinic in Sydney, Australia. A number of separate but related investigations took place to address specific questions and highlight the way forward for improved practice.

The first part of the thesis confirmed the assumption of a nutritional problem in the clinic population. *Study 1 aimed to assess the dietary intake and habits of young survivors of childhood cancer early after treatment completion.* Assessment of 3-day food diaries found that 54% of young childhood cancer survivors were consuming above their estimated energy requirements. Fifty, 32% and 44% of children did not meet requirements for folate, calcium, and iron respectively. When parents of childhood cancer survivors was questioned about their child's changing dietary habits, the majority of parents found their child's nutritional intake changed dramatically during the active treatment phase. It appears that some of the dietary habits established during treatment appeared to carry over once treatment has been

completed. Parents reported young survivors of childhood cancer had a poor fruit and vegetable intake; increased consumption of "junk food" and large portion sizes. These results provided targets for nutritional interventions at the clinic for survivors of childhood cancer.

The second part of this thesis aimed to examine feeding practices during and following treatment completion. First, a Cochrane systematic review was undertaken to assess the effect of nutritional interventions in improving dietary intake to meet the dietary guidelines, in childhood cancer survivors. Three studies were found that met the inclusion criteria. One study found an improvement in calcium intake and calcium supplementation in an intervention in adult survivors of childhood cancer aimed at osteoporosis prevention. The second study found that a single group intervention improved the self-reported intake of healthy food, though there was no improvement in self-reported 'junk' food intake. The review indicated a lack of effective interventions for preventing or improving the dietary habits of young childhood cancer survivors. Because enteral feeding is often introduced in the treatment phase, *study 2 aimed to compare and contrast views among parents, patients and healthcare workers on the positive and negative aspects of enteral tube feeding (ETF)*. There appeared to be common perceptions of the purposes and impact of ETF among patients, parents and healthcare workers. Both positive (good nutrition, weight gain and decreased anxiety) and negative (physical appearance, invasive insertion procedure and comfort) aspects of ETF were discussed. There were discordant perceptions regarding the timing and type of information provided on the use of enteral tube feeding, as well as the decision making process used. This study highlighted the need for standardizing and improving the methods used for the commencement of ETF on treatment.

The third part of the thesis considered possible changes in taste and smell that might create problems with feeding after treatment. First, a literature review was conducted on taste and smell disorders resulting from cancer and chemotherapy. The review found self-reported taste and smell alterations were prevalent in upwards of 86% of cancer patients. In some adult cancer patients, taste and smell alterations continued well after their cancer treatment had been completed. Taste and smell alterations in patients with cancer appeared to increase their distress, reduce appetite and contribute towards a poor nutritional status. There was a lack of information on the taste and smell function of survivors of childhood cancer. In light of the results from the review of taste and smell issues in cancer survivors, *study 3 aimed to assess smell and taste function in childhood cancer survivors*. The study found that survivors of childhood cancer did have a greater incidence of taste and smell changes, compared to a control sample from the well population. Twenty-seven percent of survivors of childhood cancer had some form of smell dysfunction. This was considerable higher than the 10% of smell dysfunction reported in the literature for the general population, using similar methods of assessment. The incidence of smell dysfunction was 10% of the cancer survivors studied which again is higher than the one to two percent smell dysfunction reported in the general population.

In conclusion, as childhood cancer is no longer an acute condition with poor outcomes and high morbidity and mortality, it should be treated as a chronic condition. Poor dietary habits are manifesting themselves early after treatment in paediatric cancer patients. There now needs to be greater awareness of the link between the nutrition decisions made during the cancer therapy and how they may be affecting the child's nutritional intake well after cancer therapy is completed. At the very least, nutritional interventions to improve the dietary habits of survivors of

childhood cancer need to be initiated soon after treatment completion. Ideally a focus on long-term good dietary habits may need to occur during cancer therapy.

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LIST OF ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
BMD	Bone Mineral Density
BMI	Body Mass Index
CCS	Childhood Cancer Survivors
CFQ	Child Feeding Questionnaire
DEXA	Dual-energy X-ray Absorptiometry
EAR	Estimated Average Requirement
EER	Estimated Energy Requirement
EN	Enteral Nutrition
ETF	Enteral Tube Feeding
ETOC	European Test of Olfactory Capabilities
FAACT	Functional Assessment of Anorexia/Cachexia Treatment
FFM	Fat Free Mass
FM	Fat Mass
GI	Gastrointestinal
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
GVHD	Graft- Versus-Host Disease
HSCT	Haematopoietic Stem Cell Transplant
KCC	Kids Cancer Centre
MAC	Mid-Arm Circumference
NG	Nasogastric
NHMRC	National Health and Medical Research Council
NHL	Non-Hodgkin's Lymphoma
NSW	New South Wales
ONS	Oral Nutrition Support
Ph+ ALL	Philadelphia Positive Acute Lymphoblastic Leukaemia
PN	Parenteral Nutrition
QoL	Quality of Life
RCT	Randomised Controlled Trial
SD	Standard Deviation
TBI	Total Body Irradiation
THC	Delta-9-Tetrahydrocannabinol

TSF	Triceps Skin-Fold
UPSIT	University of Pennsylvania Smell Identification Test
VAS	Visual Analogue Scale
VHRLL	Very High Risk Lymphoblastic Leukemia

1 INTRODUCTION AND AIMS

1.1 Introduction

Nutritional therapy has been a recognised part of the medical management of hospital patients since the proverbial “skeleton in the hospital closet” of malnutrition was identified in the 1970s (1). The first published paper assessing the efficacy of medical nutritional therapy for childhood cancer patients, in the form of parenteral nutrition (PN), was published in 1977 (2). This study showed an improvement in weight gain with the introduction of parenteral nutrition in 41 patients. The earliest review of malnutrition in childhood cancer patients was published in 1979 (3). This review assessed the incidence, aetiology and consequences of protein-energy malnutrition and the use of medical nutrition therapy. This was the first published paper to focus on not just macronutrient deficiencies but micronutrient deficiencies in this population (3).

Nutritional therapy in paediatric cancer patients tends to focus on weight and growth based outcomes and the maintenance of normal growth and development is the primary goal of nutritional interventions (4). Algorithms for initiating nutritional supplementation are predominantly based on weight changes (5) and the suggested interventions themselves rely on commercial supplements, enteral tube feeding and parenteral nutrition (PN) (5). Reviews of nutritional concerns of paediatric cancer patients report on the use of medical nutritional therapy but rarely discuss recommendations for food intake (4, 6-9). This may be because many paediatric cancer patients find eating difficult due to the side effects of intensive chemotherapy treatment protocols (10, 11). For those who are able to eat, food choices tend to be limited (11) or they have a preference for “junk food”(12). It also appears that

parents are not concerned about their child's overall nutritional intake during their child's cancer therapy (13). The goal of both parents and clinicians working in paediatric oncology has been the prevention of weight loss through the use of a high energy diet (14).

As medical advances have improved, outcomes for childhood cancer patients have also improved. For children with cancer, treatment is occurring during an important time of growth and development and treatment at such an early stage in life has the potential to affect them when they become adults. Chronic disease such as obesity and cardiovascular disease are being recognised as long term issues in adult survivors of childhood cancer (15). Practitioners are beginning to recognise that adult survivors of childhood cancer may have poor dietary habits (16, 17), which is likely increasing their risk of chronic health conditions such as the metabolic syndrome (18).

Interestingly, there is a lack of information regarding the dietary habits of childhood cancer survivors during and early after treatment completion. This may be because the focus of nutritional interventions during cancer therapy, have been about protein and energy and not about overall nutritional intake. Information on the dietary intake of young cancer survivors will be needed to inform nutritional interventions to help reduce the risk of chronic diseases in adult survivors of childhood cancer.

This thesis focuses on paediatric patients within a single paediatric unit. This is important to me as a clinician as it enables me to make changes in clinical practice specific to the issues with my clinical population. The results from this thesis have the potential to be extrapolated to other paediatric oncology patients, both in Australia and overseas.

1.2 The position of the researcher

I currently work as the senior paediatric dietitian in the Kids Cancer Centre at Sydney Children's Hospital, Randwick New South Wales (NSW), Australia. The Kids Cancer Centre treats children who have both cancer and haematological conditions and our catchment includes Sydney metropolitan, rural NSW and the territory of Canberra. We treat between 100-120 new patients each year and have a large haemopoietic stem cell transplant program. Our transplant unit performs both autologous and allogenic transplants (cord blood, bone marrow and stem cell transplants) and the centre receives patients for allogenic transplant from the rural NSW paediatric oncology unit (John Hunter Hospital in Newcastle) and those from the Royal Adelaide Hospital in South Australia. Once patients have completed their treatment they can be followed up by the medical teams in outreach clinics around NSW and Canberra. Our centre also has a long-term follow-up clinic that reviews survivors of childhood cancer who are more than five years from treatment completion. This clinic follows these patients into adulthood.

This thesis was born from a need identified while working with paediatric patients undergoing their treatment for cancer. Although clinician researchers in the dietetics field is not common practice (19), there is an advantage in being a clinician researcher, as I have the potential to directly improve patient outcomes (20, 21). The main goal of my position as a clinical dietitian working in paediatric oncology is the prevention of treatment related malnutrition. The majority of patients are on active treatment and once their cancer therapy is finished and they no longer require intensive nutrition support, I did not have the capacity to review these patients long term. As will be highlighted chapter two, there is now a greater focus on the

survivorship issues of cancer survivors and I found an increase in the number of referrals for paediatric patients who were overweight. Many of these patients were only a few years off their treatment and had not yet started attending the long term follow-up clinic. Interestingly, there was a dearth of literature regarding the dietary habits of cancer survivors early off treatment. It has only been since I commenced work on my thesis that there has been an exponential increase in the number of publications focusing on the nutritional concerns of young survivors of childhood cancer.

A number of dietitian students from the University of Wollongong and the University of NSW contributed to parts of the research included in this PhD. Their involvement included data collection for the research presented in chapters 3, 4, 6, and 8. The involvement of the students was approved by the South Eastern Sydney & Illawarra Health Service, Human Research Ethics Committee-Northern Hospital Network and they were heavily supervised by me (Appendix 3, 7, and 8).

1.3 Research in a clinical setting

Clinical research is any research involving human subjects who volunteer to take part in the research (22). It allows the investigator to determine the best methods for preventing, diagnosing and treating disease (22). Despite the advantages of undertaking research within the clinical setting, there are inherent issues that make research in a clinical setting more challenging. Research in a clinical setting focuses on a specific population, in the case of this thesis, paediatric cancer patients. This automatically narrows the pool of potential participants, lessening the ability to achieve adequate statistical power (23).

Much of the research presented in this thesis is of cancer survivors, many of whom have completed their therapy. A large part of our population are from rural centres living an average distance of 240km from the hospital (24). Their ongoing medical follow-up occurs in outreach clinics throughout the state. This has made face-to-face recruitment difficult, having to rely on postal recruitment. Recruitment using a mail-out approach may have decreased response rates increasing the potential for recruitment bias (25). The advantage of the use of mail-out recruitment is it is likely to reduce potential for participants feeling coerced to participate in the study.

1.4 Hypothesis

Much of the research on the nutritional management of childhood cancer patients has been done in isolation, with the long-term effect of nutritional decisions during treatment not previously considered. Now that childhood cancer is considered a chronic disease, a greater focus on how nutritional therapy during cancer treatment may affect the long-term outcomes of patients is required. The central hypothesis in this thesis is that the nutritional management decisions made during treatment for childhood cancer are primarily about the short term goal of promoting an adequate energy intake to prevent under nutrition. For clinicians to optimise the nutritional management of childhood cancer patients, issues both during and after treatment will need to be accounted for.

This thesis is divided into three sections. The sub-hypothesis of each section is:

- 1) Poor dietary habits are developing during childhood cancer therapy and these are continuing once treatment has been completed.
- 2) There are areas of clinical practice that are not accounting for the potential long-term impact of nutrition decisions on survivors of childhood cancer,

specifically related to actual feeding practices during and following treatment completion

- 3) Taste and smell dysfunction may be implicated in the problem of developing healthy eating habits in childhood cancer survivors

1.5 Aims

This broad aim of the thesis was to explore the implications for nutrition and dietetics in managing the needs of child cancer patients during therapy and following survival.

The specific aims of the thesis were:

1. To identify and articulate the problem of childhood nutrition in the cancer acute care and survival (Section 1)
2. To examine feeding practices following treatment completion both in terms of dietary intakes and parental views of childhood nutrition (Section 2)
3. To specifically consider the issue of taste and smell as implicated in the problem of developing healthy eating habits in childhood cancer survivors. (Section 3)

1.6 Thesis design and methodology

This thesis is based on research in clinical practice and is a single-site case study. An in-depth analysis from data collected from a specialist paediatric service provides a useful case study of the problem in situ. The strength of this model is the ability to translate research findings into practice and to directly influence patient outcomes (20). Eck et al (1998) recommends that research in clinical practice, also known as outcomes research, should be routinely integrated into clinical practice (20).

Traditionally, clinical dietitians' continually question and assess their practice. They then search the literature to determine the answers to their questions and subsequently alter their practice. In the model proposed by Eck et al, (1998) it is the clinician's role to design and conduct their own studies to determine the answer if not available in the literature (20).

As a clinician researcher, I was able to identify the issue of the increasing need for dietary advice on chronic disease management in survivors of childhood cancer (figure 1.1). A literature review has allowed me to identify gaps in our knowledge. This has led me to design studies confirming my hypothesis, assessing clinical practice and recommending changes.

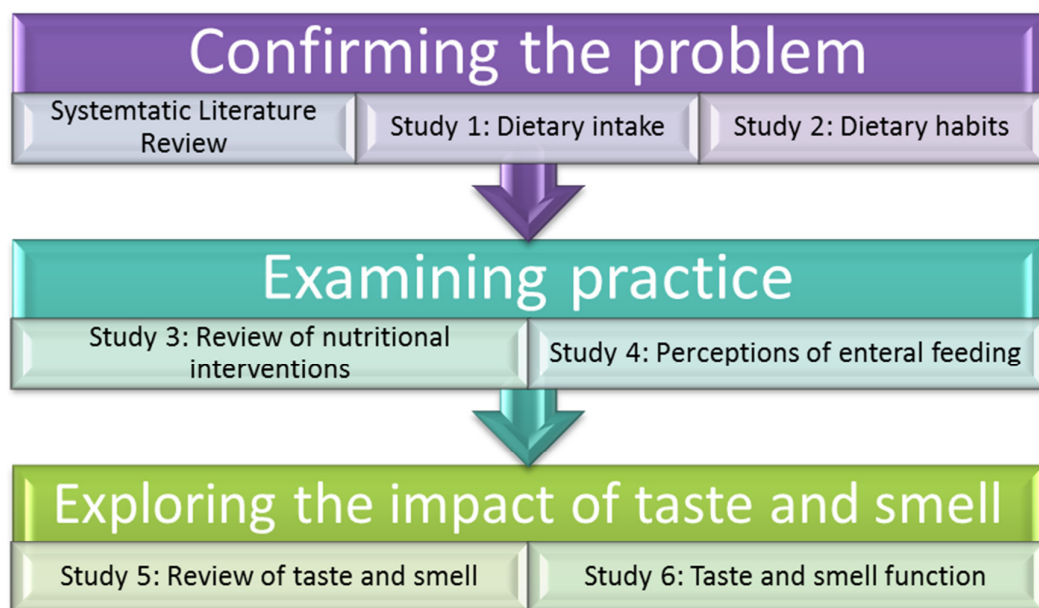


Figure 1-1 Schema of hierarchy of studies used within the context of research in practice

This thesis has used a mixed methods approach (Table 1-1) to data collection as a way of combining both quantitative and qualitative methods (26). The strength of using a mixed methods approach is that the qualitative and quantitative methods

can compensate for the limitations inherent with each model (26). A mixed methods approach also allows the researcher to consider a plethora of viewpoints, and perspectives of the cohort being studied (27). Mixed methods is particularly useful for health research because it accounts for the complexity of factors surrounding health research (28, 29). The thesis also includes both narrative and systematic reviews used to inform the quantitative and qualitative studies. Sections 1.7-1.9 provide a general background on the research methodology used in this thesis. Additional background and research methodology are presented and discussed in the individual chapters.

Table 1-1 Common research methods used in mixed methods research

Common quantitative research designs	Common qualitative research methods
Randomized controlled trials Nonrandomized studies -Case-control -Cohort study -Cross-sectional -Nonrandomized controlled trial descriptive studies -Case series -Case report -Incidence or prevalence study without comparison group	Case study Ethnography Grounded theory Narrative approaches Phenomenology Qualitative description

1.7 Quantitative research methods

Quantitative research is the most common method of research used in both medical and nutritional studies. The National Health and Medical Research Council (NHMRC) provide a framework for the hierarchy of each quantitative method in regards to its methodological strength. It allows an assessment of how likely the research method will be to answer the methodological question and the likelihood of

bias in the results obtained (30). Chapters 3 and 8 used a cross-sectional study design without concurrent controls which is level III evidence (30)

Cross-sectional study design involves the assessment of a specific group of participants at one particular point in time (31). They are used to assess prevalence and to infer causation (31). It is one of the most common methods used in empirical research (32). Data gathered from a cross-sectional study can be used to design larger cohort studies or randomised controlled trials (32). As much of the research work in this thesis was exploratory, a cross-sectional method allows hypothesis generation (30). A cross-sectional research design allows for an estimate of the prevalence of the outcome of interest (33) . In the case of this thesis, a cross-sectional study design was used to assess the prevalence of poor dietary habits and to assess chemosensory function in specific cohorts of survivors of childhood cancer. There are inherent advantages and disadvantages with this method of research (Table 1-2) which were reduced with the concurrent use of qualitative data collection with the study of the dietary intake of cancer survivors in a mixed models approach (Chapter 4).

Table 1-2 Advantage and disadvantages of using cross-sectional methodology

Advantages	Disadvantages
Inexpensive	Provides only one point in time
Ability to complete over a short time period	High risk of prevalence-incidence bias
Can assess multiple outcomes and risk factors	Unable to assess causation
Low risk of ethical issues	Cannot differentiate between cause and effect
Quick	Inaccurate with rare conditions

Adapted from Levin, 2006 (33) & Mann, 2003(31)

This thesis employed a number of research methods in the cross-sectional studies. This included dietary assessment using three-day food diaries, assessment of Quality of Life (QoL) and parental feeding behaviours using validated questionnaires, and assessment of chemosensory function using validated methods of assessment.

1.8 Qualitative research methods

The use of qualitative research in nutrition and dietetic research has been increasingly recognised as an important research method (34). Qualitative research investigates the how and why of certain behaviours (34) and is often used for hypothesis or theory generating (35). Qualitative research is also useful for assessing the perceptions about an issue from a group participants (35).

Qualitative methodology has been employed in chapters 4 and 6 using a grounded theory approach. Grounded theory provides the researcher with the ability to derive their own research questions, rather than using existing theories to structure the research (35). This thesis used semi-structured interviews to gather the data from participants. Semi-structured interviews allows an exploration of both opinion and perceptions of the participants and allows for the interviewee to probe for clarification of the answer (36) . Analysis of the interviews allowed to derive concepts and themes from the data to construct new theories(36).

Recruitment of participants in qualitative research differs from that of quantitative research sampling, with the goal to recruit a representative sample of participants (35). Maximum variation sampling was chosen in both qualitative studies in this thesis to ensure that a wide range of diagnosis groups, ages and exposure to types

of nutrition support were interviewed. Maximum variation sampling ensures that a balanced perspective of the issue is obtained (35).

1.9 Systematic and narrative review methods

A literature review allows researchers to synthesise existing research to provide a new perspective and framework on the area of interest (37). If the literature review is based on emerging topics then the literature review will provide preliminary conceptualisation of the topic. In contrast, a literature review that synthesises a large body of existing literature has the potential to reconceptualise previous models (37). There are three main types of literature reviews include the traditional quantitative and qualitative systematic reviews as well as narrative reviews (38). Systematic research reviews are a synthesis of existing literature to inform clinical practice and may or may not include a meta-analysis (39). A narrative or integrative review allows the inclusion of a range of methods including experimental and non-experimental data (39). The narrative review provides a broad perspective on a topic (38) though are at risk of bias if a systematic method of assessment is not used (39). All types of literature reviews are retrospective in nature and are at risk of both subjective and random error (40). See table 1-3 for a comparison between types of systematic reviews.

Table 1-3 Comparison of narrative and systematic reviews

	Narrative Review	Systematic Review
Question	Broad	Focused clinical question
Search strategy	Not usually defined	Well defined and comprehensive
Selection	Not usually defined	Well defined and uniformly applied
Appraisal	Variable	Rigorously performed
Synthesis	Qualitative summary	Quantitative summary (may include a meta-analysis)
Inferences	Sometimes evidence-based	Usually evidence-based

Adapted from Cook et al, 1997 (40)

Chapter 5 in this thesis uses a quantitative systematic approach to the literature review, employing the Cochrane Database of Systematic Reviews methodology (41). A Cochrane review has stringent methodology that the review must follow and undergoes several layers of peer review prior to publication, thereby reducing its risk of bias (42). A systematic review was chosen for this section to synthesise the available data in a relatively new area of study. The systematic review will be used to inform practice. Contrary to chapter 5, chapter 7 has employed the use of a narrative systematic review as a way to provide a broad summary of the topic and to identify potential gaps in the literature. The aim of the narrative review was not to inform practice.

1.10 Ethical Approval

The studies presented in chapter 3, 4 and 6 underwent both ethical and scientific review at the South Eastern Sydney and Illawarra Health Service, Human Research Ethics Committee-Northern Hospital Network prior to commencing. The study presented in chapter 8 underwent both ethical and scientific review at the Royal

Alexandra Hospital for Children Ethics Committee. All participants were provided with written study information and informed consent was obtained prior to data collection. All participants were free to withdraw from the research studies at any time.

1.11 Conclusion

Chapter 1 introduced the concepts to be explored in the thesis. It has provided information on the context of the researcher and the hypothesis and aims driving the thesis. Chapter 2 will provide a comprehensive overview of the available literature on the nutritional management of paediatric oncology patients and will further clarify the need for the research completed in this thesis.

2 NUTRITIONAL MANAGEMENT IN PAEDIATRIC ONCOLOGY

2.1 Introduction

Childhood cancer is the second leading cause of death in Australian children, aged between one to fourteen years (43). Despite these figures, childhood cancer survival rates have increased since the 1950s. Eighty-five percent of paediatric patients who are diagnosed with a malignancy, are likely to survive past five years (44). With the significant improvement in childhood cancer survival, there is now a focus on the long term consequences of treating children with chemotherapy and radiotherapy at such a young age.

In a landmark study published in 2006, 10 000 adult survivors of childhood cancer were assessed for long term health conditions. Childhood cancer survivors were three times more likely to have a chronic condition and eight times more likely to have a severe chronic condition compared to sibling controls (15). The results of this study has caused a shift in the paradigm of cancer treatment, with childhood cancer no longer considered an acute disease with high mortality, but a chronic condition associated with ongoing high morbidity.

The nutritional management of paediatric cancer patients is an important aspect of their multidisciplinary care plan and medical management. The focus has been on the prevention of under nutrition (45). Without nutritional therapy, up to 50% of paediatric oncology patients are likely to become malnourished (46). With this changing of the landscape of how paediatric oncology is viewed, the focus of the nutritional therapy of paediatric oncology patients may also need to be altered. Previously where the prevention or treatment of under nutrition has been the focus of nutritional therapy, the nutritional management of childhood cancer survivors,

from infant until adulthood needs to be considered. Childhood cancer survivors may no longer be at risk of under nutrition, but may be at risk of over nutrition or poor nutritional intake. Decisions made in regards to their nutritional management during their therapy, has the potential to influence their nutritional management in the long term.

This chapter will provide a background on the types of childhood cancers, their prognosis rates, and treatments, and how these influence the patient's nutritional management goals. The literature review will also focus on the types of nutritional therapy currently available to paediatric oncology patients on treatment and a discussion on the nutritional management of childhood cancer survivors. This information will provide a context to the thesis and allow a clear reasoning for the development of the subsequent chapters and research studies.

2.2 Overview of the medical management and outcomes of paediatric cancer

2.2.1 Types of cancers and prognosis rates

Approximately 580 children are diagnosed with cancer each year in Australia; a rate of 14 in 100 000 children (43). The prevalence of childhood cancer has remained stable in Australia in the past 12 years (43). Cure rates for this disease have increased over the past four decades. The most common form of childhood cancer, acute lymphoblastic leukaemia (ALL) has a five year survival of 80%, which is up from 58% during this time (47). Five-year relative survival for all childhood cancers combined, increased from 72.3% for the years 1983-1994 to 79.5% during 1995-2004 (44). Despite these improvements in survival, childhood cancer remains the second most common cause of death among western societies of children between the ages of 1-14 years (48), with cancer being attributed to 17% of all deaths of

Australian children aged between one and fourteen years. Unfortunately other common childhood cancers such as brain tumours and central nervous system tumours continue to have high mortality, with five year survival around 50% for some age groups (44). Table 2-1 outlines the five -year survival rates of common childhood cancers.

Table 2-1 Common paediatric cancers, their incidence, treatment and five year survival statistics

Cancer Type	Incidence	Treatment	5-year survival
Acute lymphoblastic leukaemia (ALL)	25%	Chemotherapy radiotherapy (CNS +ve) HSCT	90% (<15 years) 75% (15-19 years)
Acute myeloid leukaemia (AML)	5%	Chemotherapy HSCT	68% (<15 years) 57% (15-19 years)
Non-Hodgkin's lymphoma (NHL)	7%	Chemotherapy	88% (<15 years) 77% (15-19 years)
Hodgkin lymphoma	6%	Chemotherapy radiotherapy	90-95%
Brain and spinal cord tumours		Surgery +/- radiotherapy +/- chemotherapy	70%
Kidney tumours (Wilms' and germ cell tumours)	7%	Surgery +/- radiotherapy +/- chemotherapy	88% (Wilms' tumour)
Neuroblastoma		Surgery +/- radiotherapy +/- chemotherapy +/- BMT +/- immune therapy	87% (< 1 year) 68% (1-4 years) 52% (5-9 years) 66% (10-14 years)
Ewing's sarcoma		Surgery +/- chemotherapy +/- radiotherapy	78% (<15 years) 60% (15-19 years)
Osteosarcoma	5%	Surgery +/- chemotherapy +/- radiotherapy	76% (<15 years) 66% (15-19 years)
Rhabdomyosarcoma	3.5%	Surgery +/- chemotherapy +/- radiotherapy	67% (<15 years) 51% (15-19 years)

Adapted from the National Cancer Institute accessed 16/12/2014

2.2.2 Medical management of paediatric cancer patients

The medical treatment of paediatric oncology patients depends on the type of cancer, stage of cancer, age of the patient and the patient's prognosis. For some solid tumours, surgery is the only treatment modality recommended. For most paediatric oncology patients, chemotherapy, radiotherapy and haematopoietic stem cell transplant (HSCT) are used alone or in combination to treat the cancer. Combination therapy is used as a way of improving survival rates (49). Surgery and/or radiotherapy is used to control local disease, while chemotherapy is used to eradicate the disease (50). The goal of cancer treatment is to maximise the potential for cure, while reducing the risk of short and long term detrimental side effects (49).

2.2.3 Chemotherapy

Chemotherapy is considered the primary treatment for childhood cancers (44). Chemotherapy is the umbrella term to describe any drug that is used to treat cancer (www.cancer.org, accessed on 06/01/2015). Chemotherapy is a systemic treatment and as such, can be affective on all parts of the body. Chemotherapy is mainly administered orally or intravenously (49). Other methods of administration include subcutaneous or intramuscular injection or intrathecally (injection into the lumbar region of the spine) (49).

Chemotherapy targets actively dividing cancer cells (49), though the point of action differs for each class of chemotherapy drug (Table 2-2). Chemotherapy cannot distinguish between cancer cells and non- cancer cells that are rapidly dividing and, as such, can cause both short term and long term, potentially severe, side effects (50). The non-cancer cells that are more likely to be affected by the chemotherapy

agent include hair follicles, blood and bone marrow, gastrointestinal tract and the reproductive tract (49).

Table 2-2 Common chemotherapy agents and their mode of action

Type	How they work	Examples
Alkylating agents	Damage the cancer cell's DNA preventing reproduction	Cyclophosphamide Busulphan Thiotepa
Antimetabolics	Interfer with DNA and RNA growth of the cancer cells	6-mecaptopurine Cytarabine Fludarabine Methotrexate
Anthracyclines	Interfer with enzymes involved with DNA replication	Daunorubicin Doxorubicin
Topoisomerase inhibitors	Interfere with the cell's ability to copy DNA	Etoposide Topotecan Irinotecan
Mitotic inhibitors	Impair cancer cell reproduction	Vincristine Vinblastine
Corticosteroids	Kill or slow cancer cell growth	Prednisone Dexamethasone

Adapted from Pizzo and Poplack, 2011 (50)

Acute side effects such as nausea vomiting and diarrhoea occur during and shortly after the administration of the chemotherapy (50). Nausea and vomiting is one of the most common side effects of chemotherapy (51). Nausea and vomiting is classed as acute (within 24 hours of administration of chemotherapy), chronic (between 24 hours and five days of chemotherapy administration) or anticipatory (conditioned response before chemotherapy infusion) (51, 52).

Chemotherapy affects the blood and marrow of the patient, causing a short-term reduction in white blood cells, red blood cells, platelets (thrombocytopenia) and neutrophils (neutropenia) (51). This usually occurs seven to ten days after the start of the chemotherapy administration, and places the paediatric cancer patient at significant risk of infections and fever during this time (51). Patients are also likely to

experience side effects such as mucositis during this period. Mucositis is an ulcerative condition of the oral or gastrointestinal tract (51), leading to pain and the inability to consume and digest oral intake. Bone marrow recovery occurs approximately 21 days from the start of the chemotherapy cycle. Many of the acute side effects, such as nausea, poor appetite and mucositis have reduced by this time. Once the patient has recovered from one course of chemotherapy they are given another round of drugs and the cycle starts again. The number of cycles of chemotherapy varies between chemotherapy regimens.

Long-term side effects of chemotherapy can include secondary cancers, infertility and damage to the major organs, such as cardiovascular disease. Information on the long term side effects of chemotherapy and other cancer treatments are covered in section 2.5.

2.2.4 Radiotherapy

Radiotherapy is a treatment used to cause cancer cell death by the use of ionising radiation (49). Factors such as the age, body size, tumour type and burden, other treatment modalities and previous treatment, account for the dosing of radiation given to a paediatric cancer patient over the treatment period (49). Treatment is given over a period of one week to six weeks. The aim of radiation therapy is to target cancer cells only, attempting to minimise damage to healthy cells. This is done by data from computer tomography and magnetic resonance scans. Although treatment lasts for a short period of time, the patient is required to stay very still during the course of the treatment. This can be problematic for young paediatric cancer patients, requiring daily sedation using general anaesthetics (51, 53).

Side effects from radiation can depend on the targeted area of the radiation. Similar to chemotherapy, radiation cannot distinguish between cancer and non-cancer cells (51). Patients receiving radiation to the area of the gastrointestinal tract may experience diarrhoea, nausea or vomiting, whereas patients receiving radiation to the head area may suffer from xerostoma and nausea. Radiation is used for brain tumour patients as it is more effective than chemotherapy which is unable to cross the blood brain barrier to be carried systemically into the brain area. Side effects from radiation to the brain can also include nausea, vomiting and anorexia. Approximately 50% of radiation patients experience somnolence (extreme tiredness), though this usually resolves within a few weeks (49). Paediatric cancer patients who require daily general anaesthetics can also experience additional side effects such as nausea and vomiting. Patients who require general anaesthetics are required to fast for a portion of each day of treatment resulting in a reduction in food intake, leading to weight loss.

Radiation therapy is associated with a neurocognitive dysfunction (54, 55) and growth retardation in children (53). Growing and developing tissue is more sensitive to the effects of radiation (50) and the younger the child, the more sensitive their developing brains are to the effects of the radiation (55). Similar to the use of chemotherapy, the use of radiation is a balance between providing adequate treatment for curative intent and reducing potential long term serious side effects for paediatric cancer patients (54).

2.2.5 Haematopoietic Stem Cell Transplant

Haematopoietic stem cell transplant (HSCT) is used widely to treat children with hereditary and /or haematological disorders of both malignant and non-malignant origin (56, 57). Patients are given high dose chemotherapy +/- radiation treatment to

completely eradicate a patient's disease (56). The patient is then rescued with their own source of stem cells (autologous transplant) or a donor's stem cells (allogenic transplant) (50). This rescuing of the stem cells allows the patient to receive very high doses of anti-cancer therapy. Without the stem cell rescue the patient's own bone marrow would not recover leading to a very high risk of mortality. Patients with defective bone marrow, such as those with leukaemia, receive a donor source of stem cells (50). This is usually provided from a matched sibling, a matching anonymous donor or banked cord blood (56, 58).

As the childhood cancer patient receives very high doses of chemotherapy/radiotherapy, they are at risk of morbidity and mortality as a result of the treatment. Treatment related mortality can be as high as 20% (59). Recovery from these acute side effects can take anywhere from two to six weeks. Another significant morbidity from a HSCT is graft- versus-host disease (GVHD). This occurs when the donor stem cells (specifically the lymphocytes) consider the host's (the patient) body as foreign and starts an immune response against the host (50). GVHD can affect many body organs such as the skin, GI tract, eyes and liver resulting in severe rash, diarrhoea and liver disease (50). GVHD is classified as acute if it occurs within 100 days of the HSCT or chronic if it occurs after 100 days post HSCT. Chronic GVHD can be diagnosed up to three years after HSCT (60, 61).

Intensive conditioning regimens resulting in anorexia, nausea, vomiting, diarrhoea or mucositis (62-67) limit voluntary nutritional intake during a HSCT. This increases the risk of under nutrition (65, 68, 69). Nutrition support is especially important in the paediatric population as long periods of suboptimal nutrition can also affect growth velocity (64, 70, 71). The provision of nutrition support has become standard practice during a paediatric HSCT (68, 69, 72, 73).

The majority of the paediatric HSCT patients are well nourished at the beginning of conditioning with a reported incidence of malnutrition between 11-31% (68, 74). For most patients the goal of nutrition support during a paediatric HSCT is to maintain their nutritional status (66) and therefore to maintain normal growth patterns (64). For patients who present to transplant at risk of malnutrition, the goal may actually be to improve their nutritional status as sub-optimal pre-transplant muscle reserves are associated with a decreased height velocity post-transplant (71).

2.3 Overview of the nutritional concerns in paediatric oncology

2.3.1 Definition and consequences of malnutrition in children

Nutrition is often seen in terms of a dichotomy; under-nutrition vs. over-nutrition with the umbrella term of malnutrition being utilised to define both states. The World Health Organisation (75) defines malnutrition as

“...a pathological state resulting from a relative or absolute deficiency or excess of one or more essential nutrients....”

Under-nutrition occurs when there is a deficiency of nutrients relating to inadequate food consumption. Over-nutrition occurs when there is excessive food consumption leading to excessive calorie intake (75). Both states can lead to diminished functioning in different forms (76). The consequences of over-nutrition includes; obesity and metabolic and endocrine diseases such as heart disease, diabetes and stroke (77) whereas under-nutrition can lead to diseases such as Marasmus (75) all of which increases a person's overall mortality risk. Under-nutrition cannot only

cause nutrition-related diseases it can have other detrimental consequences on the body. These include anaemia, fatigue, apathy, extreme weakness, irritability and neurological deficits which can continue to be an ongoing issue even when nutrition is re-established (78).

Krehl, 1956 (79) described optimal nutrition as

“.....that which provides all dietary nutrients in respect to kind and amount, and in proper state of combination or balance so that the organism may always meet the varied exogenous and endogenous stresses of life, whether in health or disease, with a minimal demand or strain on the body’s natural homeostatic mechanisms”.

In Krehl’s definition he discusses meeting nutritional needs during disease (79). For many people certain diseases actually prevent the attainment of optimal nutrition, by the prevention of the consumption of adequate nutrients thereby leading to malnutrition. In such cases the nutritional issues are caused by the disease itself leading a person to be unable to consume or digest adequate nutrients or the disease state increasing their nutritional requirements. When optimal nutrition is not achieved in the setting of a disease process this can lead to poorer disease outcomes, independent of the disease state (80) by increasing morbidity as well as overall mortality (81). Clinical implications of poor nutrition include impaired immune function, delayed wound healing, and issues with physical functioning and decreasing functional status (82) all leading to increased morbidity and possibly mortality.

Defining malnutrition in children differs to that of adults due to the needs and consequences of poor nutrition on a growing child (83). The American Society of Parenteral and Enteral nutrition defines paediatric malnutrition as (83):

“An imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes.”

Malnutrition leads to increased morbidity, similar to that of adults, with the additional risk of growth stunting as a significant consequence of chronic under nutrition. This leads to a reduction in a child's weight and height velocity (84). Under nutrition in children may also cause a reduction in the attainment of appropriate developmental milestones (83).

2.3.2 Assessment of nutritional status

Assessment of malnutrition, both over and under nutrition remains difficult (83), especially when comorbidities exist, such as a diagnosis of childhood cancer. Traditional methods, such as body mass index (BMI), do provide a useful method to screen patients but do not account for issues with fluid retention (83), tumour weight (85), changes in body composition and growth failure. Body Mass Index (BMI) percentile and z scores are used as a way to standardise children across different age groups (83). A BMI percentile under the 5th indicates under nutrition, while a BMI percentile over the 85th percentile indicates a degree of over nutrition. Alternatively, a z score less than -2 indicates under nutrition and a z-score over +2 indicates over weight (86).

Percentage of ideal body weight (percentage expected weight for height) is also used as a method to define a child's nutritional status (87). A child's ideal weight is calculated using standardised growth charts, assuming their ideal weight corresponds with the weight percentile. A calculation of current weight/ideal weight x 100 is used to define their percentage of ideal body weight. The Waterlow factors are a method for classifying protein-energy malnutrition in children (87, 88). A percentage of ideal body weight greater than 110% indicates over nutrition and a percentage of ideal body weight below 90% indicates under nutrition (87).

It is important to note that a patient can remain within a healthy weight range as measured by BMI z-scores or the Waterlow factors, but still be considered malnourished. Significant reductions in body weight over a short period of time can also be a marker of malnutrition. A five percent loss of body weight over a period of one month or from pre-illness weight can also be an indicator of malnutrition (89). It is also important to consider that markers which rely on weight measurements alone to indicate a patient's nutritional status, do not take into consideration body composition (90), tumour burden (85) or fluid status (89). Using these markers of nutritional status alone could misdiagnose up to 40% of childhood cancer patients who are malnourished (90) as excess fluid or tumour burden could mask a loss of fat or skeletal muscle (7). Childhood cancer patients are likely to have a higher fat mass and a lower fat free mass compared with their peers, despite assessment of weight for height within reference ranges (91). Arm anthropometry (triceps skinfold (TSF); mid-arm circumference (MAC)) has been shown to be a reliable method for assessment of fat mass (92) but not fat-free mass (90) in paediatric cancer patients.

Other methods of nutrition assessment such as biochemical markers and physical examination can be used to provide information on a childhood cancer patient's

nutritional status. The physical examination of a patient's lower ribs, orbital fat pads, triceps skin fold, deltoids and quadriceps by a trained clinician provides a subjective assessment of fat and muscle stores (4, 93). The presence of ascites or oedema should be noted as these may influence anthropometric measures (93). Information on nutrition impact symptoms such as nausea, vomiting, taste and smell changes and anorexia can provide information on the likelihood of a poor oral intake and provide targets for dietary education and interventions.

The biochemical marker albumin which is a visceral protein had initially been used as a marker of nutritional status. The biochemical marker is an acute-phase reactant and its production by the liver is influenced by acute and chronic illness. Albumin is not considered a good marker of nutritional status in paediatric oncology patients (93). Other visceral proteins such as pre-albumin and retinol-binding protein have shorter half-lives (4) and may be a better indicator of recent protein stores (93). The cost of these tests can be prohibitive (93) leaving clinicians to rely on anthropometric measures and physical examination to provide an assessment of nutritional status.

2.3.3 Prevalence of malnutrition

Childhood cancer patients with solid malignancies, and patients with advanced cancer are at risk of under nutrition (94) before treatment has commenced. Prevalence may be as high as 25% of all patients diagnosed (94). The prevalence of under-nutrition for childhood cancer patients during treatment has been suggested to be anywhere between six to 50% of patients (6), while the incidence of malnutrition amongst children with metastatic disease approaching the upper end of this range and may be as high as 40% (14). Much of the literature on prevalence rates of malnutrition in paediatric oncology were assessed in the 1980s and 1990s using weight based assessments such as BMI z-scores. Treatment regimens and

protocols have changed since then, though there remains very little literature on the prevalence rates of malnutrition based on modern day protocols. There also remains no uniform definition of malnutrition (46) to enable comparison between prevalence studies. A recent systematic review of the literature suggests a prevalence of under nutrition for leukaemia patients of between 0-10%, 20-50% for neuroblastoma and 0-30% for other malignancies (46). These figures took into account studies that not only used weight as a measure of under nutrition, but studies that used other measures of under nutrition such as body composition and dietary intake.

Recent studies have looked at the change in body composition of childhood cancer patients over the course of cancer therapy based on measurements of weight/BMI changes. The majority of these studies focused on patients with ALL, finding increasing BMI z-scores over the course of treatment (95, 96). A recent study assessed body composition changes over the course of intensive paediatric cancer patient's treatment. Patients with haematological disease and solid tumours did have a reduction in BMI and fat free mass (FFM) during the initial phase of their treatment. BMI z-scores and fat mass (FM) appeared to increase over the course of the treatment, relating to the use of intensive nutrition support, mainly tube feedings (97).

2.3.4 Aetiology of malnutrition

The primary aetiology of weight loss is the inability of childhood cancer patients to consume adequate nutrients to meet their requirements (98). The reason for this is multi-factorial, relating to both affects from the disease itself and the treatment of the disease.

2.3.5 Inflammation & cachexia

Cachexia is a term to describe a state of depletion (99) seen in cancer patients (100), characterised by anorexia and weight loss (100). There is a distinct difference between weight loss and patients in a cachectic state. Weight loss, due to insufficient intake, is predominantly characterised by a reduction in fat mass and can be reversed with an improvement in nutritional intake or adequate nutritional support. In contrast, the weight loss seen in patients with cachexia predominantly involves a reduction in skeletal muscle mass (101) with or without a loss in fat mass (102, 103). These changes are related to an inflammatory response mediated by pro-inflammatory cytokines (100) resulting in a difficulty in reversing malnutrition using traditional methods of nutritional support (101, 104) leading to functional impairment (103).

2.3.6 Altered substrate metabolism

Fat, protein and carbohydrate metabolism appears altered in childhood cancer patients (6, 98) causing a loss FFM as well as FM resulting in weight loss and under nutrition (Table 2-3) (105).

Table 2-3 Altered substrate metabolism and the consequences

Substrate	Alteration in metabolism	Outcome
Protein	Increase muscle catabolism Decreased muscle synthesis Increased protein turnover	Skeletal muscle atrophy Hypoalbuminemia
Fat	Increased free fatty acid turnover Increased lipid breakdown Decreased lipogenesis	Marked wasting of body fat Raised plasma lipid
Carbohydrate	Increased gluconeogenesis Increased use of cori cycle Abnormal insulin response	Decreased glucose intolerance Higher energy cost to metabolise glucose

Adapted from Picton (98), Tisdale (101), Ladas (4), Bauer (7) & Andrassy (6)

2.3.7 Altered energy metabolism

The body's usual response to starvation is to conserve energy by decreasing energy expenditure (6). In adult patients with cancer, energy expenditure has been shown to increase, though this appears to be cancer specific and more likely in patients with certain solid tumours (106). Measuring energy expenditure in children has proven difficult and the studies assessing energy expenditure in young cancer patients have been limited (7, 46, 98). A recent systematic review of the literature found contradictory results regarding energy expenditure in childhood cancer patients (46). There is some suggestion that childhood cancer patients with solid tumours had higher energy expenditures at diagnosis (98). This may be related to the tumour burden.

2.3.8 Cancer and treatment related side-effects

Factors such as lethargy, pallor and nausea as a result of the disease process can lead to anorexia and weight loss prior to diagnosis (46). These symptoms are often used for a differential diagnosis (94). Poor oral intake is a common among paediatric oncology patients once treatment has commenced. As discussed in section 2.2.3, cancer therapy such as chemotherapy targets rapidly dividing cells (7) resulting in symptoms such as nausea and vomiting (10) and mucositis (107). These symptoms lead to prolonged periods of anorexia (108). In a meta-analysis of symptoms experienced by paediatric oncology patients, the prevalence of anorexia was 40% (107). Taste and smell changes have also been implicated as a factor in reducing or changing food intake in paediatric cancer patients (109).

Fatigue is commonly described in paediatric cancer patients (10, 107). Fatigue is associated with an increase in sleep as an energy conservation technique, (107) indirectly reducing a patient's food intake. Another consequence of fatigue is a

reduction in physical activity, leading to a reduction in FFM (110), contributing to a patient's risk of under nutrition.

2.3.9 Consequences and outcomes of malnutrition in paediatric oncology

Under nutrition in the paediatric hospital setting has been shown to be associated with an increased length of hospital stay as well as a reduced QoL (111). Specific consequences of under nutrition for paediatric oncology patients include a reduced treatment tolerance and increased treatment side-effects, potentially leading to poorer outcomes (6, 14). Recent literature suggests that under nutrition in paediatric patients is associated with increased infections and increased mortality (112-114), and this is likely independent of disease severity (115). Malnutrition in children reduces the absorption of chemotherapy (116) and may be one explanation of poorer outcomes in underweight patients (114). Other suggested mechanisms include an increased susceptibility to infections from hormonal changes (117).

Acute and chronic under nutrition can also have detrimental effects on a developing child as childhood is a significant time of growth and development. Acute under nutrition (less than three months in duration) can cause lean body mass depletion (83). Chronic under nutrition (greater than three month's duration) can cause growth stunting (84) and cognitive/developmental delay (83). For childhood cancer patients, whereby cancer therapy can take between up to two years to complete, their risk of extended periods of poor nutrition, in the absence of nutritional support can potentially lead to long term issues with growth and development.

Much of the focus on the literature regarding the consequences of poor nutritional status has focused on the detrimental effects of under nutrition in the paediatric oncology population. New research is showing that being overweight, especially at

diagnosis, may also be associated with morbidity and mortality in cancer therapy (114, 118). It has also been suggested that overweight patients undergoing a HSTC have poorer prognosis than their normal weight peers (119) and higher treatment related mortality (120). A recent study of over 400 survivors of childhood cancer found that obesity at diagnosis was an independent predictor of relapse in child above the age of 10 years (118). This did not appear to be a linear relationship as patients who were underweight at diagnosis also have a poorer event-free survival than their normal weight peers (114, 118).

Mechanisms for the association between over nutrition and a poor prognosis remain unknown. It has been suggested that obesity alters drug deposition decreasing the effectiveness of the chemotherapy treatment (119), but the reasoning may be more complex. Growth factors and lymphokines which are produced by adipose tissue may change the effectiveness of anti-cancer therapy (118).

2.4 Nutritional management in paediatric oncology during therapy

2.4.1 Recommendations for the timing of nutritional interventions

Nutritional therapy has been established as an integral part of paediatric cancer therapy to ensure normal growth and development (4, 8). The three primary methods for preventing or reversing under-nutrition include oral nutrition support (ONS), enteral nutrition (EN) and parenteral nutrition (PN). Ideally the prevention of malnutrition should be the goal of any nutritional intervention (4, 121), yet there remain no standardised criteria for initiation of nutrition support (7, 122). Table 2-4 indicates criteria suggested for nutritional implementation. Algorithms, providing criteria for nutritional interventions, have been shown to improve the consistency of

the nutritional management of paediatric oncology patients (5, 123), yet they are not routinely used.

Table 2-4 Recommended criteria for initiation of nutrition support

Anthropometric measure
<p>>5% loss of body weight</p> <p><90% of ideal body weight</p> <p><5th BMI percentile</p> <p><5th TSF percentile</p> <p>A decrease in weight down two percentiles</p>
Biochemistry
<p>Serum albumin #3.2 g/dL (in the absence of recent acute metabolic stress within the last 14 days).</p>
Clinical measures
<p>Anticipated gut dysfunction of > 5 days</p>
Dietary intake
<p><70% of their estimated requirements for oral intake</p>

Adapted from Rickard et al, 1986 (8)

Certain diagnosis groups and the subsequent treatment protocols used, places patients at a higher risk of nutritional depletion. (Table 2-5)

Table 2-5 Paediatric oncology diagnosis and their nutritional risk

High nutritional risk disease
<p>Advanced diseases during initial treatment</p> <p>Stage III & IV neuroblastoma</p> <p>Pelvic rhabdomyosarcoma</p> <p>Ewing's sarcoma'</p> <p>Some non-Hodgkin's lymphoma</p> <p>High risk leukemia (AML*, VHRALL**, Phi+ ALL***)</p> <p>Medulloblastoma</p> <p>Multiple relapse leukemia</p> <p>HSCT</p>
Low nutritional risk disease
<p>Standard risk ALL\$</p> <p>Non metastatic solid tumours</p> <p>Advanced diseases in remission during maintenance treatment</p> <p>Wilm's tumour</p>

Adapted from Rickard et al, 1986 (8); Bowman et al, 1998 (5); Bauer et al, 2011 (7)*
 AML: Acute myeloid leukaemia; VHRLL: Very high risk acute lymphoblastic leukaemia; Phi+ ALL: Philadelphia positive acute lymphoblastic leukaemia; \$ ALL: Acute lymphoblastic leukaemia

2.4.2 Oral nutrition support

Oral nutrition support involves the manipulation of the oral intake to provide the patient with additional nutrients by consuming nutrient-dense foods (14). The use of specialty drinks and supplements containing a concentrated source of nutrients that

can act as a meal replacement can also be used (14). Oral nutrition support also involves counselling on strategies for increasing oral intake when suffering the side-effects of cancer treatment. The literature suggest that oral nutrition support be initiated if patients have lost as little as five percent of their body weight (6, 124).

Oral nutrition support is typically the preferred first step for preventing malnutrition in children (4) as it is the least invasive method of nutritional supplementation (125) and is therefore preferred by the patient group, However success with the use of this form of nutritional supplementation for high risk paediatric oncology patients is generally poor (14), and more aggressive nutritional interventions are indicated.

Success with ONS requires the childhood cancer patient to have the ability to ingest food in a sufficient enough quantity that by adding additional energy to the food already consumed, their overall energy intake will be sufficient enough to meet their requirements (12). Oral supplements are also generally not tolerated in this patient group. Earlier published work by our centre suggests that fresh milk based supplements are preferred to other high energy supplements recommended for this patient group (ref). Side effects associated with cancer therapy such as mucositis, nausea (126), taste changes, pain and food aversions (127) preclude patients from being able to consume or tolerate adequate oral intake (14) and may also appear to change patients food preferences. These food preferences do not appear to be standardised across all patients but vary from patient to patient (126). For many childhood cancer patients, consuming an adequate oral intake is impossible (126).

Another factor to consider when choosing ONS as a method of nutritional supplementation is the longer term consequences of pushing food via the oral route when children are undergoing cancer therapy. Food aversions are a common in

both children (126) and adult cancer patients (128). Food aversions can occur when food is consumed while having negative experience (129). Food aversions are also associated with a higher level of parental pressure to eat (130). Recent work at our centre on the feeding practices that parents used during their child's cancer treatment revealed negative feeding practices. These included pressuring their child to eat, offering nutrient poor food rewards and non-food rewards (131). Many childhood cancer patients are at an age where long term feeding patterns and habits are being established. Food aversions to certain foods may continue well after the child has completed their treatment for cancer and influence their long term food preferences.

2.4.3 Enteral nutrition support

For patients who cannot maintain an adequate nutritional status via the oral route, use of EN is recommended (4). EN is the provision of nutrition in a liquid form, via a tube into the gastrointestinal (GI) tract, usually the stomach, duodenum or jejunum (47). This can be done using a silastic feeding tube which is inserted via the nose and fed through the oesophagus to the stomach or duodenum. A gastrostomy can also be used to provide EN. This method uses a tube inserted directly into the stomach, or jejunum, either surgically or endoscopically. Childhood cancer patients who receive tube feeding use formulated liquid supplements that get infused with a pump into the tube. The patient can also be given the feeds during the day via a pump or with the use of gravity.

EN has been shown to be effective in promoting weight gain in paediatric oncology patients, (132-134) especially when used prophylactically (135, 136). Similar to ONS, absorption of nutrients continues through the gastrointestinal tract. Enteral nutrition is associated with a reduced risk of bacterial translocation and maintenance

of the integrity of the GI tract when compared with use of PN alone. (137). The use of tube feeding also allows easier administration of medications and fluids (6).

Many patients also consider the tube a visible sign they are sick and therefore there is concern regarding altered body image (137). Gastrostomy feeding has been recommended for use when patients are likely to require long-term feeding during their cancer treatment (138). The use of a gastrostomy for paediatric cancer patients has been shown to be safe (136). A gastrostomy can also be hidden under the patient's clothes which is seen as an advantage for patients (137).

2.4.4 Parenteral nutrition support

Parenteral nutrition is an alternate form of nutritional intervention that can be used to prevent or reverse malnutrition in the paediatric oncology setting when this cannot be achieved using the oral or enteral route (7, 139). PN involves the intravenous administration of a solution containing a balanced mix of essential and non-essential amino acids, glucose, fatty acids, electrolytes and micronutrients (47). Ideally PN infusion should be via the central line to meet the nutrient needs of childhood cancer patients (4). Most children undergoing chemotherapy have a central line inserted for chemotherapy, making infusion of PN accessible (140).

PN has been used widely in the paediatric oncology setting (122), especially those undergoing a HSCT (67, 69, 141). High dose chemotherapy regimens may result in gastrointestinal complications such as mucositis, enteritis and typhlitis preventing nutrition being tolerated via the enteral route (50). PN is associated with a higher risk of infective complications (139) bacterial translocation (137) hyperglycaemia and hepatic stenosis (142). It is not recommended that PN be administered at home, resulting in longer hospital stays for patients requiring PN.

Issues and concerns with the implementation of enteral and parenteral nutrition

A survey of nutritional practices in North American paediatric oncology centers, found no standardised method of nutritional supplementation to prevent or reverse under-nutrition in paediatric oncology patients (143). A recent Cochrane review comparing EN with PN in the paediatric oncology setting concluded that there is inadequate evidence to allow recommendations for the best form of nutrition support. (144). The review concluded that PN may improve nutritional status in well-nourished paediatric patients compared with EN (144) but these findings are not replicated with malnourished patients. Due to a high risk of infective complications (139) associated with using PN, the literature suggests that the use of EN should be considered before using PN for nutrition support (5, 135, 137). In reality, these recommendations are not always being implemented in a clinical setting (143).

Reasons for the choice of PN being chosen over EN appear multifactorial. A recent study of paediatric oncology patients, and their parents, suggests that the perceived discomfort of EN influences patient/parent decision to allow EN to be used (145). There is also suggestion that EN is more likely to be initiated in younger patients (< 6 years) (135). The healthcare team's recommendations influence the initiation of EN (145). In non-oncology settings, such as paediatric patients with developmental delay, it appears that timing of the initiation of EN may also be influenced by the views and support of the medical teams (146, 147). Literature also suggests that parents use EN as a threat to get their child to eat (131), thereby potentially exacerbating the negative views of EN with the childhood cancer patients.

2.5 Nutritional management in paediatric oncology after therapy completion

The majority of the literature focuses on the management (both medical and nutritional) of childhood cancer patients during the active phase of their treatment. In the last 10 years, there is a shift in focus, and the long term consequences of giving cancer therapy to children at a young age have been studied. In a landmark paper published in 2006, the health status of 10 000 long term survivors of childhood cancer was compared with sibling controls. This study showed that childhood cancer survivors have a relative risk of developing a chronic condition of 3.3 and a relative risk of a severe or life-threatening condition of 8.2 when compared with their siblings (15). Female sex and older age at diagnosis are independent risk factors for developing chronic conditions (148). These chronic health conditions include (but are not limited to) secondary cancers, endocrine disorders, renal dysfunction and severe musculoskeletal problems. However, it may be many years before patients' display these conditions which tend to worsen over time (149).

Specific chronic health conditions of long-term survivors that have the potential to be managed by lifestyle factors include osteoporosis, metabolic syndrome, endocrine disorders and cardiovascular disease (150). Adult survivors of childhood cancer have a greater chance of being diagnosed with the metabolic syndrome than healthy controls(151). There prevalence of the metabolic syndrome in childhood cancer survivors may be as high as 30% (18). Yet many adult survivors of childhood cancer do not meet guidelines for fruit and vegetable intake, consume excessive fat and have an inadequate calcium intake (17, 152). Adult, survivors of childhood cancer, diagnosed with metabolic syndrome, are 2.2 more likely to have poor diets than those without the metabolic syndrome (18). This is independent of disease type and treatment. Long-term survivors report barriers to consuming a healthy diet that

include taste preferences for higher fat foods and the lack of availability of healthier foods (153). They may also be unaware of their risk of chronic disease (150), lessening the motivation to change their lifestyle. As childhood cancer survivors are already at a higher risk of long-term metabolic complications as a result of their cancer therapy, poor nutritional intake may be exacerbating this risk.

2.6 Role of the dietitian in paediatric oncology

The role of the dietitian in the clinical management of paediatric oncology patients has focused on the prevention and treatment of under nutrition during cancer therapy. The goals of nutritional interventions have focused on ensuring adequate energy and protein to prevent or reverse under nutrition, potentially at the detriment of good nutrition principles. The dietitian must also balance the recommendations from the literature regarding the initiation and type of nutrition support recommended with the realities of working with sick children and their parents.

For many parents, the more aggressive forms of nutrition support, such as enteral nutrition, are seen as a last resort and as such parents are tending to force their child to consume meals or using the more invasive forms of nutritional supplementation as a threat to encourage eating. In turn, clinicians are encouraging paediatric oncology patients to “consume whatever they liked,” as a way of preventing the child from losing weight. The reality of intensive cancer therapy is that most patients with a high nutritional risk diagnosis are unable to maintain their nutritional status using food and supplements alone.

Paediatric oncology used to be considered an acute disease with poor short-term outcomes. For patients who were “cured” there was no focus on the long term

morbidity associated with a cancer diagnosis at such a young age. Since cure rates have increased, there has been a shift of thinking to realising that cancer is now a chronic disease. The goal of treatment is to provide cure without causing long term harm. It appears that nutritional recommendations have been slower to shift the paradigm. Childhood cancer survivors are at a greater risk of lifestyle diseases such as diabetes, obesity, osteoporosis and metabolic syndrome. The literature also shows that adult survivors of childhood cancer are not consuming diets that would help to reduce the risk of these diseases, yet there remains a dearth of literature regarding the dietary intake and habits of younger cancer survivors.

2.7 Contribution of this thesis

The literature review in this chapter provided a context for the placement of this thesis. The concepts of malnutrition in childhood cancer and the goals of nutritional therapy were introduced. The recent focus by clinician working in paediatric oncology on the impact that cancer therapy has on the lives of childhood cancer survivors and the concept that clinicians need to maximise cure while minimising harm was introduced. This thesis aims to explore the impact that cancer therapy has on the dietary intake of childhood cancer survivors. Contrary to the focus of previous work on the nutritional management of childhood cancer patients in which protein and energy has been the primary outcome, this thesis will explore childhood cancer patients' nutritional intake based on their diet as a whole.

The studies in this thesis were designed using a cumulative approach, with each new study being informed by the results of other studies. The first phase of work in this thesis focuses on determining the dietary intake and habits of childhood cancer survivors early off treatment. The second phase of the thesis then explores

nutritional interventions both on and off treatment. The thesis assesses the nutritional interventions that may be available for young cancer survivors and specifically determines the reasons for the inadequate use of enteral tube feeding as a method of nutritional intervention. The third phase of the thesis explores factors that may be responsible for the poorer dietary habits of older cancer survivors, specifically taste and smell changes.

3 DIETARY INTAKE AFTER TREATMENT FOR CHILD CANCER SURVIVORS¹

Chapter 2 provided the background to the medical and nutritional management of childhood cancer patients. The majority of research has focused on the nutritional management of cancer patients during their cancer therapy. With the improvement in survival rates, and an increasing number of adult survivors of childhood cancer, childhood cancer therapy can no longer be considered an acute disease. There is evidence for poor dietary intake in adult survivors of childhood cancer but there is a dearth of information regarding the dietary intake of young cancer patients early after treatment completion. Part 1 of this thesis will examine the hypothesis that there is significant nutrition related problems in childhood cancer survivors. This chapter will report on the findings of a study assessing the dietary intake of young cancer survivors early after treatment completion. This study has been published in *Pediatric Blood and Cancer*.

3.1 Introduction

Childhood cancer survivors have a relative risk of developing a chronic condition of 3.3 when compared with their siblings (15). These conditions include, but are not

¹ This chapter has been published in the following peer reviewed journal:

Cohen J, Wakefield CE, Fleming CAK, Gawthorne R, Tapsell LC, Cohn RJ. Dietary intake after treatment in child cancer survivors. *Pediatric Blood and Cancer*. 2012;58(3):752-7
JC designed the study, JC, CF & RG contributed to data collection and analysis and JC, CW, RC & LT contributed to the manuscript.

The key findings have been peer reviewed and presented by JC at the 16th International Congress of Dietetics, COSA 37th Annual Scientific Meeting, the Australasian Society for Health and Behavioural Medicine ASM & the ANZCHOG Long-term Follow-up Symposium.

The abstracts included in the following publications:

Cohen J, Goodenough B, Cohn RJ. Parental attitudes to their child's nutrition at completion of cancer treatment. *Pediatric Blood and Cancer*. 2009; 53 (5); 853

limited to, endocrine disorders, metabolic disorders, cardiovascular disease and pulmonary disease (154, 155). Specific conditions such as obesity, type II diabetes and osteoporosis have the potential to be managed by lifestyle interventions (156). Even though behaviours such as consuming a healthy diet and/or maintaining adequate physical activity could prevent or lessen the impact of some of these chronic diseases (157) health-protecting behaviour prevalence is similar to the general population (150, 158, 159). Many adult survivors of childhood cancer consume high fat diets, do not meet guidelines for fruit and vegetable intake, and have an inadequate calcium intake (16, 17), though their overall energy intake does not appear excessive (153). Long-term survivors report barriers to consuming a healthy diet that include taste preferences for higher fat foods and the lack of availability of healthier foods (153).

The treatment completion period of the cancer trajectory has been described as a teachable moment (152). Young patients who have recently completed treatment may be the more appropriate target group in whom to intervene and develop preventative strategies. This is especially the case as younger age at diagnosis has been documented as a risk factor for these chronic conditions, especially obesity (160). There is limited information about the dietary intake of childhood cancer survivors (CCS) who have recently completed their treatment and almost no data examining how this may influence lifelong dietary practices and long-term metabolic and endocrine outcomes (161). A small number of studies have assessed the dietary intake of childhood cancer patients during treatment with varied findings (162-164), though this is unlikely to be generalisable to patients who have completed treatment.

For dietary intervention plans to be effective in a young population, parental involvement is important (150). It is known that parents of children not affected by cancer strongly influence their child's eating patterns, playing a pivotal role in the development of their child's food preferences and energy intake, (165) and playing a role in long-term feeding practices (166). Evidence suggests that parents who restrict their child's dietary intake when they are young may place their child at risk of obesity when they are older as they may not develop the skills necessary to regulate their own intake (167, 168). This is more likely to occur in parents who are highly invested in their child's health (169). Only one study has specifically examined parental influences on child cancer patients' health behaviours, reporting that many parents lessen their control over their child's eating (and their other lifestyle behaviours) during their child's cancer therapy (13). What is unknown is what parenting styles are used at completion of their child's cancer therapy and whether these have the potential to place their child at risk of nutritional issues in the future.

The aim of this study was to assess the weight status, dietary intake and associated parent feeding practices of a cohort of childhood cancer survivors less than 13 years of age and less than 5 years after treatment completion.

3.2 Methods

3.2.1 Study participants

The participants were parents and/or carers of CCS who were: a) less than 5 years post treatment for any type of cancer; b) under 13 years of age; and c) attending the Centre Kids Cancer Centre (KCC) at Sydney Children's Hospital, Australia for follow

up. Eligible participants were identified using KCC records and posted a study invitation, a participant information sheet and an opt-in card. Participants were excluded if they had insufficient English language skills to complete the questionnaire. Participants were recruited between the June 2009 and June 2010. The study protocol was approved by the South Eastern Sydney & Illawarra Health Service, Human Research Ethics Committee-Northern Hospital Network. Written informed consent was received.

3.2.2 Demographics

CCS-related demographic data including gender, age, cancer diagnosis, and dates of diagnosis and completion of treatment were compiled from medical records. Historical data on anthropometric measures at diagnosis was also collected. CCS weight and height were used to calculate BMI, using the formula: weight in kilograms divided by height in meters squared. To allow for comparisons across age groups, BMI percentiles were calculated using Epi Info™ (Version 3.5.1, 2008; Centres for Disease Control and Prevention, USA). A BMI percentile of <5th percentile was classified as underweight, those between the 5th-84th percentile were classified as a healthy weight, those between 85-94th percentile were classified overweight and >95th percentile were classed as obese (170).

3.2.3 Child Feeding Questionnaire (CFQ)

The 31-item CFQ (Appendix 4) was used to assess participant beliefs, attitudes and practices about their child's feeding (171). Mean CFQ item scores were calculated for each of the seven subscales which fall under 2 categories (Table 3-1) Risk factors and concerns; 2) Control in child feeding, attitudes and practices (171). Response options are scored on a 5-point likert scale (1='disagree' to 5='agree').

Scores in each of the seven subscales were averaged. Higher mean scores in each subscale indicated higher levels of parental concern and control over child feeding. The CFQ has been validated for use in parents of children aged two up to the end of primary school age (171).

Table 3-1 Child Feeding Questionnaire (CFQ) sub-scales and operational definitions

Sub-scale	Operational Definition	Example
Perceived feeding responsibility	Extent in which parents takes responsibility for feeding the child	“How often are you responsible for deciding what your child’s portion sizes are?”
Perceived parent overweight	Parent’s perception of their own weight at various stages	“ Perception of weight during adolescence”
Perceived child overweight	Parent’s perceptions of their child’s weight at various stages	“Perception of their child’s weight when they were a toddler”
Concerns about child overweight	How concerned the parents are that their child is overweight	“How concerned are you about your child having to diet to maintain a desirable weight?”
Restriction	Parent’s attempts to control their child’s eating by restricting access to foods.	“ I intentionally keep some foods out of my child’s reach”
Pressure to eat	Parents’ attempts to control their child’s eating by encouraging the amount and type of food	“If my child says “I’m not hungry”, I try and get her to eat anyway”
Monitoring	The extent to which a parent reports keeping track of their child’s consumption of energy dense foods”	“How much do you keep track of the high fat foods”

3.2.4 Dietary intake

A three-day food diary was used to assess CCS nutrient intake (parent report). Participants were given written instructions on how to complete the food diary and were asked to complete this over two weekdays and one weekend day. Although this method can lead to high respondent burden and is subject to bias (including selection of the sample, reporting bias and issues associated with measurement of the diet) (172), this prospective method of a three-day food record was utilized as it has been shown to be appropriate for measuring individual, short term nutrient intake (172). Information on multi-vitamin use was not collected as dietary intake from food sources was the focus of this study.

3.2.5 Data analysis

The three-day food records were analyzed using the Foodworks nutrient analysis software program (version 5, 2007; Xyris Software, Brisbane, Australia). For foods and beverages not represented in the Foodworks database, nutrient content was obtained from nutrition panels. From these dietary data, the CCS mean daily energy intakes were calculated and expressed as a percentage of their estimated energy requirement (%EER). EER is the mean energy intake predicted to maintain energy balance including the needs related to tissue deposition (173). The age-appropriate Schofield equation was used to calculate basal metabolic rate (174) and a physical activity level of 1.5 (sedentary) was used to calculate EER. Use of a physical activity level of 1.5 was based on research of the physical activity levels from previous studies of childhood cancer survivors (164, 175). The CCS mean daily nutrient intake was calculated and expressed as a percent of their age-appropriate estimated average requirement (EAR) (173) to allow comparisons across age groups. EAR is used for group assessment of the prevalence of inadequate intake of

nutrients in a particular life stage and gender (173). For certain nutrients, EARs have not been established and therefore these nutrients were excluded in this analysis.

Remaining data were analyzed using the statistical software package SPSS (version 17.0, 2009; SPSS Inc, Chicago, IL, USA). Descriptive statistics were calculated for demographic and anthropometric, dietary intake and CFQ data. A p-value of <0.05 was considered statistically significant.

Paired t-tests were used to compare differences between BMI percentiles at each assessment time-point. Likewise, paired t-tests were used to determine whether there was a significant difference between the three factors in the attitudes and practices category of the CFQ and the 4 factors in the risk factors and concerns subscale. As the data were normally distributed, Pearson's correlation coefficients were used to assess correlations between the subject's %EER, BMI percentiles, CFQ factors, gender, age and time since completion of treatment. A backwards linear regression model was used to determine the degree of the relationship between each of the CFQ subscales and the patient's BMI percentile. Time since treatment completion was included as a covariate.

3.3 Results

3.3.1 Patient demographics

A total of 139 participants were invited to participate in the study and 50 volunteered to take part, yielding a response rate of 36%. Reasons for refusal to participate could not be determined. The CCS mean age at diagnosis (SD) was 3.47 (2.41)

years and the mean age at the time of their parent's study participation was 7.12 (2.59) years. See Table 3-2 for further demographic details.

Table 3-2 Demographic and medical characteristics of child cancer survivors

Characteristic	N (%)
Sex (male:female)	60:40
Cancer diagnosis, %	
ALL	25 (50)
ALL - relapsed	2 (4)
AML	2 (4)
Neuroblastoma	5 (10)
Wilms Tumour	6 (12)
Rhabdomyosarcoma	2 (4)
Lymphoma	2 (4)
Medulloblastoma	2 (4)
Other	4 (8)
Age at cancer diagnosis, years	
Mean (SD)	3.47 (2.41)
Range	0.7-8.8
Age at assessment, years	
Mean (SD)	7.12 (2.59)
Range	3.1-12.3
Time since treatment completed, years	
Mean (SD)	2.29 (1.56)
Range	1.0-4.8

3.3.2 Dietary intake

Results from the three-day food diaries revealed that 54% of the CCS was consuming more than 110% of their %EER, while 50, 32 and 44% of children did not meet their requirements for folate, calcium and iron respectively (Table 3-3). Only 6% percent of the CCS was consuming less than 75% of their %EER. There was no significant difference in %EER between those treated for Acute Lymphoblastic Leukemia (ALL) and other diagnoses (110% vs. 121% respectively, $t = -1.164$ $p = 0.26$).

Table 3-3 Mean nutrient intake

	Mean (SD) (%)	Range (%)	Percent not meeting requirements	Normative data*.
Percent of estimated energy requirement (EER)				
	115.6 (34.0)	59-235	54% (>110% EER)	
Nutrient intake				
Protein	359.5 (158.5)	124-955	0%	0%
Thiamin	267.0 (177.3)	75-1180	2%	0%
Riboflavin	307.9 (150.5)	74-834	2%	0%
Niacin Equivalents	392.3 (167.9)	158-1068	0%	0%
Vitamin C	314.8 (202.2)	72-917	4%	2%
Folate	119.7 (85.0)	43-630	50%	2%
Vitamin A	203.9 (106.7)	73-549	8%	2.3%
Magnesium	214.2 (142.9)	62-860	4%	2%
Calcium	126.5 (56.6)	39-323	32%	31.5%
Phosphorus	226.1 (91.4)	56-504	4%	4%
Iron	111.1 (49.8)	49-370	44%	1%
Zinc	232.4 (112.9)	75-780	2%	0%

* Australian National Children's Nutrition and Physical Activity Survey- Main Findings. In: Department of Health and Ageing, editor. Australian Government; 2007. Based on ages 2-13 years.

Table 3-4 presents the distributions of mean BMI percentiles as measured at diagnosis (T1), end of treatment (T2) and at the time of parent's study participation (T3). Data for BMI percentiles of CCS under the age of two cannot be calculated and were therefore not included in the analysis. Historical anthropometric data was

not available for four CCS (T3). Paired t-tests showed a statistically significant increase in BMI percentiles from T1 to T3 (56.29 vs. 67.17 $t = -2.758$, $p = 0.01$).

Table 3-4 Mean body mass index (BMI) percentiles for subjects over the age of 2 years

	n	Mean (SD)	Range	p-value
Diagnosis (T1)	30	56.3 (29.4)	0.14-99.3	0.06 (T1-T2)
End treatment (T2)	37	65.4 (31.0)	0.1-97	0.28 (T2-T3)
Time of study (T3)	46	67.1 (24.9)	0.75-99.9	0.10 (T1-T3)*

* Value is significant at $p < 0.05$

The majority of children were within the healthy weight range at the three assessment points with 10% of children overweight and 10% obese at T3 (Figure 3-1). There was no difference in BMI percentiles between those treated for ALL and those treatment for another diagnosis (65.88 vs. 67.10; $t = -0.167$, $p = 0.87$).

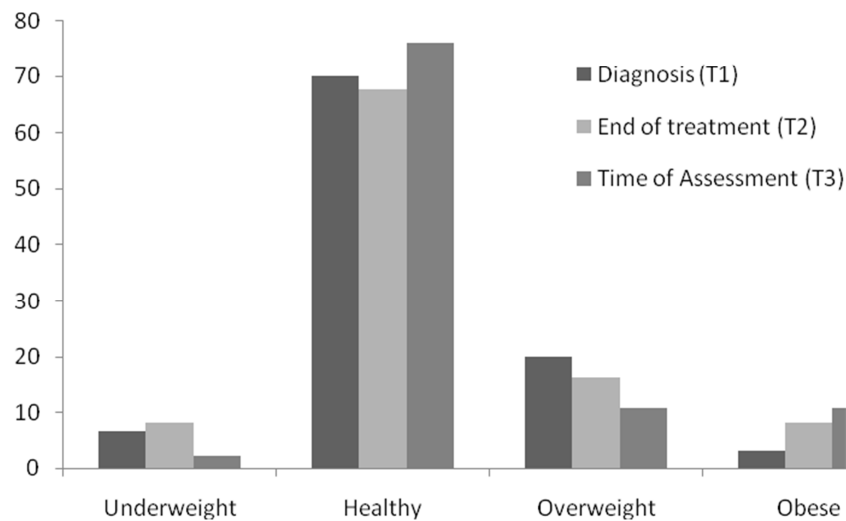


Figure 3-1 Percentage of children in each weight category over three assessment time points

3.3.3 Child feeding practices

From the risk factors and concerns subscale of the CFQ, parents appeared to have had a high perceived responsibility in regards to their child's intake and were the least concerned about their child's risk of being overweight ($t=8.249$, $p=0.001$) (Table 3-5). In the control of child feeding, attitudes and practices subscales parents had significantly higher scores for monitoring their child's intake ($t=-6.621$, $p=0.001$) and using a restrictive form of parenting ($t= 3.822$, $p=0.001$) compared with pressuring their children to eat.

Table 3-5 Mean scores for the 7 subscales of the child feeding questionnaire

Categories	Sub-scales	Mean \pm SD*	Range
Risk factors and concerns	Perceived responsibility	4.18 \pm 0.48	3-5
	Perceived parent weight	3.10 \pm 0.40	2-4
	Perceived child weight	2.91 \pm 0.41	2-4.3
	Concerns about child weight	2.52 \pm 1.28	1-5
Control in child feeding, attitudes and practices	Restriction	3.43 \pm 0.80	1.5-4.75
	Pressure to eat	2.77 \pm 0.99	1-5
	Monitoring	3.99 \pm 0.71	2-5

* Possible values: 1=low levels of concern or control; 5=high levels of concern

The full additive regression model with 8 independent variables (CFQ sub-scales and time since end of treatment) explained 38.4% of the variance in BMI z-scores ($F= 2.803$; $p= 0.016$). The final model with only 3 variables (parental perception that their child was overweight, parental concern about their child being overweight and time since treatment completion) explained 36% of the variance in BMI z-scores ($F= 7.672$, $p=0.001$), a loss of only 2%.

3.4 Discussion

Assessment of the dietary intake of childhood cancer survivors is essential to allow the development of appropriate nutritional interventions. Yet there is a paucity of literature in this area, especially relating to young childhood cancer survivors. This study assessed childhood cancer survivor's dietary intake less than five years from completion of treatment to determine overall nutritional adequacy, as well as to describe parental attitudes and beliefs about their child's feeding practice.

Obesity is associated with CCS both less than 18 years of age (176) and adult survivors of childhood cancer, especially those treated for ALL and with cranial irradiation (177, 178). The present study found that 10% of the CCS was overweight and 10% were obese at the time of the study using BMI percentiles as a marker of obesity. It has been suggested that BMI is not an accurate marker of abdominal obesity, (156), (179) potentially underestimating obesity rates in this cohort. However there was a statistically significant increase in BMI percentiles from the start of treatment (T1) to the time of assessment (T3). Although this has the potential of being more a reflection of the catabolic state associated with diagnosis resulting in lower BMI percentiles, recent literature suggests that malnutrition rates at diagnosis in this population may only be around 9% (180) .

This study found that a large proportion of the CCS (54%) were consuming above their estimated energy requirement. This finding is important because energy imbalances as small as 1-2%, sustained over a period of time, are likely to promote weight gain in this population (181). This may, in part, explain the increasing BMI percentiles of our cohort, though this will need to be confirmed with future studies. This is clinically important as it provides a potential target for dietary intervention

programs, namely to decrease energy intake in this population, which may go some way towards preventing obesity and associated endocrine and metabolic complications in young childhood cancer survivors (16). Additionally, obesity prevention in these patients is more likely to be successful than treatment of obesity in long term survivors (182, 183).

It is noted that the energy intake of this cohort of paediatric cancer survivors appears similar to that of the general Australian population (184). Although it was not assessed in this study, it may be that paediatric cancer survivors need to consume less than their peers to prevent long-term weight gain due to the fact that childhood cancer survivors may have lower total energy expenditure than the general population (caused by reduced physical activity levels rather than reduced resting energy expenditure) (164, 185). Issues such as motivation, fear and pain (186, 187) have been reported as reasons for adult cancer patients having sedentary lifestyles and lower physical fitness levels (188) both during and after cancer treatment (189). Targets for energy intake for CCS may therefore need to be set at lower ranges or an increase in physical activity will need to be encouraged so as to prevent long-term weight gain.

Our findings regarding micronutrient intake indicate that inadequate calcium intake may be an important concern soon after the treatment period (with 32% of our population not meeting daily requirements). Inadequate calcium intake also appears to be a concern for older CCS, with the literature reporting up to 68% of CCS were not meeting guidelines for calcium intake(16). Although this trend is similar to the general Australian population this is more concerning for survivors of childhood cancer, particularly those treated for ALL, as they are at higher risk of osteopenia

(190). Altered bone metabolism during treatment may interfere with the attainment of peak bone mass, predisposing survivors of childhood cancer to premature onset and complications related to osteopenia and osteoporosis (191). While treatment greatly affects bone mineral density (BMD), BMD is multi-factorial and lifestyle factors including nutritional status, adequate calcium intake (particularly dairy calcium) and weight-bearing exercise are important modifiable factors in the prevention of osteoporosis (190, 192). Survivors of childhood cancer must ensure they have a positive calcium balance to build bone and attain peak bone mass to prevent these problems (190).

The finding that 50% of the CCS failed to meet their folate EAR is also of concern, as current epidemiological research suggests a link between decreased folic acid intake and increased homocysteine levels (193). Increased homocysteine levels are associated with endothelial dysfunction, decreased nitric oxide bioavailability, decreased vasodilatation and increased low-density lipoprotein deposition in arterial walls, resulting in atherosclerosis and ultimately increased risk for cardiovascular disease (193). Good food sources of folate include green leafy vegetables and citrus fruit (194). Studies of adult cancer survivors have found inadequate vegetable intake (17) which has the potential to lead to inadequate folate intake. These habits may be manifesting early in the off treatment period, leading to inadequate folate intake, however this needs to be confirmed in future studies. It also appears that an inadequate folate intake is unique to the childhood cancer population compared with children unaffected by cancer (Table III).

Although studies assessing parental influences, (including beliefs, attitudes and practices), on child's eating patterns and weight status could not be found for the

paediatric oncology population, research in children not affected by cancer has demonstrated that parent feeding methods are linked to child weight status (171). Parent child feeding behaviours of monitoring, pressure and restriction are highly correlated with an increased energy intake and BMI in children (167) . This study failed to find any relationship between CCS BMI percentiles and %EER between all 7-domains of the CFQ. It is possible this was due to a floor effect, given that only 20% percent of children were classified as overweight/obese. The parents in this study were more likely to endorse behaviours such as monitoring and restrictive style of parenting and felt responsible for their child's intake which has the potential to lead to increasing weight and risk of obesity over time. These results provide possible targets for interventions in the future.

3.4.1 Limitations

This single centre study was limited by a low response rate, which increased the chance of bias and reduces generalisability to the broader paediatric oncology survivor population. The high participant burden associated with completing 3-day food diaries (172) may have reduced participation rates. Recruitment via a letter invitation instead of face-to-face recruitment may also be a factor in the poor response rate. The lower representation of overweight children may also have introduced bias into the study whereby only parents of CCS within a healthy weight were willing to participate in this study out of concern for being judged for their child feeding practices. It is also important to note that using BMI percentiles may not be a sensitive marker of obesity in this population, as the measure may not reflect changes in body fat (179). Waist circumference may be more predictive of cardiovascular risk in the CCS (156). Another limitation of this study was the lack of a control group. Although it is recommended that future studies utilise a control group, these studies need to be consider that the control children may also not be

meeting the dietary guidelines. It is recommended that future studies compare the dietary intake of childhood cancer patients with both control groups and age-appropriate dietary guidelines.

3.4.2 Conclusion

This study has provided preliminary data regarding the dietary intake of childhood cancer survivors less than 13 years of age, within five years of completing cancer therapy. It provides potential targets for nutritional interventions that may be implemented to prevent some of the deleterious long-term effects associated with cancer therapy. It appears that a large proportion of the CCS are consuming more than their recommended energy requirements, and if this continues, their intake may place this group at increased risk of obesity and other associated endocrine and metabolic disorders. Large proportions are also consuming inadequate calcium, folate and iron, which could increase the risk of late-effects associated with cancer therapy. Parents used both monitoring and restriction to regulate their child's intake, which may also contribute to poor dietary habits by decreasing their child's self-regulation of intake. This is especially of concern considering they do not appear to be concerned about their child's risk of being overweight. It is imperative that interventions are established soon after treatment completion, targeting parents to enable us to improve the long-term dietary habits of this population.

3.4.3 Implications

The findings from this chapter provide a quantitative assessment of the nutritional intake of a cohort of child cancer survivors. This study is the first to provide evidence that the poor dietary intake seen in adult survivors of childhood cancer is manifesting itself recently off treatment. Although we hypothesised that the poor nutrient intake seen in this population may be related to an inadequate fruit and

vegetable intake or an intake of high energy foods, this cannot be confirmed with the results from this current study alone. The next chapter will provide further insight into the dietary habits of the cancer survivors.

4 EXPLORING THE VIEWS OF PARENTS REGARDING THE DIETARY HABITS OF THEIR YOUNG CANCER-SURVIVING CHILDREN²

Chapter 3 provided information on the nutrient intake of young survivors of childhood cancer early after their cancer therapy has finished. This chapter will provide further insight into the dietary habits of the childhood cancer survivors and how these habits have change over their cancer trajectory. It will provide clinicians with the information on the dietary habits that could be targeted when developing appropriate nutritional interventions. The findings of this chapter have been published in Supportive Care in Cancer.

4.1 Introduction

Poor dietary intake during childhood cancer treatment is well documented. Treatment side-effects such as nausea, vomiting, diarrhoea, mucositis and anorexia

² This chapter has been published in the following peer reviewed journal:

Cohen J, Wakefield CE, Fleming CAK, Tapsell LC, Walton K, Cohn RJ. Exploring the views of parents regarding the dietary habits of their young cancer-surviving children. Supportive Care in Cancer. 2015;23(3);463-471

JC designed the study, JC & CF contributed to data collection and analysis and JC, CW, RC, KW & LT contributed to the manuscript.

The key findings have been peer reviewed and presented by JC at the 16th International Congress of Dietetics, COSA 37th Annual Scientific Meeting, the Australasian Society for Health and Behavioural Medicine ASM & the ANZCHOG Long-term Follow-up Symposium with the abstracts included in the following publications:

Cohen J, Wakefield C.E, Fleming CAK, Cohn RJ. A qualitative study of parent attitudes to nutrition after completion of their child's cancer treatment. Asia-Pacific Journal of Clinical Oncology. 2010; 6(3): 205.

Cohen J, Wakefield, CE, Fleming CAK, Cohn RJ. Consequences of treatment on food preferences and dietary habits of childhood cancer survivors. Pediatric Blood and Cancer. 2011; 57(5); 827

lead to poor oral intake and, in some cases, malnutrition (14, 195, 196) Childhood cancer patients' dietary habits appear to be altered during cancer treatment. Preferences for sweeter or sour tasting foods and significant challenges with food refusal of previously tolerated foods have been reported. (127)

Child feeding behaviours can be strongly influenced by positive and negative associations when young. (197) Dietary habits that are established when a child is young are also more likely to continue into their adult life. (198-201) Adult survivors of childhood cancer also have a poor dietary intake, with an inadequate intake of fruit and vegetables, consumption of high fat diets and an inadequate calcium intake. (17, 153) These dietary habits are manifesting themselves early after the treatment period, with child cancer survivors (CCS) recently off treatment displaying an excessive energy intake and an inadequate calcium and folate intake. (202) The concern is that the dietary habits and food preferences that are established during childhood cancer therapy are persisting once treatment has been completed.

There remains a dearth of literature regarding the dietary habits of CCS at treatment completion. The determination of parental views about their child's nutritional habits is important, as parents can influence child dietary behaviours.(200) Dietary interventions for younger children will also need to be parent focused. The more concerned a parent is about their child's intake the more likely they may take steps to intervene. (203) The study aimed to compare parental views of CCSs' current dietary habits with their habits prior to their cancer diagnosis, during their treatment, and with those of children in the general population. In doing so, this study aimed to contribute to the evidence-base regarding the dietary habits and patterns of young child cancer patients.

4.2 Methods

4.2.1 Study participants

Participants were parents and/or carers of CCS who were: a) less than 5 years post treatment for any type of cancer; b) not attending a long-term follow-up clinic; c) under 13 years of age; and d) attending the Kids Cancer Centre (KCC) at Sydney Children's Hospital, Australia for follow up. Eligible participants were identified using KCC records and were posted a study invitation, a participant information sheet and an opt-in card. Participants initially participated in a study assessing their child's dietary intake after cancer treatment using a questionnaire and three-day food diaries. (202) Participants who participated in this study were able to indicate whether they would participate in the follow-up qualitative study. All participants of the dietary intake study agreed to participate in this follow-up qualitative study (n=51). A cohort of parents/carers of child cancer survivors who had participated in the dietary intake study (202) were selected to participate in semi-structured telephone interviews. Participants were purposefully sampled to build on the insights gained thus far. Maximum variation sampling was implemented to allow a range of diagnosis groups and ages of parents of childhood cancer patients to be interviewed. Incentives for participation were not used in the dietary intake study or the qualitative study.

4.2.2 Controls

Control participants were recruited via advertising in the hospital and through community organisations. Control participants were well children who were not patients of the hospital and were age-matched. Parents of multiple children were asked to focus on the dietary habits of one child only. Parents of age and sex

matched children without cancer or another disease that could affect their dietary intake or required food restrictions were interviewed regarding their child's current intake. Excluded diseases included, but were not limited to, food allergies or intolerance, diabetes, coeliac disease, crohn's and ulcerative colitis, cystic fibrosis, renal failure, metabolic conditions and failure to thrive. Children were also excluded from the control arm of the study if they required supplemental nutrition via a nasogastric tube or gastrostomy. The parent/carer who was interviewed for both the cancer and control groups was the main carer responsible for food purchasing and meal preparation. The study protocol was approved by the South Eastern Sydney and Illawarra Health Service, Human Research Ethics Committee-Northern Hospital Network. Informed, written consent was obtained from each participant.

4.2.3 Procedure

Interviews for both the CCS and the control group were conducted via the telephone. This method of interviewing was chosen to ensure participation by a geographically diverse group, specifically those living in rural and remote regions, to reduce the bias associated with studying a group in the same geographic region. Telephone interviews have been shown to be as effective in eliciting reliable information as face-to-face interviews (25). Telephone interviews may also have some advantage due to the anonymity that telephone interviews provide, favouring a more in-depth response (25).

The interview schedule was prepared by a multidisciplinary team (dietitian, psychologist and oncologist) and used a semi-structured approach. The interviews further explored previous insights gained from our previous study regarding their dietary intake.(202) The interviews for the parents of the young child cancer survivors were separated into their current intake, intake during treatment and intake

prior to the cancer diagnosis. The interviews focused on determining parental views regarding their child's eating habits, food volumes, food types and weight at each stage of their cancer journey. There was also a focus on self-reported parent feeding practices. The parents of controls were asked similar questions; however the focus was on their current intake (Table 4-1). As prescribed by Miles and Huberman (204), results from early interviews were used to suggest additional lines of questioning in subsequent interviews and all interviews were conducted by one researcher. Interviews were conducted until thematic saturation was reached. Thematic saturation was determined when there was a continual repetition of themes and when no new themes were mentioned in subsequent interviews. In accordance with gold-standard guidelines (204), participant's responses were recorded and transcribed verbatim.

Table: 4-1 Questions used during the telephone interview to parents of young child cancer survivors and healthy controls

Young child cancer survivors	Healthy controls
<p>Nutrition prior to treatment</p> <p>Could you tell me how you viewed your child's eating habits before they were diagnosed?</p> <p>Compared to other children their age how did you feel about the amount your child ate?</p> <p>Did you use any strategies to help your child to eat?</p> <p>How did you feel about their weight compared to other children before they got sick?</p>	
<p>Nutrition during treatment</p> <p>How did you feel about your child's eating during their cancer therapy?</p> <p>How did you feel about the types of foods your child was eating?</p> <p>Did your child need any other forms of nutrition?</p> <p>Did you use any strategies to get your child to eat?</p> <p>How did you feel about your child's weight during treatment?</p>	
<p>Current nutrition</p> <p>How do you view your child's intake and diet?</p> <p>How do you view your child's portion sizes?</p> <p>What are your thoughts about the types of foods your child eats?</p> <p>Do you use any strategies to help your child to eat?</p> <p>How do you feel about your child's weight?</p>	<p>Current nutrition</p> <p>How do you view your child's intake and diet?</p> <p>How do you view your child's portion sizes?</p> <p>What are your thoughts about the types of foods your child eats?</p> <p>Do you use any strategies to help your child to eat?</p> <p>How do you feel about your child's weight?</p>

4.2.4 Qualitative data analysis

Transcripts were coded line-by-line and analysis was facilitated by the qualitative data analysis software NVivo, 2008, Version 8 (QSR International, Victoria, Australia) which allows the researcher to store, code and retrieve raw data as well as to collate secondary information such as researcher observations/ideas. To ensure accuracy with regards to the coding and analysis and to meet gold-standards(205), a multi-level consensus coding methodology was used. (206, 207) Fifteen percent of interviews from the CCS (n=3) and the control group (n=3) were coded independently by two investigators, who met to review the coding and address any disagreements (204). The final coding was analyzed and emerging themes were categorized and enumerated (204).

All coding was done by an Accredited Practising Dietitian. Any mention of individual foods by the participants were classified into food groups based on the Australian Guide to Healthy Eating (208). Accredited Practising Dietitians, are skilled in food composition, to be able to conduct this categorisation. Terminology used by parents such as “junk food” and “unhealthy foods” were coded separately and counts were done on the number of times these words were mentioned. “Junk foods” and “unhealthy foods” were classified as such, if they were energy dense, nutrient poor foods that were providing a large number of calories for relatively few nutrients.

4.3 Results

4.3.1 Demographics

Eighteen parents/carers of CCS and 18 controls participated in the semi-structured interviews. The CCS represented a range of ages and diagnosis groups (Table 4-2).

There was no significant difference between the CCS and control group in regards to age or gender. The control group all resided within metropolitan Sydney. Fifty-five percent (n=10) of the parents worked full time and 39% worked part time (n=7). One parent was a full time career.

Table 4-2 Demographic characteristics of parents, young child cancer survivors and healthy controls

	Young child cancer patients (n=18)	Healthy control (n=18)
Child demographic		
Sex (M:F)	11:9	11:7
Age (SD) years	8.50 (2.71)	8.5 (2.90)
Diagnosis (number)		
ALL ^a	8	
Neuroblastoma	3	
Wilm's Tumour	3	
Rhabdomyosarcoma	1	
Lymphoma	2	
Brain Tumour	1	
Age at diagnosis (yrs (SD))	3.47 (2.41)	
Time since treatment completion (yrs(SD))	2.29 (1.56)	
Nutrition intervention during treatment (number)	6	
Nutrition education	5	
Enteral nutrition	2	
Oral supplements	2	
PN ^b		
Parent demographics		
Sex (M:F)	0:18	1:17
Area of residence (urban:rural)	8:10	18:0
Employment (full:part:unemployed)		7:8:3

^a ALL-acute lymphoblastic leukaemia; ^bPN=total parenteral nutrition

4.3.2 Remembered dietary habits prior to diagnosis of CCS

The majority of the parents described their child as a “healthy eater” prior to their cancer diagnosis (Table 4-3). Most parents appeared satisfied with the amount of food their child was consuming. Four parents described their child as consuming inadequate volumes of food and one parent considered their child to be consuming an excessive volume of food. Parents did not appear to be experiencing concerns about their child’s weight prior to their diagnosis. A small number of parents believed their child was underweight and two considered their child to be overweight. Parents appeared to use a variety of strategies to encourage their child to eat, though none of the parents recalled providing “unhealthy” foods as an alternative to their normal foods as a way of ensuring that their child had an adequate intake.

Table 4-3 Summary of themes from parents of young child cancer survivors of their child's remembered dietary habits prior to their cancer diagnosis

	Number of respondents (n=18)	Quote
Dietary habits		
Healthy eater	16	<p><i>"....was a very healthy little eater, you know fruits, vegetables - look [he] love[d] his lollies and chocolates like any other kid but ...just pretty normal eating..." (male;12 yrs; Wilms)"</i></p> <p><i>"Yeah, she was a good eater....I can't really remember exactly what she was like but there was no problems with what she ate and she ate very healthy foods" (female; 5yrs, ALL ^a)</i></p>
Volumes of food		
Adequate	13	<i>"I wasn't worried about the amount either. I didn't have to watch it. It was fine" (male; 10yrs, ALL)</i>
Weight perception		
Healthy weight range	13	<i>"(Her weight) you know like a chubby up baby, a good weight, healthy" (female; 5yrs, ALL)</i>
Parent feeding practices		
Restricting foods	5	<i>"I do everything in moderation....I don't, I never stock junk food at home" (female; 8yrs, ALL)</i>
Pressuring to eat	5	<i>"our strategy was, if you don't eat your vegies, you don't get dessert, it's that simple" (male, 11yrs, Lymphoma)</i>
Bribery	3	
Positive encouragement	3	<i>"It always used to be if you eat all of your dinner you get yoghurt for dessert. It was never bribe him with lollies or anything like that" (male; 10yrs, lymphoma)</i>

Monitoring	2	<p><i>“(I) always tell them that like for example she didn’t like carrot and I said “carrot has good colour, so if you eat carrot it gives you good colour for your skin” (female; 8yrs, ALL)</i></p> <p><i>“ I mean sometimes he’d have to pull back on the chips” (male; 13yrs, ALL)</i></p>
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^a ALL: Acute Lymphoblastic Leukaemia

4.3.3 Remembered dietary habits during treatment of CCS

Parents reported a significant change in CCSs’ eating habits while their children were receiving their anti-cancer treatment (Table 4-4). The main themes that emerged from the parent report regarding their child’s eating habits during their cancer therapy included: 1) A decreased preference for fruits and vegetables; 2) An increase in preferences for carbohydrate-based foods such as bread, pasta or savoury biscuits; 3) An increased desire for foods they considered “junk food”. It also appeared that savoury foods were chosen by the CCS in preference for sweet foods. Parents also considered the foods eaten by CCS during treatment to be “unhealthy”.

Parents’ views regarding the volume of foods appeared to be evenly split. Half of the parents were concerned that their child was not eating adequate volumes of food while the majority of the remaining parents described their child as overeating at certain phases of treatment.

Parental concern about their child’s weight also appeared to change when their child was on treatment. A larger number of parents were concerned that their child was

underweight or overweight. Parent feeding practices also changed on treatment. Parents appeared to allow CCS to eat “whatever they liked” during treatment and several pushed their child to eat. None of the parents interviewed restricted their child’s food intake or type of foods eating during treatment.

Table 4-4 Summary of themes from parents of young child cancer survivors of their child’s remembered dietary habits during their child’s cancer treatment.

	Number of respondents (n=18)	Quote
Dietary habits		
Decreased fruit and vegetable intake	13	<i>“She was not interested in fruit, vegies, anything like that which.... it was certainly something I noticed because my toddler had always been a really good fruit and vegie eater...” (female;6 years; neuroblastoma).</i>
Increased preference for carbohydrate-based foods	11	<i>“you know he would eat lots of crackers probably more than anything ... maybe that was like the salt content” (4)</i>
Increased desire for “junk foods”	18	<i>“....definitely with the treatment of chemo, more carbs, more sugar, more salt.” (female; 11 yrs; ALL ^a).</i>
Increased preference for savoury foods	18	<i>“As long as it was savoury and it was crap, she would eat it...” (female;8yrs; Wilms’).</i>
Volumes of food		
Excess	8	<i>“...[the patient] was put on to steroids. I couldn’t feed him enough. He just wanted to eat anything and everything... He would have a full meal; he would eat more than me and then say, “Can I have a pie now please?” (male; 13yrs;ALL).</i> <i>“I would say lack of eating, (the patient) couldn’t really stomach food” (male; 12yrs; Wilm’s)</i>
Inadequate	9	
Weight perception		

Underweight	11	<i>"my husband was taking him down to the shower, and just looking at him from behind it was like, oh my God, he had no bum, no legs, there was nothing (male; 13yrs, ALL)</i>
Overweight	3	<i>"She ate a lot. Puffed up obviously with the steroids and gained a bit of weight" (female; 11yrs, ALL)</i>
Parent feeding practices		
Encourage any types of foods	18	<i>"We didn't care as long as he ate. It didn't matter if he wanted a cupcake for breakfast ... and we would go and get him McDonalds, he wanted garlic bread one time when he woke up from an anaesthetic so we went and got him garlic bread" (male;10 yrs; lymphoma).</i>
No food restrictions	18	<i>"I mean as a mum it goes against everything that I would normally do for my child. As I say, I was pretty pedantic about what they ate and how I prepared their food and then all of a sudden I'm begging this child to eat absolutely anything just to be able to get something into him...." (male; 11 yrs;Lymphoma).</i>
Forcing their child to eat	5	<i>"I did not reward him but I actually begged him (to eat)"(male; 8yrs, neuroblastoma)</i>

^a ALL: Acute Lymphoblastic Leukemia

4.3.4 Current dietary habits of CCS and controls

4.3.4.1 Young child cancer patients

When parents were questioned about their observations on CCSs' nutritional habits after treatment compared with prior to the cancer diagnosis, three main themes emerged (Table 4-5): 1) Decreased fruit and vegetable intake; 2) Increased consumption of "junk food"; 3) Increased portion sizes. However, not every parent

interviewed reported concerns about their child's excessive dietary intake, with some reporting that they were concerned that their child did not consume adequate portions of food.

There appeared to be a shift toward increased parental concern about their child's weight, with parents reporting their child was gaining too much weight after treatment had been completed. The strategies parents used to encourage CCS to eat appeared to change once the cancer treatment had been completed. Many parents started restricting their child's food intake and two parents continued to provide their child with unhealthy foods to ensure adequate intake. Parents also tended to use a larger variety of methods to encourage their child to eat than they did during cancer treatment.

4.3.4.2 Controls

A small number of parents of healthy children considered their child to be a fussy eater. The majority of parents believed that their child ate a sufficient amount of foods, while only a small number of parents expressed concerns that their child consumed excessive volumes of food. A smaller number of parents of healthy children compared with parents of CCS did report that their child did not consume adequate vegetables, though even these children appeared to eat some vegetables or salads. The majority of parents of healthy children considered their child to be a healthy weight for their age and height.

The feeding practices of parents of healthy children appeared to differ to those of CCS after treatment. A smaller number of parents of healthy children felt the need to restrict food. The most common parenting practices used in this group to encourage their children to eat was providing education to their children on healthy

eating. None of the parents of the control children felt the need to provide “unhealthy” food as a way of ensuring that their child “ate something”.

Table 4-5 Summary of themes from parents of young child cancer survivors compared with parents of healthy children regarding their child’s current dietary habits.

	Young child cancer patients		Healthy controls	
	Number of respondents (n=18)	Quote	Number of respondents (n=18)	Quote
Dietary habits				
Inadequate fruit and vegetable intake	16	“...[he] won’t eat vegetables and fruit since coming off treatment ...”(male;4 yrs; neuroblastoma).	6	“he is fussy with his vegetables...the main vegies he eats is carrots, bok choy and broccoli...”
High intake of “junk foods”	18	“she’d eat more junk food now if I allowed it, whereas before she would eat carrots and apples over lollies.” (female; 8 yrs;Wilms’).	13	“[he} loves lollies; loves chips; loves cake and all that sort of stuff but we don’t not let him have it” (male; 11yrs)
Volume of food				
Excessive	11	“there are days when she overeats, like she might go to someone’s house and they say, ‘God she eats a lot’.” (female;4yrs;ALL ^a).	2	“I think he eats more than other kids his age” (male; 11yrs)
Inadequate	5	“Only eats salty carb foods so [her] mother has her on multi vitamins... she	2	“She goes through phases. Some

		<i>still doesn't put on any weight."</i> <i>(female;4 yrs;Wilm's).</i>		<i>days she barely eats at all" (female; 4yrs)</i>
Weight perception				
Underweight	3	<i>"...she's quite tiny, she's quite thin...I always look at her and think she's small" (female; 5yrs, ALL)</i>	0	
Overweight	7	<i>"we've spent half his life, most of his life, concerned with him not putting weight on and not eating and now we have gone the other way and he is actually a bit overweight for his age and size" (male;9 yrs; rhabdomyosarcoma).</i>	2	<i>" ...I think he's too heavy and it's all around his tummy" (male; 11yrs)</i>
Parent feeding practices				
Food restriction	14	<i>I am probably quite strict because a lot of parents would think that that's too controlling but I think I see the difference after treatment and it's in order to help her (female; 11 yrs; ALL)</i>	6	<i>"I think that one of the secrets is that you can't have too much junk in the house, because if it is in there, if you're not in the kitchen, then they are easily sneaking it you know..." (male;10 yrs)</i>
Bribery	6	<i>'If you eat it then I'll let you watch TV.'</i> <i>(male; 8yrs; neuroblastoma)</i>	5	
Pressuring their child to eat	5	<i>"you know we sit there and make her eat one piece</i>	4	<i>"We've bribed him; we've paid him; we've hidden them</i>

Food as reward	5	<i>that's about the only way I can get her to do that (eat)" (female; 5yrs, Wilms')</i>	1	<i>[vegetables]" (male; 11 yrs)</i> <i>"He doesn't eat a great deal of fruit during the day, ... at home I have to cut it up and put it in front of him and tell him to eat it to get fruit into him." (male; 13 yrs)</i>
Concealing vegetables	5	<i>".. (we) try and bribe her so if she eats that she can have something else" (female; 5yrs, Wilms')</i>	2	<i>"Before he can have dessert ... he has got to eat his dinner" (male; 10yrs)</i>
Positive encouragement	4	<i>"...with spaghetti bolognaise I'll put a lot of vegies in the bolognaise sauce ... I'll grate the zucchini and the carrot in there" (male; 5yrs, ALL)</i> <i>"..I acknowledge that I'm losing a degree of control, I'm trying to educate him about healthy foods ... and making healthy choices himself" (male; 10yrs, ALL)</i>	7	<i>"Because she doesn't try a lot of other vegetables ... I put about six to seven vegetables in a very, very powerful food process, and I cook it in the mince and she won't see it and she'll eat it." (female; 4yrs)</i> <i>"We talk about what's good for you and what's not good for you and what's going to help</i>

				<i>you grow and be strong and have energy.” (female; 4yrs)</i>
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^a ALL: Acute Lymphoblastic Leukaemia

4.4 Discussion

This study revealed a parent-reported change in CCS dietary habits across the cancer journey. CCS may not return to their pre-diagnosis dietary habits once their treatment is completed, instead developing new eating habits. The three main themes that emerged from parental report of their CCS's current eating habits were; 1) Decreased fruit and vegetable intake; 2) Increased consumption of “junk food”; 3) Increased portion sizes. The majority of parents appeared less concerned with their child's weight, dietary intake or dietary habits prior to the cancer diagnosis, but developed concerns about excess weight gain and poor eating habits after treatment completion. These results were in contrast to the control group, in which the majority of parents viewed their child to be a healthy weight, consuming reasonable volumes of food. Although one-third of control parents reported that they were not satisfied with their child's vegetable consumption, this proportion was lower than the number of parents of CCS who were concerned about their child's inadequate intake of vegetables.

Reasons for this change in CCS dietary habits and intake are likely multi-factorial. Previous studies of cancer patients (both child and adult) suggest a role of learned food aversions influencing dietary habits (127, 209-211). Cancer patients experience significant side-effects such as nausea, vomiting, mucositis and diarrhoea (195, 196) that can lead to anorexia, weight loss and malnutrition (14, 195, 196). There is an emphasis on preventing treatment-related weight loss during cancer therapy, especially in children, to maintain adequate growth and development (105, 122).

Parents of CCS reported changing their parenting styles regarding food during their child's cancer treatment and allowed their child to eat "whatever they wanted". One third of parents also reported pushing their child to eat as a way of preventing weight loss. It may be that this emphasis on food and eating during the intensive cancer treatment may be a contributing factor to learned food aversions and a subsequent change in their dietary habits long term.

Many parents appeared to allow and encourage the intake of "unhealthy" foods during their child's treatment and reported that their child continues to consume these foods once treatment has been completed. Healthcare workers may also encourage parents to allow their child "eat whatever they want" during treatment, as a way of preventing weight loss. Dietary habits, food preferences and oral skills are established at a young age and these habits, once established, are likely to be carried into adulthood (198-201). Young children also have an innate preference for energy dense foods and constant exposure to these types of foods at a young age can increase the desire for these foods through associative learning (200). Although parental reports indicated eating habits did improve after treatment, there was a consistent parental theme regarding their child's strong, and ongoing, preference for "Junk food" and larger portions of these foods. As these patients are being treated at such an important time in the establishment of long term eating habits, not only the cancer therapy, but the foods they are exposed to during this time, may strongly influence their dietary habits at treatment completion.

Repeated exposure to certain foods during childhood is also needed for long-term acceptance of foods. (198) Parental reports of the dietary habits of their children suggest a significant reduction in the preference for vegetables and other "healthy" foods. The majority of parents in this study allowed the consumption of unhealthy

foods during the cancer treatment as a way of getting their child to eat. If CCS has a reduced exposure to other (healthier) foods during their cancer treatment, this may influence their acceptance of these foods once treatment had been completed.

4.4.1 Limitations and conclusions

Although the study numbers were small, this qualitative study provides insight into parent-reported change in dietary habits of child cancer patients across the cancer journey. It appears that child cancer survivors may not re-establish pre-cancer dietary habits, once their cancer treatment has been completed. Limitations of this study include the control group not being matched for socio-economic status and the reliance on parent memory and recall. This study does provide insight that the dietary habits of CCS may differ from that of the age-matched, non-oncology population. This study provides evidence that future studies, to longitudinally explore childhood cancer patients' dietary habits and food intake during and after cancer treatment are justified. This study suggests that not attending to the development of healthy dietary habits during cancer therapy may have adverse long-term effects. This may be more so for some diagnostic groups, such as ALL, for whom weight loss is not as common. Information about healthy dietary habits may need to be provided during cancer therapy, in particular during maintenance phase therapies, rather than waiting until treatment completion or long term follow-up. Information on the predictors, such as diagnosis, treatment type and use of nutrition support on the dietary habits of child cancer patients and survivors, is also needed to allow the development of appropriate dietary interventions. Future research may need to assess the influence of medical treatments on the dietary habits of children with other chronic diseases.

4.4.2 Implications

This chapter provides evidence that the dietary habits of childhood cancer survivors are changing throughout the cancer journey. This chapter also shows that young childhood cancer survivors are not returning to the dietary habits that they had prior to their cancer diagnosis. Part 2 of the thesis will be exploring the hypothesis regarding the areas of concern for clinical practice, specifically related to actual feeding practices during and following treatment completion. In light of the evidence from both this thesis and the literature, regarding the poor dietary habits of survivors of childhood, it is important to determine whether nutritional interventions have been able to improve their nutritional intake. The next chapter is a systematic review of the literature, assessing the availability and efficacy of nutritional interventions in cancer survivors.

5 SYSTEMATIC REVIEW OF NUTRITIONAL INTERVENTION IN CHILDHOOD CANCER SURVIVORS³

Chapters 3 and 4 provided evidence that young cancer patients have a poor dietary intake and habits early after their cancer therapy is complete. The literature review (chapter 2) also revealed that the predominant studies on the nutritional management of childhood cancer patients focuses on the prevention of under nutrition. This chapter is a systematic review of the literature assessing the number and effectiveness of nutritional interventions for survivors of childhood cancer. This chapter has been accepted for publication as a Cochrane Review in the Cochrane Collaboration of Systematic Reviews.

³ This protocol for this systematic review has been published in the following peer review journal:

Cohen J, Wakefield CE, Bartle J, Cohn RJ. Nutritional interventions in childhood cancer survivors. Cochrane Database of Systematic Reviews (Protocol). 2012.

This chapter has been peer reviewed and accepted for publication in the following peer review journal:

Cohen J, Wakefield CE, Cohn RJ. Nutritional interventions in childhood cancer survivors. Cochrane Database of Systematic Reviews

JC designed the systematic review, undertook the screening of abstracts, data collection, and assessment of bias, data analysis and synthesis and developed the manuscript; CW designed the review, undertook the screening of the abstracts and the assessment of bias and contributed to manuscript preparation; RC designed the review and contributed to manuscript preparation.

The key findings have been peer reviewed and presented as a poster at The 45th Congress of the International Society of Pediatric Oncology with the abstract being included in the following publications:

Cohen J, Wakefield CE, Cohn RJ. A systematic review of interventions for childhood cancer survivors. *Pediatric Blood and Cancer*. 2013; 60(S3); 163

Background

5.1.1 Description of the condition

In the last thirty years, detection and treatment methods for childhood cancer have improved to such an extent that up to 80% of paediatric patients now survive their cancer (48, 212). This has resulted in a growing number of child cancer survivors and an increased clinical and research interest in the survivorship issues as a consequence of treatment, in particular treatment-related morbidity and quality of life (212). Childhood cancer survivors have a relative risk of developing a chronic condition of 3.3 and a relative risk of a severe or life-threatening condition of 8.2 when compared with their siblings (15). Female sex and older age at diagnosis are independent risk factors for developing chronic conditions (148). These chronic health conditions include (but are not limited to) secondary cancers, endocrine disorders, renal dysfunction and severe musculoskeletal problems (15, 154, 155, 213). However, it may be many years before patient's display these conditions which tend to worsen over time (15).

There is now much focus in the literature on the importance of long-term monitoring of these patients (160, 214, 215) and increasing recognition of the need for both secondary and tertiary interventions that may lessen the burden of these chronic conditions (15, 216, 217). It may be possible to reduce the incidence of these chronic conditions with focused prevention strategies (15, 150) aiming for quality of life similar to peers (218). Specific chronic health conditions of long-term survivors that have the potential to be managed by lifestyle factors include osteoporosis, metabolic syndrome, endocrine disorders and cardiovascular disease (150). An individual's risk of these conditions varies depending on factors such as disease and

treatment type, age and sex. For example, survivors of acute lymphoblastic leukemia (ALL) who were treated with radiotherapy are at a greater risk of obesity, whereas those who received treatment for brain tumours are at risk of inadequate growth hormone (160). Those who received chemotherapy agents such as anthracycline are at risk of cardiovascular disease (219).

5.1.2 Description of the intervention

Despite the fact that health-promoting behaviour, such as consuming a healthy diet or maintaining adequate physical activity, could lessen the impact of these chronic issues (157), the prevalence of health-protecting behaviour in adults who have survived childhood cancer is similar to that of the general population (150, 158). There is a strong association in the general population between inadequate physical activity combined with a diet high in saturated fat and sugar and low in fruit and vegetable intake, and symptoms associated with the metabolic syndrome (220). This is of concern since many adult survivors of childhood cancer do not meet guidelines for fruit and vegetable intake, consume excessive fat and have an inadequate calcium intake (16, 17). These poor eating habits appear to be manifesting themselves early after treatment completion. Long-term survivors report barriers to consuming a healthy diet that include taste preferences for higher fat foods and the lack of availability of healthier foods (153). They may also be unaware of their risk of chronic disease (150), lessening the motivation to change their lifestyle. As childhood cancer survivors are already at a higher risk of long-term metabolic complications as a result of their cancer therapy, poor nutritional intake may be exacerbating this risk.

Interventions may need to be age-specific and differ between the older and younger childhood cancer survivor cohorts. Interventions may also need to target specific conditions and high risk groups or may target the general paediatric population. For example, childhood cancer survivors treated for ALL using cranial irradiation are at a higher risk for obesity and subsequently metabolic syndrome (221) and, therefore, they could be targeted with specific nutritional interventions to reduce obesity rates. In contrast, patients treated with anthracycline are at risk of cardiovascular sequelae (221) and, therefore, interventions may target not only weight reduction but also aim to reduce cardiovascular risk (222). Strategies to manage these chronic conditions may involve prevention interventions for younger cancer survivors or treatment interventions for older cancer survivors. Due to these variations in risk, a “one-size fits all” approach may not be indicated.

5.1.3 How the intervention might work

There is clear evidence that lifestyle changes, including improved diet and physical activity, are effective in the prevention or reduction of metabolic and cardiovascular risk factors in the general adult population (223). A range of nutritional interventions have been reported to be effective in preventing or reducing risk factors associated with the metabolic syndrome. These include: low glycaemic index/high protein diets, increased fruit, vegetable and fibre intake, reduced salt diets and a Mediterranean-style diet (224, 225). A recent Cochrane review assessing nutritional interventions for reducing or preventing cardiovascular risk found that interventions were more likely to be effective in participants who were told of their higher risk of disease (225).

In the general paediatric population, little research has focused on the prevention of metabolic syndrome. Rather, there is a focus on prevention and treatment of childhood obesity. The literature suggests that family-targeted behavioural lifestyle interventions using a combination of nutrition, physical activity and behavioural components are effective for bringing about change in overweight children (226). There does not appear to be research focusing on the efficacy of specific types of nutritional interventions. As the mechanisms for the increased incidence of these chronic diseases may be different in the general population to the oncology population, the results and recommendations from these studies may not be able to be extrapolated to childhood cancer survivors. Interventions focusing on older and adult survivors of childhood cancer may not be appropriate for the younger survivors.

5.1.4 Why is it important to do this review?

As this is a new area of study, there are minimal data in the literature with regard to the most effective nutritional interventions available to reduce the incidence of chronic disease after childhood cancer, despite the ongoing focus on long-term follow-up of these patients. The purpose of this Cochrane review was to assess the literature regarding nutritional interventions developed for childhood cancer survivors, to facilitate the production of best-evidence management guidelines.

5.1.5 Objectives

To assess the efficacy of a range of interventions designed to improve the dietary intake of children who have completed treatment for cancer, as compared to a

control group of childhood cancer patients off treatment who did not receive the intervention.

5.2 Criteria for considering studies for this review

5.2.1 Types of studies

All randomized controlled trials were included in this review. There was no limit to length of the intervention, type of intervention and length of follow-up.

5.2.2 Types of participants

Studies that involved childhood cancer survivors of any age, who were diagnosed with any type of cancer type when less than 18 years of age were eligible for the review. Participating childhood cancer survivors had completed their treatment with curative intent prior to the intervention. Studies including parents and/or carers of this participant group were also included if the parents/caregivers were involved in the intervention or reported on the participant outcomes. Treatment included chemotherapy and/or radiotherapy. Studies which included participants with a co-morbidity that may have affected eating such as autism (227), developmental delay (228) and Down's syndrome (229) were excluded.

5.2.3 Types of interventions

5.2.3.1 Strategies

Interventions that included educational and counselling strategies, health promotion or behavioural interventions with either individual or family-based interventions were included in this review.

5.2.3.2 Topics

Nutritional interventions involving cancer survivors with or without their family members were captured. Physical activity interventions for cancer survivors (230) and nutritional interventions for childhood cancer patients receiving active treatment (231) were excluded as these have been targeted by an alternate Cochrane reviews.

5.2.3.3 Settings

There was no restriction on the settings for the interventions. Settings may have included community, home-based or hospital-based interventions.

5.2.3.4 Delivery

All methods of delivery of the intervention were eligible, including face-to-face, telephone and online interventions. There were no restrictions regarding the interventionist. That is, eligible interventions were those that were delivered by

specialist and non-specialist medical and allied health professionals, as well as by other non-health professionals.

5.2.3.5 Types of comparison

We included studies which compared nutrition interventions to a non-intervention control group that received usual care or another intervention.

5.2.4 Types of outcome measures

We included studies that reported one or more of the following primary outcomes listed below. These outcomes needed to be assessed at baseline and at a minimum of one follow-up time point.

5.2.4.1 Primary outcomes

A change in nutritional intake which was measured by one or more of the following:

1. Weighed food diaries;
2. Self-reported food diaries;
3. Single or multiple 24 hour recalls;
4. Food frequency questionnaires.

The nutrients may include but are not limited to:

1. Energy;
2. Protein;

3. Fat;
4. Carbohydrate;
5. Calcium;
6. Iron;
7. Folate;
8. Vitamin(s);
9. Mineral(s).

5.2.4.2 Secondary outcomes

1. Metabolic risk factors, i.e. glucose and insulin metabolism;
2. Cardiovascular risk factors, i.e. resting blood pressure, blood lipids, and cholesterol;
3. Measures of weight and body fat distribution, i.e. body mass index (BMI), Dual-energy X-ray Absorptiometry (DEXA) and weight/height percentiles;
4. Behavioural change, i.e. changes in nutritional intake;
5. Changes in knowledge regarding disease risk and nutritional intake;
6. Participant views of the intervention;
7. Measures of health-status and quality of life;
8. Measures of harm associated with the process or outcomes of the intervention;
9. Cost effectiveness of the intervention;

5.2.5 Search methods for identification of studies

5.2.5.1 Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 3, 2013), MEDLINE/PubMed (from 1945 to April 6th, 2013) and EMBASE/Ovid (from 1980 to April 6th, 2013). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in the appendices (Appendix 2, Appendix 3, Appendix 4).

5.2.6 Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE/PubMED, EMBASE/OVID, either published or unpublished, by searching the reference lists of relevant articles and review articles. We hand searched the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2008 to 2012) and The International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (2008-2012). We scanned the ISRCTN register and the register of the National Institute of Health (NIH) (<http://www.controlled-trials.com>) for ongoing trials at the first half of 2013. We did not impose language restrictions on the search.

5.2.7 Data collection and analysis

5.2.7.1 Selection of studies

Two review authors (JC, CW), worked independently, screening all the titles and abstracts resulting from the searches and excluded articles that were clearly irrelevant. Full text copies of all relevant articles were retrieved. Using the defined eligibility criteria, the two review authors determined their eligibility for inclusion. We resolved any disagreement between review authors on classification of an article between the review authors. Third party arbitration was not necessary. There was a need for clarification of detail of one trial. One of the review authors (JC) contacted the study authors from Rai 2008 (232), to obtain clarification for a complete assessment of the trial's relevance for the review. The reasons for exclusion of any study considered for review are summarised in Table 5-1.

Table 5-1 Characteristics of excluded studies

Excluded study	Reason for exclusion
Hudson 1999 (233)	This study described the study protocol and participant baseline data only.
Hudson 2002 (234)	The nutrition component of this study was described in another publication which has been included for assessment in this review.
Mays 2012 (235)	This was a validation study and did not include an intervention.
Moyer-Mileur 2009 (236)	The study included participants on maintenance therapy
Nathan 2009 (150)	This study contains a review of the literature and only reported on a smoking cessation intervention in childhood cancer survivors.

5.2.7.2 Data extraction and management

Two review authors (JC and CW) independently extracted data, using a standardised form, from each article. For each trial, the following data was extracted:

1. Characteristics of the studies including the study sponsors and the authors' affiliations, study design, risk of bias items, duration of study, loss to follow-up and compliance;
2. Characteristics of study population including country where participants enrolled, inclusion and exclusion criteria, number randomised in each arm, information on the control group, demographic characteristics, type of cancer, age at diagnosis, cancer treatment, time since diagnosis, time beyond active treatment;
3. Characteristics of the intervention including type of nutritional intervention, details of the intervention, frequency, duration, intensity, number of sessions, intervention format (i.e. individual or group, professionally led or not, home- or facility-based), description of control intervention, adherence and contaminations as well as co-interventions (i.e. physical activity, medication use);
4. Characteristics of the outcomes as stated previously.

We entered and combined the trial data using Review Manager 5.2. One review author entered the data into RevMan 5.2 (JC), and another review author worked independently to verify the data entry (CW). We resolved any disagreement between review authors on classification of an article between the review authors. Third party arbitration was not necessary.

5.2.7.3 Assessment of risk of bias in included studies

Two independent reviewers (JC, CW) assessed the validity of each study using the risk of bias items. We reported the following criteria for each trial: adequate sequence generation and allocation concealment (selection bias), masking or blinding of personnel, participants and outcome assessors (performance or detection bias), incorporate incomplete data (attrition bias) and selective outcome reporting (reporting bias). Baseline imbalance (gender, ethnicity, diagnosis, age and health behaviour or nutritional intake) and differential diagnostic activity were also assessed as other potential sources of bias.

We assessed and graded each trial's risk of bias parameter as "adequate", "inadequate", or "unclear". Trials with one or more unclear or inadequate risk of bias components were be considered to have a high risk of bias. We resolved any disagreement between review authors on classification of an article between the review authors. Third party arbitration was not necessary.

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to rate the overall quality of evidence for each outcome by two independent reviewers (237, 238). The GRADE approach defines the quality of a body of evidence as "High", "Moderate", "Low" or "Very Low" (239). Factors that may have resulted in a decrease in the quality of evidence included: 1) risk of bias; 2) inconsistency; 3) indirectness; 4) imprecision; and 5) publication bias.

5.2.7.4 Measures of treatment effect

For continuous outcomes, the mean difference between groups was assessed. For dichotomous outcomes, a relative risk was assessed.

5.2.7.5 Unit of analysis issues

We aimed to include cluster-randomised, cross-over and repeated measures trials in this analysis, though none of the eligible studies used these methodologies.

5.2.7.6 Dealing with missing data

It was necessary to contact the authors of the Rai 2008 study (232), to gather further detail on the nutrition intervention.

Intention-to-treat analysis was performed for all studies.

5.2.7.7 Assessment of heterogeneity

As none of the data was able to be pooled due to the different outcome measures and interventions between the trials, assessment of heterogeneity using the I^2 analysis was unable to be performed.

5.2.7.8 Assessment of reporting biases

We had planned to assess reporting bias by constructing funnel plots. As there were less than 10 studies included in this review, the power of the tests was too low to distinguish chance from real asymmetry (239) so this was not able to be completed.

5.2.8 Data synthesis

The data of the included studies were entered into Review Manager 5.3 software. Data analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions (239). As the data was not able to be combined in a meta-analysis, we provided a narrative summary of the trial findings according to the review objectives. For data that was provided as medians and ranges, the mean difference was converted to mean and SD based on the methodology of Hozo 2005 (240).

5.2.9 Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analysis based on the following categories: 1) age at intervention (< 13 years; 13 to 18 years; > 18 years); 2) forms of intervention (face-to-face; phone etc.); 3) duration of intervention; 4) childhood cancer type; and 5) type of treatment received. Due to insufficient trials, this was unable to occur. Due to lack of data in the included studies subgroup analyses were not possible

5.2.10 Sensitivity analysis

As pooling of the results was not possible, we were unable to use sensitivity analyses to explore the impact of the inclusion of studies with a high risk of bias and studies with an unclear risk of bias.

5.3 Results

5.3.1 Results of the search

A total of 3607 studies were identified from running the search through three electronic databases CENTRAL, MEDLINE/PubMED, EMBASE/OVID. An additional study was identified from searching the ongoing trial registries. No studies were identified upon screening reference lists of relevant articles and reviews. No studies were identified from the conference proceedings from The International Pediatric Oncology Society and The International Conference on Long-Term Complications of Treatment of Children and Adolescents for cancer. Initial screening of the title and abstracts of each study allowed the exclusion of 3599 publications. We obtained the full text articles of nine studies, of which three met the inclusion criteria. Five studies did not meet the inclusion criteria and one of the studies was classified as ongoing (Figure 5-1).

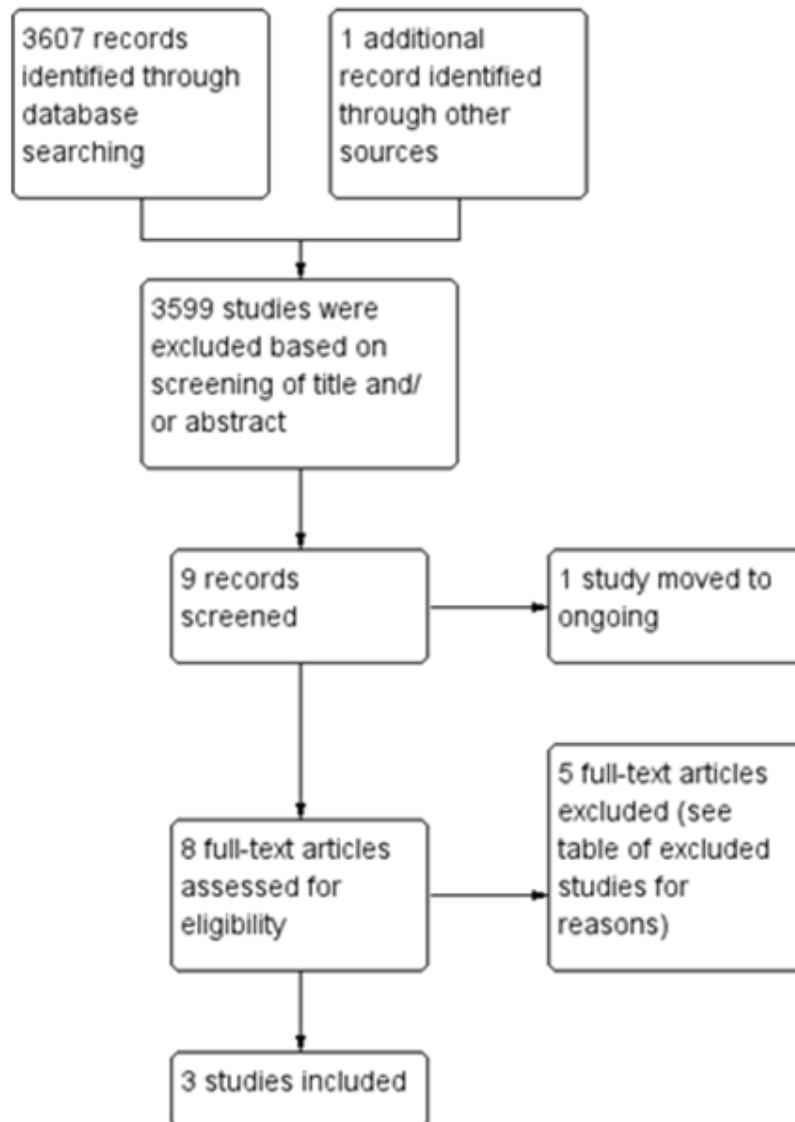


Figure 5-1 Study flow diagram

5.3.2 Included studies

Three studies were included in this review. All three studies were RCTs. For further details on the studies see Table 5-2

Table 5-2 Characteristics of included studies

	Cox 2005	Mays 2011	Rai 2008
Methods	<p>Design: Parallel RCT</p> <p>Setting: Single-site paediatric oncology unit, USA</p>	<p>Design: Parallel RCT</p> <p>Setting: Two site, Pediatric oncology units, USA</p>	<p>Design: Parallel RCT</p> <p>Setting: Single site, paediatric oncology unit, USA</p>
Participants	<p>Number</p> <p>Intervention: n=131 (4 lost to follow-up)</p> <p>Control: n=135 (1 lost to follow-up)</p> <p>Age at study entry</p> <p>Group:12-18 years</p> <p>Intervention (mean \pm SD): 15.09 \pm 1.90 years</p> <p>Control (mean \pm SD): 14.96 \pm 1.97 years</p> <p>Sex</p>	<p>Number</p> <p>Intervention:38</p> <p>Control: 37</p> <p>No information on attrition was available.</p> <p>Age at study entry</p> <p>Group:11-21 years</p> <p>Intervention (mean \pm SD): 14.2 \pm 2.0 years</p> <p>Control (mean \pm SD): 14.2 \pm 2.8 years</p> <p>Sex</p>	<p>Number</p> <p>Intervention: n=141 (45 dropouts)</p> <p>Control: n=134 (49 dropouts)</p> <p>Age at study entry</p> <p>Intervention (mean; range): 16.6 (9.4 35.3) years</p> <p>Control (mean; range): 17.2 (9.4 33.5) years</p> <p>Sex</p> <p>Intervention: 78 males: 63 females</p> <p>Control: 78 males: 56 females</p>

	<p>Intervention: 57 males: 74 females</p> <p>Control: 61 males: 74 females</p> <p>Diagnosis</p> <p><i>Leukaemia/Lymphoma</i></p> <p>Intervention: 73</p> <p>Control: 72</p> <p><i>Solid Tumour:</i></p> <p>Intervention: 58</p> <p>Control: 63</p> <p>Treatment</p> <p>Information not available</p> <p>Age at diagnosis</p> <p>Information not available</p> <p>Time since diagnosis</p> <p>Intervention (mean \pm SD): 15.09(1.90) years</p>	<p>Intervention: 17 males: 21 females</p> <p>Control: 19 males: 18 females</p> <p>Diagnosis</p> <p>Intervention: 21 Leukaemia: 17 others</p> <p>Control: 18 Leukaemia: 19 others</p> <p>Treatment</p> <p>Information not available</p> <p>Age at diagnosis</p> <p>Information not available</p> <p>Time since treatment completion</p> <p>Information not available</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Previously treated for any form of oncologic malignancy 2. One or more years off treatment 3. One or more years cancer-free 4. Able to comprehend and speak English 	<p>Diagnosis</p> <p>ALL</p> <p>Treatment</p> <p>Radiation</p> <p>Intervention:53</p> <p>Control:34</p> <p>Chemotherapy</p> <p>Intervention: 141</p> <p>Control:134</p> <p>Age at diagnosis</p> <p>Intervention (mean; range): 4.7 (0.7; 17.4) years</p> <p>Control (mean: range): 4.6 (1.0; 16.39) years</p> <p>Time since treatment completion</p> <p>Intervention (mean ; range): 7.1 (5.0 18.2) years</p>
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	<p>Control (mean \pm SD): 10.31 (2.94)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. 12-18 years 2. In remission 2+ years from completion of therapy 3. Adequate cognitive functioning 4. English as a primary language <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Not U.S. residents 2. English not their primary language 	<p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Suffering from renal insufficiency or end stage renal disease 2. Currently taking a thiazide diuretic 3. Suffering from a pervasive developmental or other major psychiatric disorder precluding valid informed consent 	<p>Control (mean ; range): 7.2 (4.6 19.1) years</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Treated on St Judes Children's Research Hospitals total XI, XII or XIII treatment protocol 2. At least five years from completion of cancer therapy 3. In first remission <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Active disease 2. Pregnant or lactating females 3. Inability to chew or swallow pills 4. Currently consuming more than 800mg of supplemental calcium or 800IU of Vitamin D 5. Anaemia
Interventions	<p>Intervention</p> <p>The intervention consisted of standard</p>	<p>Intervention</p> <p>The intervention consisted of a single</p>	<p>Intervention</p> <p>This study was a 24 month nutrition</p>

	<p>care plus a single multi-behavioural intervention provided by a clinical physician or nurse practitioner during a routine visit to the long-term follow-up clinic. The multi-behavioural intervention consisted of:</p> <ol style="list-style-type: none"> 1. Discussion of after therapy clinical summary 2. Health behaviour training of health goal 3. Health goal commitment to practice <p>Telephone reinforcement of the education was provided at 3 and 6 months after their initial clinic visit</p> <p>Co-interventions:</p> <p>Other health behavior practices were targeted during the intervention. These included; smoking cessation, sun protection and exercise.</p> <p>Contraindications:</p> <p>None</p>	<p>half-day, group workshop in addition to standard care. The workshop was given by a registered dietitian. The workshop included an interactive behavioural session and focused on risk reducing health promotion behaviours. The workshop had a focus on bone health.</p> <p>Co-interventions:</p> <p>None</p> <p>Contraindications:</p> <p>None</p> <p>Control group</p> <p>The control group received standard care and were offered the intervention at the conclusion of the study.</p>	<p>and supplementation intervention. The intervention group received nutrition education sessions every 6 months. At baseline and 12 months these were given face-to-face by a registered dietitian, and at 6 months and 18 months these were given in the form of mailed information. The education included information such as:</p> <ol style="list-style-type: none"> 1. Number of serves of dairy products 2. Serve sizes of dairy foods 3. Healthy diet <p>The intervention group was also be given 24 months of calcium and vitamin D supplementation which were taken daily</p> <p>Co-interventions:</p> <p>None</p> <p>Contraindications:</p> <p>None</p>
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	Control Group Standard care consists of: <ol style="list-style-type: none"> 1. Breast or testicular self-examination 2. Targeted late-effects screening 3. Clinical assessment 4. Late effects risk counselling 		Control group The control group received education sessions identical to the intervention group. They also received placebo tablets instead of calcium and vitamin D supplements.
Outcomes	The outcomes were measured at baseline and 12 months post-intervention for both the intervention and control groups. Outcome measure: Behavioural change 1) Frequency of nutrition as a health protective behaviour 2) Frequency of junk food consumption as a health risk behaviour	The outcomes were measured at baseline and 1month post-intervention for both the intervention and control groups. These outcomes were: Outcome measure: Change in nutritional intake: 1) Dietary calcium intake measured with 24-h recall Outcome measure: Behavior change: 1) milk consumption frequency 2) Use of calcium supplementation	The outcomes were measured at baseline, 12 months, 24 months and 36 months post-intervention for both the intervention and control groups. Outcome measure: Body composition 1) Bone mineral density
Notes	Study Sponsors Oncology Nursing Society Foundation	Study Sponsors	Study Sponsors National Institutes of Health; Grant

	<p>(2003-2005)</p> <p>American Lebanese Syrian Associated Charities (ALSAC)</p>	<p>American Cancer Society</p> <p>Lance Armstrong Foundation</p> <p>National Cancer Institute (CA091831)</p>	<p>number: P30 CA-21765</p> <p>Centre of Excellence grant from the State of Tennessee</p> <p>Le Bonheur Foundation (Memphis TN)</p> <p>American Lebanese Syrian Associated Charities (ALSAC)</p> <p>NIH; Grant numbers: R21 HD059292; GM 92666 Grant sponsor</p> <p>Gabrielle's Angel Foundation</p>
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5.3.3 Participants

A total of 616 participants from the three studies were included in the analysis. One of the studies included participants who had been treated for ALL (232). Cox 2005 and Mays 2011 included participants with all forms of paediatric cancer (212, 241). The number of participants in each study varied. The smallest study included a total of 38 participants in the intervention and 37 in the control group (241). It was unclear whether any participants were lost to follow-up. Cox 2005 study included a total of 266 participants (131 in the intervention and 135 in the control group) (212). Four and one participants respectively were lost to follow-up. The largest study included a total of 275 participants (141 in the intervention and 134 in the control group) (232). Ninety-four participants (45 in the intervention and 49 in the control group) did not complete the study.

The ages of the participants varied among the three studies. Two studies recruited adolescent childhood cancer survivors [ages 11-21 years (241) and 12-18 years (212)]. The third study included childhood cancer survivors of all ages up to 18 years (232). None of the included studies had participants older than 21 years at study entry.

5.3.4 Intervention

The timing of the interventions after the childhood cancer therapy varied among the studies. Cox 2005 and Mays 2012 included participants within two years of diagnosis (212, 241) and Rai 2008 included participants who were more than five

years since therapy completion (232). The intervention and timing also varied among the three studies included in this analysis. Two of the studies included interventions that consisted of an initial, single, face-to-face health education session focusing on health behaviour change (212, 241). One of these studies focused on general health behaviours such as reducing junk food intake(212). The individual education session was provided by a clinician or nurse practitioner during a routine visit to the hospital. These participants were giving education reinforcement, via the telephone, at three and six months after the intervention. The other intervention focused on bone health, calcium and dairy intake and the final assessment was done one month after the intervention (241). The education session was provided in a group setting by a registered Dietitian.

The final study (Rai 2008) (232) had a 36 month follow-up, with the focus of the intervention being on bone health. The intervention consisted of calcium and vitamin D supplementation. Nutrition education was provided at baseline and every 6 months for 24 months. At baseline and 12 months post baseline, the education was given face-to-face by a registered dietitian. At 6 months and 18 months the nutrition education was in the form of mailed information. For further information on these studies, see Table 5-2.

The study of Cox 2005 also included a co-intervention of changing the health behaviour practices of smoking cessation, sun protection and exercise (212). This study did not have any contraindications. The studies of Mays 2011 and Rai 2008 (232) did not include any co-interventions or contraindications (232, 241).

5.3.5 Control

Of the three studies included in this review, the control groups of two of those studies received standard care (212, 241). The standard care between these groups did vary. The standard care of the control group for the study of Cox 2005 included late-effects screening and education on their risk factors which was provided during routine clinic visits (212). The standard care of the control group for Mays 2011 was no education on nutrition related risk factors (241). The control group of the final study received an identical nutrition education component as the intervention group in combination with placebo tablets (232).

5.3.6 Outcomes

The primary outcomes of the studies in this review were dietary/nutrient intake. The secondary outcomes measured by the included studies were body composition (BMD) and health behaviours. The control group measurements were assessed at the same time points as the intervention groups for all three of the studies. The time points for the outcome measures, differed between the studies. The study of Mays 2011 measured their outcomes (milk consumption frequency, calcium supplementation, dietary calcium intake) at baseline and one-month post intervention (241). The study of Cox 2005 measured their outcomes (frequency of nutrition as a health protective behaviour; frequency of junk food consumption as a health risk behaviour) at baseline and 12 months post-intervention (212). The final study of Rai 2008 measured their outcomes (bone mineral density) at baseline, 12 months, 24 months and 36 months post intervention (232).

The other secondary outcomes were not addressed in any of the three included studies. These secondary outcomes were: metabolic risk factors, cardiovascular risk factors, changes in knowledge, participant views of the intervention, health status and QoL, measures of harm or cost effectiveness of the intervention. All three studies had different methodology and different outcomes being measured and for this reason the data was unable to be pooled.

5.3.7 Excluded studies

The full text publications of five studies were analysed but were subsequently excluded. Three of the studies (Hudson 1999; Hudson 2002; Mays 2012) described the study protocol and provided results from other components of the study. The study data relating to the aims for this review were reported in other articles which were included in this review (212, 241). The fourth study (Nathan 2009) contained a review of the literature and the results of a smoking cessation intervention and was subsequently excluded from the review. The final study (Moyer-Mileur 2009) included participants on maintenance therapy and had not completed their cancer therapy. For information on the excluded studies see Table 5-1.

5.3.8 Risk of bias in included studies

See Table 5-3 and Figure 5-2 and Figure 5-3 for detailed information on the risk of bias assessment.

Table 5-3 Risk of bias in included studies

	Cox 2005		Mays 2011		Rai 2008	
	Risk	Reason for judgement	Risk	Reason for judgement	Risk	Reason for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was stratified by gender and age because of the clinical impression that risk perception could carry by gender or age".	Unclear risk	Comment: The paper states that the participants were randomly allocated but no further information on the methodology was provided.	Low risk	Comment: The participants were stratified when randomised into sex, race, age and BMD z-score.
Allocation concealment (selection bias)	Unclear risk	Comment: Although randomisation was performed using the procedure as set out by Zelen 1974,(242) it was unclear which actual randomisation technique	Unclear risk	Comment: There was no information provided on participant attrition.	Low risk	Quote: "Only the St Jude pharmacy had access to the randomisation system, which is maintained by the Department of Biostatistics at St Jude".

		was used.				
Incomplete outcome data (attrition bias)	Unclear risk	Comment: The study reported that five participants (four in the intervention group and one in the control group) were lost to follow-up. There was no discussion on how this data was handled. We were unable to assess how this would influence the outcome or whether this would have a clinically relevant effect.	Unclear risk	Comment: This study reported data at baseline and follow-up on all outcomes cited in the protocol or methodology section	Unclear risk	Comment: There were a large number of dropouts in both the intervention (n=45) and control groups (n=49). It is unclear how this data was treated.
Selective reporting (reporting bias)	High risk	Comment: This study presented a secondary analysis of data. This analysis was not in the original publication of the results.	Low risk	Comment: Minimal baseline imbalance: At baseline, there was no significant difference between the intervention and the control group for demographic and other reported characteristics.	High risk	Comment: This study did not publish all outcomes that were reported on the clinical trials registry

				No differential diagnostic activity: All assessments were performed at baseline and follow-up for both the intervention and the control group.		
Other bias	Low risk	<p>Comment:</p> <p>Minimal baseline imbalance: At baseline, there was no significant difference between the intervention and the control group for demographic and other reported characteristics.</p> <p>No differential diagnostic activity: All assessments were performed at baseline and follow-up for both the intervention and the control group.</p>	Low risk	<p>Comments: This study does not discuss whether participants or personnel were blinded. Due to the nature of the study and the form of the intervention, it would be impossible for the participants and personnel to be blinded.</p>	Low risk	<p>Minimal baseline imbalance: At baseline, there was no significant difference between the intervention and the control group for demographic and other reported characteristics.</p> <p>No differential diagnostic activity: All assessments were performed at baseline and follow-up for both the intervention and the control group.</p>
Blinding of participants and personnel (performance bias)	High risk	<p>Comment: This study does not discuss whether participants or personnel were blinded. Due to the nature of the study and the</p>	High risk	<p>Quote: "All telephone interviews were administered by a trained research assistant who was</p>	Low risk	<p>Comment: Both the participants and the research personnel were blinded.</p>

		form of the intervention, it would be impossible for the participants and personnel to be blinded.		masked to the trial condition".		
Blinding of outcome assessment (detection bias)	High risk	Comment: The outcome is subjective (a self-reported outcome) and the participants are not blinded.	Low risk	Comment: The paper states that the participants were randomly allocated but no further information on the methodology was provided.	Low risk	Comment: Both the participants and the research personnel were blinded.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Cox 2005	+	?	?	-	+	-	-
Mays 2011	?	?	?	+	+	-	+
Rai 2008	+	+	?	-	+	+	+

Figure 5-2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

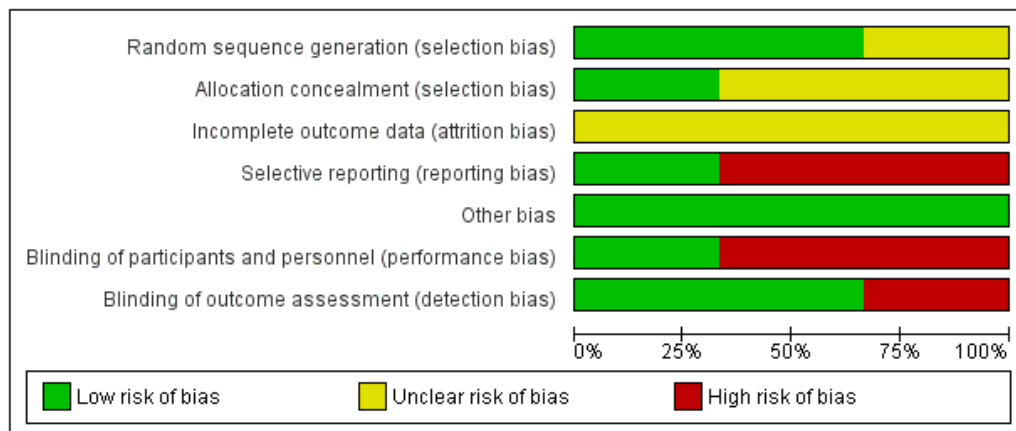


Figure 5-3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

5.3.9 Allocation (selection bias)

Two of the studies (Cox 2005; Rai 2008) described an adequate random sequence generation and were assessed as low risk (212, 232). In the study by Rai 2008, the randomisation was completed by the pharmacy after participants had been stratified into sex, race, age and BMD (232). The study of Cox 2005 used a randomisation procedure that was stratified by gender and age (212). The final study was assessed as “unclear” in the use of random sequence generation (241). Mays 2011 reported that the participants were randomised, but no further information was provided on the procedure (241). Two of the studies were assessed as having an unclear allocation concealment as there was no mention of the procedures used in the study methodologies (212, 241). The study of Cox 2005 referred to the methodology used by another author, though the methods used were still not clear (212). The study of Rai 2008 used a well described randomisation procedure and was assessed as having a low risk of allocation concealment (232).

5.3.10 Performance bias

Due to the nature of the interventions, blinding of the personnel or the participants was impossible with two of the three studies (Cox 2005; Mays 2011) assessed as having a high risk of performance bias (212, 241). In the final study (Rai 2008), the participants and the personnel were blinded to the intervention as participants were given a vitamin supplement or a placebo (232). This study was assessed at having a low risk of performance bias.

5.3.11 Detection Bias

Although personnel cannot be blinded when delivering nutrition interventions such as these, it is possible for detection bias to be minimized by blinding the outcome assessment. One study (Cox 2005) did not provide any information regarding blinding of the outcome assessment but the outcome was subjective (a self-reported outcome) and therefore the blinding of the outcome assessment was assessed as high risk (212). In the remaining two studies (Cox 2005; Rai 2008), detection bias was assessed as low risk because the assessors were blinded to the study groups (212, 232).

5.3.12 Incomplete outcome data (attrition bias)

Two of the three studies reported drop-outs during the study (Cox 2005; Rai 2008) (212, 232). No further information was provided on how the missing data was handled and the studies were assessed as having an unclear risk of attrition bias. Although the fourth study had a short follow-up time of one month and was less likely to have drop-outs, no information was provided on study attrition. This study was assessed as having an unclear risk.

5.3.13 Selective reporting (reporting bias)

The study of Mays, 2011 was the only study to be assessed as having a low risk of reporting bias (241). This study reported data at baseline and follow-up on all outcomes cited in the protocol or methodology section. Cox 2005 presented the results of a secondary analysis, not mentioned in the original protocol. Hudson 2002 and Rai 2008 did not publish all outcomes that were reported on the clinical trials

registry (232, 234). These two studies were assessed to be at high risk of reporting bias.

5.3.14 Other potential sources of bias

All studies were assessed for baseline imbalances and differential diagnostic activity as other potential sources of bias. In regards to baseline imbalances, there was no significant difference between the baseline data between the intervention and the control group for all studies (212, 232, 241). All three studies were assessed at being low risk.

All three studies were classified as a low risk of differential diagnostic activity because the studies performed the same assessments in the intervention and the control group at all time-points (212, 232, 241).

5.3.15 Effects of interventions

The three studies included in this review focused on different outcomes. We were unable to pool the data and the findings reported were from individual studies only.

5.3.16 Change in nutritional intake

Calcium intake was the only nutrient that was assessed across any of the studies (241). Use of a single, group-based behaviour change intervention showed no statistically significant difference in the calcium intake (as measured by a 24-hour

recall) between the intervention (n= 38) and control group (n=37) at the one month follow-up (MD 111.60; 95% CI -258.97 to 482.17; P value = 0.56) (Figure 5-4) (241). As analysed by Mays 2011, after regression analysis, adjusting for baseline calcium intake and changes in knowledge and self- efficacy, there was a significantly greater calcium intake for the intervention as compared with the control group at the one month follow-up (Beta coefficient= 4.92; 95% CI 0.33 to 9.52; P value = 0.04) (241).

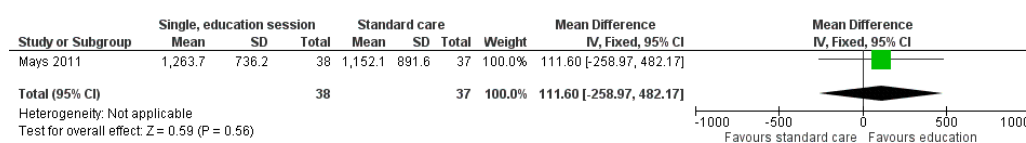


Figure 5-4 Forest plot of change in nutritional intake (calcium)

5.3.17 Body Composition

Body composition was used as an outcome measure in one study (Rai 2008) (232). The data was provided as medians and ranges. This data was converted to mean and SD based on the methodology of Hozo 2005 (240). There was no statistically significant difference in bone mineral density (measured with a DEXA scan) at the 36 month follow-up (MD -0.05; 95% CI -0.26 to 0.16; P value = 0.64) (Rai 2008) (Figure 5-5) between those who received the calcium and vitamin D supplementation in conjunction with nutrition education (n=141) and those participants who received nutrition education alone (n=134) (232). There was no statistically significant difference in bone mineral density between the intervention and the control group at the 12 month (median difference -0.17: P value 0.99) and 24 month follow up (median difference -0.04: P value 0.54).

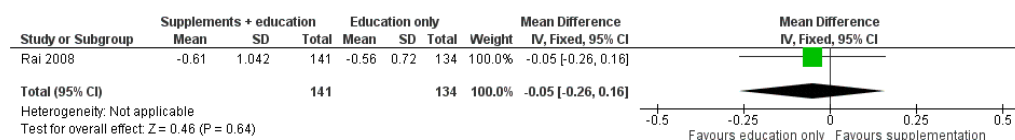


Figure 5-5 Forest plot of change in body composition (bone mineral density)

5.3.18 Behavioural Change

The behaviour change outcome was assessed in two studies. In the first study, health behaviour change was measured using single questions on a four-point Likert scale (212). The participants were asked how often they practiced health practicing behaviours and rated this from 1=never to 4=always. A single, face-to-face, multi-component health behaviour change intervention with two telephone follow-ups brought about no statistically significant difference in the use of nutrition as a health protective behaviour (n=131) compared with those who received standard care (n=135) (MD -0.05; 95% CI -0.24 to 0.14; P value = 0.60) (Figure 5-6) (212).

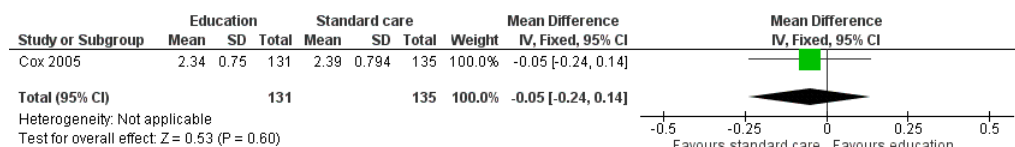


Figure 5-6 Forest plot of behaviour change (nutrition)

The same intervention brought about a statistically significant reduction in self-reported junk food intake (measured on a four-point likert scale: 1= never to 4= always) in the intervention (n=131) compared with the control group (n= 135) (MD -0.17; 95% CI 0.33 to -0.01; P value= 0.04) (Figure 5-7).

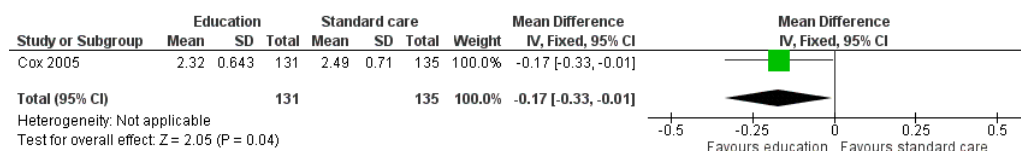


Figure 5-7 Forest plot of behaviour change (junk food)

A single, face-to-face, group health behaviour session focusing on bone health brought about a statistically significant increase in the intervention group's self-reported milk consumption (measured in number of days) (MD 0.43; 95% CI 0.07 to 0.79; P value = 0.02) (Figure 5-8) as compared with those who received standard care (241).

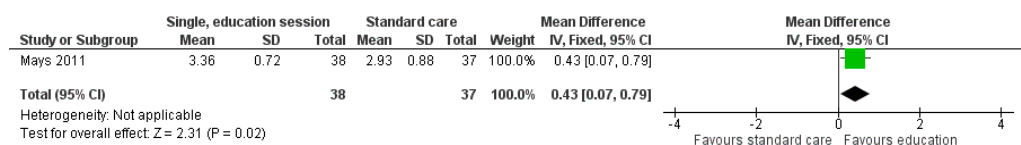


Figure 5-8 Forest plot of behaviour change (milk consumption)

The intervention was also effective in increasing the participants days on calcium supplementation (MD 11.42; 95% CI 7.11 to 15.73; P value <0.00001) (Figure 5.9) (241).

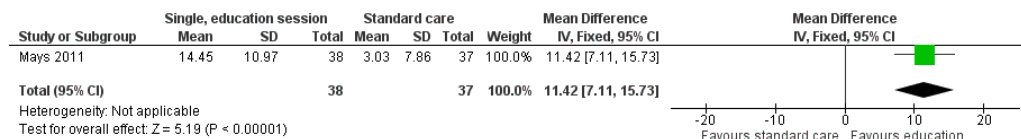


Figure 5-9 Forest plot of behaviour change (days on calcium supplementation)

There was a statistically significant increase in calcium supplementation in the group that received the education sessions compared with those who received standard care (RR 3.35; 95% CI 1.86 to 6.04; P value < 0.0001) (Figure 5-10). A total of 31

participants took some form of calcium supplementation after the intervention and nine participants took some form of calcium supplementation in the standard care group.

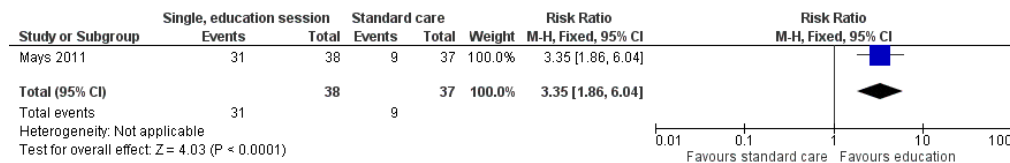


Figure 5-10 Forest plot of behaviour change (any calcium supplementation)

5.4 Discussion

5.4.1 Summary of main results

Childhood cancer survivors are at higher risk of health conditions such as osteoporosis, metabolic syndrome, endocrine disorders and cardiovascular disease than their peers (150). Targeted nutritional interventions may prevent (216, 217) or reduce (15, 150) the incidence of these chronic diseases. This systematic review included three studies (212, 232, 241) that have studied the efficacy of a nutritional intervention, in a randomised manner, in childhood cancer survivors. These studies utilised differing methodologies, and as a consequence, pooling of the results did not occur.

The interventions that appeared to bring about a significant positive change were those that focused on health behaviour change. A single, group health behaviour education session significantly increased self-reported milk intake (MD 0.43; 95% CI

0.07 to 0.79; P value = 0.02), use of calcium supplementation (RR 3.35; 95% CI 1.86 to 6.04; P value < 0.0001) and the number of days on calcium supplementation (MD 11.42; 95% CI 7.11 to 15.73; P value <0.00001) as compared with standard care (241). The intervention did not improve calcium intake (MD 111.60; 95% CI -258.97 to 482.17; P value = 0.56), though a regression analysis, adjusting for baseline calcium intake and changes in knowledge and self-efficacy, found a significantly greater calcium intake for the intervention as compared with the control group at the one month follow-up (Beta coefficient= 4.92; 95% CI 0.33 to 9.52; P value = 0.04). This study had a short follow-up time of one month and the effect of the intervention long term was not assessed.

A face-to-face, multi-component health behaviour session with two telephone follow-ups with education reinforcement, over a 12 month period, reduced self-reported junk food intake (MD -0.17; 95% CI -0.33 to -0.01; P value= 0.04) but did not improve childhood cancer survivors' use of nutrition as a health-protecting behaviour (MD -0.05; 95% CI -0.24 to 0.14; P value = 0.60) (Cox 2005) as compared with standard care.

The study of Rai 2008 was the only study to assess the efficacy of nutritional supplementation on childhood cancer survivors' body composition. This study was a randomised, double-blind RCT of calcium and vitamin D supplementation versus placebo. Both the intervention and control group received nutrition education by a registered Dietitian. There was no statistically significant difference on bone mineral density as measured by DEXA between the intervention and the control group at the 36 month follow-up (MD -0.05; 95% CI -0.26 to 0.16; P value = 0.64). There was

also no statistically significant difference in bone mineral density between the intervention and the control group at the 12 month (median difference -0.17: P value 0.99) and 24 month follow up (median difference -0.04: P value 0.54).

5.4.2 Overall completeness and applicability of evidence

This review does not provide evidence that the nutritional interventions used in these studies improved dietary intake or body composition in childhood cancer survivors. The study of Mays 2011, was the only included study that assessed the primary outcome of a change in nutritional intake (241). Mays 2011 found no statistically significant improvement in calcium intake with a single, group, education session (241). A regression analysis, adjusting for baseline calcium intake and changes in knowledge and self- efficacy, found a significantly greater calcium intake for the intervention as compared with the control group at the one month follow-up (241). The study had a short follow-up time of one month and long-term compliance with the nutritional changes were not assessed. There was a modest, positive effect for health behaviour change interventions on improving self-reported health behaviours such as junk food consumption (212), and milk intake (241). Although no statistically significant differences were found for many of the outcomes this could be the result of low power in the studies. It should be noted that no evidence of effect is not the same as evidence of no effect.

The following outcomes were not assessed in any of the included studies: metabolic and cardiovascular markers, changes in knowledge, and participant views of the intervention, health status and QoL, measures of harm or the cost effectiveness of the intervention.

The two studies that did show a positive change in health behaviours may not be applicable in all settings. The intervention required an initial face-to-face information session. This type of intervention may not be possible for survivors of childhood cancer who come from geographically diverse regions who may not travel to the primary care centre for long-term follow-up. An efficacy of interventions utilising computer and other technologies may need to be assessed.

Many of this systematic review's predetermined outcomes (e.g. metabolic risk factors, cardiovascular risk factors, changes in knowledge, and measures of harm) were not assessed in the included studies. Only one of the studies assessed the primary outcome of dietary intake. Although two of the interventions found a significant positive change in health behaviours, there is no evidence to suggest that this translates to the prevention of risk factors such as cardiovascular disease, metabolic syndrome or obesity. Future interventions should consider assessing outcomes such as body composition and blood lipids in combination with dietary intake and changes in health behaviours.

All three of the captured studies were from paediatric oncology units in the USA. The findings therefore may not be generalisable to childhood cancer survivors from other countries, especially low income countries.

5.4.3 Quality of the evidence

By applying the GRADE criteria (237, 238), the quality of findings varied between moderate (bone mineral density) and low (all other outcomes). All outcomes were

downgraded one level for imprecision. Due to a lack of blinding of participants, personnel and outcome assessors, the quality of evidence for the outcomes “self-reported nutrition) and “junk food” was further downgraded. Due to lack of details regarding the randomisation procedure and lack of blinding of participants and personnel, the outcomes “calcium intake”, “milk consumption” and “calcium consumption” were downgraded to low quality. The study of Cox 2005 had a high risk of reporting bias (results were from a secondary analysis) and performance bias (inadequate blinding of the personnel) (212). The study of Cox 2005 had an unclear selection bias, attrition bias and detection bias and results from this study therefore need to be interpreted with caution (212).

The study of Rai 2008 was the only study to be assessed as having a low risk of performance bias as both the participants and personnel were blinded (232); Mays 2011 had a high risk of performance bias (241). Although it is difficult to blind participants to the intervention due to the nature of many nutritional trials, two studies blinded the assessors (232, 241). Adequate allocation concealment would be possible for all nutritional intervention trials, though the study of Rai 2008 was the only study to be assessed as a low risk of selection bias (232); Mays 2011 had an unclear risk (241). The studies of Mays 2011 and Rai 2008 had a low risk of reporting bias (232, 241). All three studies were assessed as unclear in their attrition bias. All three studies were assessed as having a low risk of other bias (212, 232, 241). The studies had minimal baseline imbalance and no differential diagnostic activity.

5.4.4 Potential biases in the review process

The search strategies for the electronic databases (CENTRAL, MEDLINE/PubMED, EMBASE/OVID) were developed in collaboration with the Cochrane Childhood Cancer Group. Additional searching was done of clinical trials databases, reference lists and proceedings from conferences. Although it is always possible to miss studies, an earlier published review did not identify any different additional interventions prior to 2010 (217).

5.4.5 Agreements and disagreements with other studies or reviews

Only one other review paper was identified in the literature systematically reviewing diet (and exercise) in childhood cancer survivors (217). This review included studies that focused on diet in childhood cancer survivors, though the majority of these were observational studies and unable to be included in the current review. They identified one nutritional intervention in childhood cancer survivors which was also included in our review (212) but did not identify any other type of interventional studies. Stolley 2010 concluded that the literature on the dietary intake of childhood cancer survivors is methodologically weak (217). There were very limited intervention studies and use of control groups in the observational studies was rare. Stolley 2010, highlights the minimal use of validated methods of dietary assessment (217). Since the paper by Stolley 2010 was published, there are an increased number of intervention trials (three) which were included in this review though the use of validated dietary methods remains poor (217).

5.5 Authors' conclusions

5.5.1 Implications for practice

Due to the heterogeneity of the studies included in this review, the authors are unable to draw conclusions regarding the effectiveness of nutritional interventions for childhood cancer survivors. Although there is weak evidence for the improvement in health-behaviours using health behaviour change interventions, there remains no evidence as to whether this translates into an improvement in dietary intake. It is important to note that 'no evidence of effect' is not the same as 'evidence of no effect'. Many outcomes were not assessed in the included studies. There remains no evidence that there is a subsequent reduction in the risk of cardiovascular and metabolic disorders in childhood cancer survivors from the interventions.

5.5.2 Acknowledgements

The authors would like to thank the Cochrane Childhood Cancer Group for their support with the development of this protocol, in particular Edith Leclercq for help with development of the search strategy and running of the search strategies in the different databases. The authors would also like to thank Susan Kaste for providing additional data for the study of Rai 2008 and Jodie Bartle for input into the initial protocol. The editorial base of the Cochrane Childhood Cancer Group is funded by Stichting Kinderen Kankervrij (KiKa).

5.5.3 Implications

This review highlights the need for further intervention trials to be implemented in survivors of childhood cancer. Chapters 2 and 3 found that poor dietary habits are manifesting early after treatment completion. Nutritional interventions are more likely to be effective if they are implemented early after treatment completion. The use of a randomised design with a blinding of personnel to the outcome measures is possible with this type of nutritional intervention and is recommended in future studies. It is also suggested that future studies utilise validated measures of dietary intake. Objective measures of body composition, cardiovascular and metabolic risk should also be included as outcome measures in these studies. The next chapter will focus on the nutritional management of paediatric cancer patients during cancer therapy.

6 ENTERAL NUTRITION IN PAEDIATRIC ONCOLOGY: A MULTIPERSPECTIVE STUDY⁴

Chapters 3 and chapter 4 provided evidence that poor dietary intake seen in adult survivors of childhood cancer, is manifesting itself early after treatment completion. It also appears that these dietary habits are occurring during the treatment. Section 2.4.2. of the literature review discussed recent work at our center regarding the feeding practices used by parents to encourage a child to eat during cancer therapy. These practices were predominantly negative. The literature review also indicated that the threat of tube feeding was also used as a method of coercion to eat. Negative feeding practices during cancer therapy may be contributing to the long term poor dietary habits seen in survivors of childhood cancer. This chapter focuses on the views of parents, patients and healthcare workers surrounding the use of tube feeding as a method of nutritional supplementation.

⁴ This chapter has been submitted for publication in the following peer review journal:
Cohen J, Wakefield CE, Tapsell LC, Walton K, Cohn R. Enteral nutrition in paediatric oncology: a multiperspective study. *Nutrition & Dietetics*.
JC & CW designed the study, JC coded and analysed the data, JC, CW, LT, KW & RC contributed to data analysis and manuscript preparation.
The key findings have been peer reviewed and presented at the 16th International Congress of Dietetics and The 43rd Congress of the International Society of Pediatric Oncology with the abstract included in the following publications:
Cohen J, Wakefield CE, Fleming CAK, Cohn RJ. What do parents of childhood cancer patients actually think about enteral nutrition. *Pediatric Blood and Cancer*. 2011;57(5); 835

6.1 Introduction

Nutritional therapy is an important part of the management of childhood cancer patients to ensure adequate growth and development (4). Oral intake can be reduced due to the presence of oral mucositis, nausea and vomiting (14, 51) or taste and smell changes (243). Child cancer patients' nutritional status may also be compromised due to intestinal malabsorption (14) and inflammation (46). Without nutritional therapy, the prevalence of under-nutrition during treatment for childhood cancer may be as high as 50% of patients in developed countries (46). Maintenance of a good nutritional status during cancer therapy can also improve a childhood cancer patient's tolerance to chemotherapy, reduce their risk of infection and improve quality of life (8, 244). Enteral tube feeding (ETF) is an important part of nutritional therapy in paediatric cancer patients. It is used when oral nutritional therapy is no longer effective (4). Evidence shows that ETF promotes weight gain in paediatric oncology patients (133, 134, 245, 246), especially when used prophylactically (135). Despite the evidence for its effectiveness as a method of nutritional intervention, the criteria for the use of ETF for paediatric oncology patients are inconsistent (122).

The prevention of hospital malnutrition has become a focus in the clinical setting (247). Prompt nutritional interventions are considered a key to prevention (248). To achieve appropriate and timely nutritional interventions, multidisciplinary collaboration is considered paramount (248). Although the healthcare team's recommendations influence the initiation of ETF in the paediatric setting, recommendations for the utilization of ETF can differ between healthcare

practitioners (122), leading to inconsistencies in ETF initiation. A cohesive team management of nutritional therapy will likely enhance appropriate utilisation of ETF.

Patient centered decision making is also important when initiating ETF (249). Parents and patients have a strong influence over the initiation of nutrition support, with many refusing the use of ETF for their children. A recent study of paediatric oncology patients, and their parents, suggested that the perceived discomfort of ETF influences patient/parent decisions to allow ETF to be initiated (145). Parents also use the threat of the use of ETF as a way to coerce their child to eat (131). There is also suggestion that ETF is more likely to be initiated in younger patients (< 6 years) (135), than in older patients.

To ensure that the appropriate initiation of ETF is optimized, collating the views of paediatric oncology clinicians, parents and patients on ETF in a paediatric oncology setting would be beneficial. This would enable the development of psycho-educational interventions for families and staff. The aim of this study was therefore to compare and contrast views among parents, patients and healthcare workers on the positive and negative aspects of ETF, the ways in which information was provided on ETF; and, how the decision making process was conducted for the initiation of ETF.

6.2 Methods

6.2.1 Study participants

Two groups of participants were recruited at the Kids Cancer Centre (KCC), Sydney Children's Hospital, Australia, for this study: 1) Paediatric cancer patients <18 years of age, who were currently on treatment or who had undergone treatment at the KCC in the previous three years; and 2) Healthcare professionals. There is no literature determining the minimum age in which a child can participate in qualitative research (250). For our study, for participants under the age of 12 years, the parents were interviewed. The healthcare professionals included medical, nursing and allied health staff. Potential participants were mailed a study invitation letter, a participant information sheet and an opt-in card. Participants were also invited, in person, through the outpatient clinic of the KCC. Participants were excluded if they were unable to speak English. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the South Eastern Sydney and Illawarra Health Service, Human Research Ethics Committee-Northern Hospital Network. Informed, written consent was obtained from each participant.

6.2.2 Procedure

Interviews were conducted via the telephone by a research assistant. She was not associated with, or known by, the participants and had extensive training and experience with semi-structured interviews. Telephone interviews were offered as many participants lived in rural or remote areas (24), and did not attend hospital on a regular basis. Telephone interviews are considered to be as effective as face-to-

face interviews for eliciting reliable qualitative data (25). All interviews were recorded.

Semi-structured interviews were used to elicit information from the participants (Table 6-1). After an extensive literature review, the initial core discussion guide was developed. The interview focused on: 1) Attitude and impact of ETF; 2) Information and support regarding ETF; and 3) Clinical management of ETF. The discussion points were based on themes elicited in previous research on attitudes towards enteral feeding in a general pediatric setting (146, 251). Once the initial discussion guide had been developed, a multidisciplinary team (dietitian, psychologist and oncologist) who have extensive experience in conducting qualitative research and understood many of the challenges faced by families in this situation reviewed the discussion guide. Results from the early interviews were also used to determine additional lines of questioning for subsequent interviews (204). The health professional discussion guide was based on the same domains as the parent/patient discussion guide. There was also a focus on the criteria they used to initiate EN.

Table 6-1 Discussion guide for semi-structured interviews for parents/patients and healthcare workers

Parents/Patients
<p>Views prior to use of enteral tube feeding</p> <ul style="list-style-type: none"> ▪ What information were you given about enteral tube feeding at the beginning of your/your child's treatment? ▪ Who gave this information to you? ▪ What did you think about the use of enteral tube feeding at the beginning of your/your child's treatment?
<p>Views during and after use of enteral nutrition</p> <ul style="list-style-type: none"> ▪ Can you describe whether there were any positives of you/your child receiving enteral tube feeding? ▪ Can you describe any negatives of you/your child receiving enteral tube feeding? ▪ Did your feelings about enteral tube feeding change after you/your child received it? ▪ Did you/your child experience any complications with receiving enteral tube feeding? If so, what? ▪ Could you tell me how you felt when you/your child received the nasogastric tube or gastrostomy? ▪ Do you think enteral tube feeding affected your life in any way? For example, your social life, your family relationships, how you/your child coped with your cancer treatment. ▪ Did you have any issues or concerns with the enteral feeding process? ▪ Do you have any advice or recommendations about enteral tube feeding for other patients/parents? ▪ How about for doctors or other healthcare workers?
Healthcare workers
<ul style="list-style-type: none"> ▪ What are the first two things that come to mind when you think about enteral tube feeding in the pediatric oncology setting? ▪ What are the positive aspects of enteral tube feeding? ▪ What are the negative aspects of enteral tube feeding? ▪ What are your thoughts about how enteral tube feeding is managed on the ward? ▪ What criteria do you use to decide whether or not you should initiate enteral tube feeding? ▪ What materials and resources do you use to make this decision? ▪ How do you think enteral tube feeding impacts on the patients and their families? ▪ Can you comment on how you would approach a family about initiating enteral tube feeding in their child?

- Can you comment on the support given to health professionals to initiate enteral tube feeding in oncology patients?
- Do you have any other advice or recommendations regarding the use of enteral tube feeding in the paediatric oncology setting?

6.2.3 Data analysis

All participant responses were transcribed verbatim by an independent, trained transcriber. This methodology was performed in accordance with gold-standard guidelines (204). Transcripts were coded line-by-line, and analysis was facilitated by the qualitative data analysis software NVivo, 2008, Version 8 (QSR International, Victoria, Australia). To ensure accuracy with regards to the coding and analysis, fifteen percent of the interviews were coded independently by two investigators, and their coding was compared for consistency (204, 205). The final coding was analyzed and key themes were categorized and enumerated (204).

6.3 Results

Interviews were conducted with 30 families (Table 6-2), representing a response rate of 24.5%. Twenty parents (2 fathers, 18 mothers) were interviewed as their child was under 12 years of age. Ten interviews were conducted with the childhood cancer patients. Interviews were conducted with 18 healthcare workers, yielding a response rate of 33%. Responses from participants were divided into three main themes: 1) Attitude and impact of ETF; 2) Information and support regarding ETF; and 3) Clinical management of ETF. Responses from the patient participants and the healthcare workers were compared.

Table 6-2 Demographics of participants and healthcare workers

Patient (n=30)	
Age (mean \pm SD) years	9.54 \pm 5.16
Sex (M:F)	13:17
Stage of treatment (n)	
On treatment	10
Receiving maintenance therapy	5
Post treatment	15
Diagnosis	
ALL*	9
AML†	3
Wilms' Tumour	3
Brain Tumour	8
Neuroblastoma	2
Other	5
Healthcare Workers (n= 18)	
Position	
Consultant	5
Fellow	2
Clinical Nurse Consultant	2
Clinical Nurse Educator	1
Registered Nurse	6
Allied Health	2

* ALL, Acute Lymphoblastic Leukaemia; †AML, Acute Myeloid Leukaemia

6.3.1 Attitudes toward, and impact of, enteral nutrition

Participants were asked to recall their views regarding ETF prior to and after use.

The emerging themes and representative comments are displayed in Table 6-3.

Table 6-3 Views of enteral tube feeding from patients, parents and healthcare workers

Themes	n	Representative Patient Comments (n=30)	n	Representative Healthcare worker comments (n=18)
Prior to enteral nutrition				
Positive				
Ensure good nutrition	9	"It would just give you piece of mind that they are getting the nutrition that they need" (Mother: female, CNS tumour, 8 yrs).	4	"Positives in terms of delivery of essential nutrients, vitamins" (Fellow).
Less pressure on the child to eat/less conflict	7	"When I found out about it I felt a huge amount of relief that I wouldn't have to struggle with trying to eat" (Patient: male, Biphenotypic Leukaemia, 17 yrs).	4	"Enteral feeding is often a way of diffusing conflictthe last thing you need is to have the [patient] fighting with the mother and father about what they can and can't get in" (Consultant).
Weight gain	7	"When a child is sick and thin its body can't fight as well as it can if it is healthy and nourished so if she had dropped enough weight we would have definitely have done it" (Mother: female, ALL*, 2 yrs).	1	"It means that they are going to either hopefully maintain their weight or not lose significant weight, so to try to minimise toxicity of regimens" (Fellow).
Easier to give medication	2	"NG† tube might be really easy because of the medication...It needs to get in and...with NG tube at least you have that option to just give it even if [the patient] like[s] it or not. (Mother, male, ALL, 5	4	"It is often also a good way to give medications" (Fellow).

		yrs).		
Less time in hospital	0		1	"[EN \pm] usually means getting out of hospital [and] having some control and having some time at home" (Consultant).
Negative				
How it looks/makes them look sick	8	"I didn't want him to have [ETF], maybe it was just admitting that he was really sick then just to look it" (Mother: male, medulloblastoma, 11 yrs).	16	"..the patients are quite reluctant...because of ... the body image, and you can see it and it makes them look sick it certainly separates them from normal teenagers" (Clinical Nurse Consultant).
Invasive	7	"I never, ever wanted to have a tube down my nose the central line ... just seems to be ... less intrusive in a way but down the nose and down my throat that always appeared horrible to me and I wasn't very happy with it" (Patient: male, MDS, 13 yrs).	1	"I think parents view things like NG tubes as invasive" (Fellow).
Uncomfortable	7	"I have noticed just from being in hospital was that the children who had it ...find it incredibly uncomfortable and they couldn't understand why they had to have it and so they were constantly pulling it out" (Mother; female, ALL, 5 yrs).	4	"I think parents view NG tubes as uncomfortable in the children...when they have not experienced it firsthand probably the only time they witness NG tubes in other kids on the ward is when they watch them go in that is a little bit traumatic, but once it is in, it is not a major issue" (Fellow).
Insertion procedure	0		4	"We have to pass the NG tube and so i think that frowned upon by the

				parents, they try and avoid the tube feeding for as long as possible because they don't want that tube inserted" (Registered Nurse).
Worried about how the patient will cope	3	"You are sort of anxious about it, how [the patient] would cope with it" (Mother; female, NHL§, 8 yrs).	0	
Failure by parents	2	"I think is some of [the parents] feel that they are not succeeding as parents" (Mother: male Wilms' Tumour, 2 yrs).	2	"Some parents see it as a failure on their part and so they are reticent to admit defeat" (Consultant).
Having to use formula	2	"I was still breastfeeding [and] I felt a little bit funny because I hadn't particularly wanted her to have formula at all. I was expecting her to go from breastfeeding to solids and then just cut out the breastfeeding and purely solids" (Mother; female, AML, 2 yrs).	0	
Extra work at home	1	"You have the other machines at home and you have to put it all in at night and you know it's kind of another add on thing" (Mother: male, ALL, 5 yrs).	0	
Unnatural	1	"It are just my own gut feeling that there must be a reason why when we are sick we don't want to eat. ... but, wouldn't it make sense that if our body doesn't want to eat that we don't need food?" (Mother: female, AML, 4	0	

		yrs).		
Concerns about reaction to the tape used	1	"I would have had no problem with it, only that she seriously sensitive skin and it has got to get tapped to her face" (Mother: female, neuroblastoma, 6 months).	0	
After enteral nutrition				
Positive				
Weight gain	10	"I really hate it to be honest but I do know that right now, it's the only way I can really gain weight" (Patient: male, MDS, 13 yrs).	8	"The main positives is maintaining weight, maintaining nutrition and that's getting the calories in and having them healthier" (Consultant).
Better nutrition	9	"You felt reassured that [the patient] was getting the nutrition in because even when she was eating, it was just like crappy stuff so there was nothing good or nutritious about it" (Mother: female, NHL, 8 yrs).	9	"I do think the relief of knowing that your child is getting their nutritional requirements can remove some stress. Especially if you're a family where food is a big part of your life and nutrition" (Social worker).
Less stress/anxiety	8	"Once we said okay and he got [ETF] we sort of [felt] relieved, like this pressure just lifted off our shoulders and we didn't have to fight with him" (Mother; male, medulloblastoma, 7 yrs).	9	"I think a big plus with it, is that it does relieve a lot of the eating stress at the home, so [the parents] can chill out and have good times instead of constantly fighting about, [food]" (Consultant).
Patient got used to the tube	7	"Every time [the patient] cried, [when] they tried to put in [the tube], but after	1	"One of the big advantages is once you get the tube in it is well

		that she was fine again” (Mother: female, Wilms’ Tumour, 8 yrs).		tolerated, once you get past the first couple of days and it is not uncomfortable anymore” (Consultant).
Less pressure to eat	6	“We didn’t have to be stressed any more about making [the patient] eat all the time which is a real constant battle between him and I” (Mother: male, medulloblastoma, 11 yrs).	3	“[ETF] is a lot easier on the patient as well when they are not getting forced to eat a whole bunch of stuff that they just can’t tolerate” (Registered Nurse).
Easier for medications	4	“All the medicines [the patient] didn’t like to take and the pills ... we could throw straight down the tube that was an advantage” (Mother: male, neuroblastoma, 11 yrs).	2	“[ETF] makes medications easier” (Registered Nurse).
Could feed while child was asleep	2	“It gave me a bit of piece of mind that if she didn’t eat during the day at least she was getting some nutrition overnight” (Mother: female, AML, 2 yrs).	1	“[ETF] makes the feeding easier; the parents can do it at night time” (Registered Nurse).
Less time in hospital	1	“I don’t have that stress that if I don’t eat I am going to end up back in hospital” (Patient: female, medulloblastoma, 17 yrs).	4	“[ETF] as opposed to TPN, is very helpful, and ... you can do it as an outpatient so it increases [the “[Patient’s] discharge capability too, because in the past the children might have needed to stay in hospital because they can’t eat” (Fellow).
Negative				
How it looks	12	“I didn’t particularly like the way that it identifies you as a sick person” (Patient: male, 17 yrs,	0	

		Biphenotypic Leukaemia).		
Insertion procedure	11	"The negatives, when they had to put it down, I really was quite insistent that they put it down when she was under general anaesthetic because she had them pretty much every week." (Mother: female, AML, 2 yrs).	9	"NG tubes are very traumatic putting them down is horrendous it doesn't really matter about the age of the child" (Registered Nurse).
Vomiting up the tube	7	"There was always that part of me that didn't like it because I felt like it was causing [the patient] so much discomfort with the vomiting and also with the tube itself." (Mother: female, AML, 4 yrs).	10	If it's [ETF] not successful, and the tube keeps getting thrown up or the child keeps throwing up, then.... it's just too hard" (Clinical Nurse Consultant).
Uncomfortable	6	" [The patient] kept saying that it felt really funny on her neck, an uncomfortable feeling having that thing going down your neck" (Mother: female, NHL, 8 yrs).	3	"It [ETF] feels uncomfortable and they [the patient] often say that discourages them from feeling like they want to eat at other times because it sits at the back of their throat and it hurts a bit to swallow" (Clinical Nurse Consultant).
Makes patient feel sick	5	"I've always felt sick and I've always felt worse having the feeds continuous" (Patient: male, MDS, 17 yrs).	0	
Issues with tape on the face	5	"The tape and stuff was a bit irritating, ... I thought it would get a bit inflamed, [on the face]" (Mother: male, neuroblastoma, 11 yrs).	1	"You have got the tape on the cheek; there was one child who has a bad fungal infection underneath that so that is again a rare downside" (Consultant).
Sleep deprivation	2	"During the night the machines always turning	6	"I imagine if you lived in the house, you would find

		and it constantly makes noise and when it runs out it beeps and everyone has to get up and fix it" (Patient, female, medulloblastoma, 17 yrs).		they have got a fair bit of sleep deprivation around it" (Consultant).
Type of formula	2	"The nutritionist was fairly hesitant to switch from the ordinary milk to the pre-digested stuff and once he was on the pre-digested stuff he really settled down" (Mother: male, ALL, 5 yrs).	0	
Impact on family	2	"I was opening my baggage all the time because I would be carting different tins, with the food" (Mother: male, neuroblastoma, 11 yrs).	5	"It [ETF] limits what you can do. In terms of where you want to go or if you go on holiday, you have to bring pump" (Clinical Nurse Consultant).
Impact on long term feeding	1	"I was concerned that because she was being tube fed for most of it, it would affect her [eating] long-term" (Mother: female, AML, 2 yrs).	1	"Once they [the patient] have been out from transplant for many months and still on nasogastric feeds, then certainly there can be some anxiety about the return of normal appetite and normal feeding habits" (Fellow).
Risk of aspiration	0		3	"I have been involved in where there has been a concern about aspiration on a chronic basis which might have been exacerbated by having a nasogastric tube in" (Consultant).
Cost	0		2	"It can be an ongoing cost issue trying to get feed." (Clinical Nurse

				Consultant).
Diarrhoea	1	"At one stage he did 17 diarrhoeas a day" (Mother: male, ALL, 5 yrs).	1	"Negatives for nasogastric enteral feeding is diarrhoea" (Fellow).
Tube blocking	0		4	"Problems occur if the tubes then blocks and we have to take it out and put a new one in; you get some frustration and aggression as to why did the tube block" (Fellow).

* ALL, Acute Lymphoblastic Leukaemia; † EN, Enteral Nutrition; ‡ NG, Nasogastric;
§ NHL, Non-Hodgkin's Lymphoma

6.3.1.1 Prior to use of enteral nutrition

The main positive aspects expressed by the participants regarding ETF prior to its use were: 1) Ensuring good nutrition (n=9); 2) Less pressure on the patient and family to get the child to eat (n=7); and 3) To promote weight gain (n=7). The healthcare workers described similar positives which included: 1) Better nutrition (n=4); and 2) Less conflict between parents and patients relating to oral intake (n=4). Healthcare workers also described a positive of ETF as being '*easier to give medications*'

"When I found out about it I felt a huge amount of relief that I wouldn't have to struggle with trying to eat" (Patient: male, Biphenotypic Leukaemia, 17 yrs).

The main concerns expressed by participants prior to its use included: 1) The physical appearance on the child's face (n=8); 2) Their concern it was invasive (n=7); 3) The degree of discomfort from the enteral feeding tube once inserted

(n=7). The same negative aspects were expressed by healthcare workers. The healthcare workers confirmed that the most common reason for concern from parents and patients was the physical appearance after insertion of the tube (n=16). They also suggested that concerns about discomfort from the tube would be a challenge for patients (n=4).

“I think parents view nasogastric (NG) tubes as uncomfortable in the children...when they have not experienced it firsthand..... probably the only time they witness NG tubes in other kids on the ward is when they watch them go in that is a little bit traumatic, but once it is in, it is not a major issue” (Oncology Fellow).

6.3.1.2 After use of enteral nutrition

Once ETF had been initiated, the positives described by both the patients and parents appeared to match their views prior to insertion. The key positives included: 1) Weight gain (n=10); 3) Better nutrition (n=9); 3) Less worry (n=8); and 4) Less pressure to eat (n=6). A proportion of this group also commented that their child “*did get used*” to the tube (n=7). The positive views of the healthcare workers also remained the same and were similar to the views of the parents and patients.

“Once we said okay and he got [ETF] we sort of [felt] relieved, like this pressure just lifted off our shoulders and we didn't have to fight with him” (Mother; male, medulloblastoma, 7 yrs).

Parent and patient negative views regarding ETF, however appeared to change once the tube had been inserted, with the primary concern expressed relating to the insertion procedure. This did not appear to have been a focus prior the initiation of

ETF. Participants also commented that the constant emesis of the tube was a problem. The other negatives of ETF after the insertion, described by the participants, related to feeling awkward in public with the tube as it was so visible.

“There was always that part of me that didn't like it because I felt like it was causing [the patient] so much discomfort with the emesis and also with the tube itself.”
(Mother: female, AML, 4 yrs).

The healthcare workers' views regarding the negative perceptions surrounding ETF once it had been utilised, appeared to agree with that of the parents and the patients. The healthcare workers were aware of the concerns with the tube insertion process and emesis of the tube. Healthcare workers also viewed sleep deprivation, as a result of use of the feeding pump at home, as a potential difficulty for parents and patients. None of the parents or patients interviewed spontaneously described this as a concern. Healthcare workers did not spontaneously discuss the possibility that the physical appearance of the tube would continue to be a challenge for families after insertion

“I imagine if you lived in the house, you would find they have got a fair bit of sleep deprivation around it” (Physician).

6.3.2 Information about enteral nutrition

Parents reported first receiving information about ETF from various sources. These included: doctors (n=13), the dietitian (n=11) and nursing staff (n=3). One parent reported that they sought information regarding ETF from other families. For parents

of children who did not receive ETF during their treatment (n=8), many reported that tube feeding was not mentioned as a possibility during their child's treatment (n=5). Some parents reported that they may have found out information on ETF when their child was first diagnosed, but were unable to confirm this. They reported that they received a lot of information at diagnosis and were unable to focus on all the information provided due to the stress of their child's cancer diagnosis (n= 6).

"It is all a bit of a blur, there may have been information in amongst everything but until it was actually, like you say, crunch time, we didn't really think about it" (Mother: female, AML, 4 yrs).

Half of the patients interviewed did not recall receiving any information on the use of ETF (5/10) during their treatment.

"I wasn't given any information. It was just "You're going to get a NG [nasogastric] tube put in" (Patient: female, AML, 17 yrs)

Three of the seven physicians reported that they raised the possibility of the use of ETF at the initial diagnosis. One physician stated they did not mention it at diagnosis.

"The amount of detail you go into can vary from family to family and you wouldn't talk about it at the very beginning of diagnosis generally because they are still getting over the shock of the new diagnosis and the treatment plan so it wouldn't feature in those discussions but at a later stage it definitely does." (Pediatric oncology fellow)

It appears that ETF is mentioned as a possibility to patients and their parents when there is a concern about weight loss or poor feeding. The majority of healthcare workers reported that the dietitian was the one to discuss the use of ETF with parents and patients (n = 9).

“Our greatest resource is our dietitian . We are very much guided by that in terms of whether there are concerns about calories.... a large proportion of [ETF] is guided by a combination of looking at the weight and clinical assessment and then getting guidance from the dietitian as to what is appropriate.” (Paediatric oncology fellow)

6.3.2.1 Decision process

The decision process and criteria for the use of ETF appeared to vary, with no standardized criteria. Half of the healthcare workers (n=9) reported that weight loss was the main criteria used for ETF initiation, though the amount of weight loss varied from five percent to 15% loss of body weight. Many healthcare workers relied on the dietitian to provide advice as to when ETF needed to be initiated (n=6). It appeared that some healthcare workers and parents would have preferred there to be a more specific criteria for initiation.

“I think there is a lot of um-ing and ah-ing and from a decision about whether we enteral feed or not..... We still don't have a line in the sand.... kids need a line of sand” (Clinical Nurse Consultant).

6.3.3 Clinical management of enteral nutrition

6.3.3.1 Insertion procedure

There appeared to be similar views regarding the insertion procedure between the parents, the patients and the healthcare workers. Of the parents and patients interviewed, eight (40%) and three (30%) respectively, reported that the insertion procedure was a negative experience due to the pain and discomfort with the procedure.

“I found that really quite traumatic for her and for me” (Mother: female, AML, 2 yrs).

A similar percentage of healthcare workers (50%; n=9) considered the insertion procedure a negative experience for patients.

6.3.3.2 Use of sedation for insertion

A small number of parents (n=4) and patients (n=2) reported that the use of midazolam, improved the insertion procedure. The parents reported that each nasogastric tube insertion was different and that the methods used varied.

“It is much more comfortable for him to have the Midaz[olam]. It just takes the edge off, just relaxes him I think a little bit more than, you know he knows what's coming” (Mother: male, medulloblastoma, 7 yrs).

A number of healthcare workers (n=8) reported that using Midazolam, for the insertion procedure, improved the experience of tube insertion.

“A lot of the time we use Midazolam and it tends to be a bit ad hoc. There's been one occasion where I've tried to get the pain team to do some nitrous [oxide] but they refused.” (Physician).

6.3.4 Recommendation to other parents

Despite the large number of problems with the ETF insertion procedure, blockage of tubes, and emesis, a large number of parents (n=12) would still recommend the use of ETF to other families. Many parents (n=13) also felt that their perception of ETF changed to a more positive view after use.

“I'd be surprised if rational parents didn't see the positive... I don't see how overall you can't see it as a net positive. It is another thing to have to manage and it's another thing protruding out of the patient's body and all that stuff but it's a means to an end. I certainly wouldn't have it any other way because what's the alternative?” (Father: female, Brain tumour, 3 yrs).

6.4 Discussion

Nutrition interventions, in the form of ETF, play a key role in the management and treatment of pediatric oncology patients. Recent literature has shown that proactive ETF is achievable (135). This study showed that parents/patients and healthcare workers could all see positive and negative aspects of ETF, as well as the management of ETF, in a similar way. Discordant views between the patients/parents and healthcare workers appeared around the decision making process and when information was provided on the use of ETF.

Decision making of patients (and their parents) in the healthcare setting is complex. Information provision alone may not be adequate enough to enable quality decisions to be made (252). Physician understanding of the patient's experience in combination with the provision of information on evidence for the use of the medical intervention (253) is more likely to encourage compliance with the recommended treatment. This study demonstrated that healthcare workers appeared to understand patients' and parents' challenges surrounding ETF. Therefore effective information provision and decision support may be the missing link in the process for initiating ETF use. Differences in perceptions between parents and physicians regarding the sufficiency of information surrounding ETF has been shown to be a difficulty with parents of non-oncology children (146). This difference in perceptions between the parents/patients and the healthcare workers also appeared in the pediatric oncology setting. A focus on the form and timing of the information provision may be needed to ensure that uptake of ETF in an appropriate timeframe is achieved.

The physicians varied in regards to whether they provide information on ETF at diagnosis or at other points during treatment. The parents did acknowledge that even if this information had been provided at diagnosis, they may not have been able to recall this information due to the stress receiving a cancer diagnosis for their child. The literature has shown that parents feel overwhelmed by the information given at their child's cancer diagnosis (254, 255). This may lead to a poor recall of all of the information provided to them (256). It may be that providing information on ETF at diagnosis is not appropriate at such a stressful time. Physicians may need to ensure information on ETF is given to parents and patients separate to diagnosis but before nutrition becomes a concern for the patient and parents. This information

may also need to be standardized across all the medical teams. Further work is needed to determine the appropriate timing of information provision to families regarding the use of ETF during cancer treatment.

Shared decision making is a process in which patient treatment decisions are made in collaboration with the patient (257). The clinician provides information on the benefits and harms for all treatment options and a joint decision is made regarding the treatment plan (257). Shared decision making is not always used in the clinical setting but is encouraged to improve patient outcomes, including patient satisfaction (258). Shared decision making may allow the discordant views between patients and clinicians regarding the use of ETF to be improved (257). Use of decision aids may be one way of standardizing and improving the provision of information on ETF to pediatric oncology patients and their families, especially when facing a decision that involves competing values (such as balancing appearance and comfort with better nutrition) (259). Decision aids provide unbiased, balanced, and non-directive information about a procedure. They differ from standard education materials as they provide options to the patient (260) and allow them to participate in the decision making process (261). Decision aids have been shown to have a positive influence in patient-physician decision making (261). The use of decision aids has been suggested as a way to improve the quality of decision making for use of ETF for parents of children with neurological disabilities (147) and carers of adults with severe dementia (262). Incorporating decision aids into the pediatric oncology setting may be one way to improve uptake of this form of nutritional intervention. Use of a decision aid with standardised information may also address challenges around the differing criteria for use of ETF between clinicians. Development of the decision aid in consultation with clinicians may allow agreement to be reached on the criteria for initiation of ETF based on published literature.

Peer knowledge sharing has also been discussed as a factor for improving decision making in the healthcare setting (260). Few parents and patients in this study sought information from their peers. The majority of information on ETF came from healthcare workers, such as their physician, dietitian and nursing staff. Many parents stated they would recommend the use of ETF to other parents if asked. Peer knowledge sharing could be utilized as a standard practice to improve the information provision and subsequently improve the decision making process.

After ETF was commenced, the concerns from parents and patients, centered on the practical aspects of the tube. These negatives included the invasive nature of the insertion procedure, emesis of the nasogastric tube, and discomfort in using the nasogastric tube and how visible the nasogastric tube was in public. Interestingly, none of the parents or patients who participated in the study mentioned the tube insertion procedure as an area of concern prior to the tube being inserted. Although it is not possible to alter some of the negative aspects discussed above, such as the physical appearance of the tube, introduction of psychological preparation (4), cognitive-behavioural techniques (263) and utilization of play therapists may lessen the distressing nature of the procedure.

6.4.1 Limitations

This study provides insight into potential reasons for a reluctance to use ETF for many patients and parents, though there are several limitations of this study that need to be addressed. For the majority of participants, this study relied on retrospective recall of their views of ETF and could have subsequently introduced

recollection bias. Future studies should assess patient and parental views on ETF prior to and after initiation. A participation rate of 24% could suggest that the results from this study were not representative of all childhood cancer patients and their parents. We did, however, continue interviewing until information saturation was achieved. A recent review of qualitative study sample sizes revealed that our sample size is similar to many other qualitative studies that also achieved saturation (264).

6.5 Conclusion

Parents, patients and healthcare workers perceived the positive and negative aspects of ETF in a similar way. There appears to be discordance between patients/parents and the healthcare workers in relation to the information provided to them on the use of ETF. This uncertainty in the methods and timing of information provision on the use of ETF may be contributing to a less than optimal use of this method of nutrition support. By standardizing and improving the methods used for the information provision of ETF, the concerns surrounding the use of ETF with pediatric oncology patients may be reduced. Introduction of tools such as decision aids and peer knowledge sharing may help to optimize the use of ETF in pediatric oncology patients.

6.5.1 Implications

This chapter provides information on the decision making process for the initiation of enteral tube feeding. The uncertainty in the methods and timing of information

provision on the use of tube feeding may be contributing to a less than optimal use of this method of nutrition support. This may also be a reason for parents using enteral tube feeding as a way of coercing their child to eat. Improving the methods of information provision around, not only enteral tube feeding, but all methods of nutrition support may not only improve uptake of the appropriate nutritional interventions but improve the feeding practices of parents during their child's cancer therapy. This may have implications on long-term dietary intake of survivors of childhood cancer. The third section in this thesis examines the hypothesis that taste and smell dysfunction may be implicated in the problem of developing healthy eating habits in childhood cancer survivors. The next chapter is a review of the prevalence of taste and smell dysfunction in cancer patients, both during and after treatment. The review also assesses the relationship between taste and smell dysfunction and oral intake

7 REVIEW OF TASTE AND SMELL DISORDERS RESULTING FROM CANCER AND CHEMOTHERAPY⁵

Chapters 3 and 4 found young survivors of childhood cancer are not meeting recommended nutritional guidelines. It also appears that young survivors of childhood cancer are not returning to the dietary habits they had established prior to their cancer diagnosis. The reason for these changing dietary habits seen in cancer survivors is unknown. Cancer patients report a change in taste and smell during their cancer therapy but the role this plays on dietary habits during and after cancer treatment is not clear. This chapter summarises the literature on taste and smell changes during and after cancer therapy. This chapter also summarises the evidence for the association of taste and smell changes and food intake and whether taste and smell changes are seen in cancer survivors. The findings of this chapter have been accepted for publication in Current Pharmaceutical Design

7.1 Introduction

Smell, taste and food intake are tightly intertwined (265, 266). Flavour perception is not solely related to taste but is also mediated by olfactory receptors when mastication of food occurs (267, 268). The sensory properties of foods can influence

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JC undertook the review, JC & CW contributed to data analysis and JC, CW & DL contributed to manuscript development

both the selection and amount consumed of that food (269). An alteration in taste or smell function can lead to a change in a person's quality of life as well as altering food intake and nutritional status (270). In the general population, those with a chemosensory dysfunction that occurred after birth may have one of three reactions regarding food. They may increase their food intake to compensate for the lack of food flavour, decrease their food intake because of the lack of enjoyment of the food (271, 272) or continue to eat their normal diet. For many people suffering with chemosensory disorders the aetiology is idiopathic (273). Other causes of chemosensory disorders include sinus diseases, upper respiratory infection and head trauma (273). Chemosensory loss is an under-recognized issue in the general population, and there are conflicting data regarding prevalence of smell or taste loss (273-279)

Radiotherapy, used as a treatment modality for cancer treatment, is another well recognized cause of chemosensory dysfunction (273, 280). However, for many cancer patients, chemotherapy is the primary form of treatment and its short and long term effect on chemosensory dysfunction is less well understood. Chemotherapy targets rapidly dividing cancer cells (49). Unfortunately, chemotherapy cannot distinguish between cancer and non-cancer cells (50, 281), resulting in potentially severe short and long term side effects. Non-cancer cells that are more likely to be affected by chemotherapy include cells in hair follicles, blood and bone marrow, gastrointestinal tract and the reproductive tract (265), causing side-effects such as nausea, vomiting, mucositis and diarrhoea. Taste and smell receptor cells also rapidly turn over (282, 283) and the division mechanism has been suggested to be sensitive to the effects of chemotherapy (281, 284).

Anorexia and poor appetite are commonly described in cancer patients (285). Malnutrition is a significant challenge for patients undergoing treatment for cancer, and rates may be as high as 80% in adult patients (286) and 50% in paediatric patients (46). Malnutrition in cancer patients is associated with increased infections, leading to an increase in mortality (112-114), and this is likely to be independent of disease severity (115). Poor nutrition during cancer treatment can lead to an increased length of hospital stay (111), reduced quality of life, reduced treatment tolerance and increased treatment side-effects, potentially leading to poorer outcomes (6, 14). Malnutrition also reduces the absorption of chemotherapy drugs (116) and may be one explanation of poorer survival outcomes in underweight patients (114). In children with cancer, malnutrition can have more significant long term effects such as growth stunting (84) and cognitive/developmental delay (83).

An alteration of chemosensory function could also affect a patient-whose oral intake is already affected by cancer (287). The senses of taste and smell are integral in motivating a person's food preferences (270, 288) and both child and adult cancer patients commonly attribute difficulties maintaining food intake to the altered taste developed during treatment (127, 265, 289). Altered chemosensory function in patients with cancer may also lead to food aversions (266), further changing food preferences. Chemosensory dysfunction has been associated with a decreased energy and nutrient intake (271), nutrient deficiencies (290) and malnutrition (287). A loss in sensory perception can also affect a person's quality of life (291).

Given the potential medical, behavioural and psychological impact of chemosensory dysfunction in adult and child cancer patients, this review aims to provide a comprehensive overview of the prevalence of taste and smell disorders in cancer patients undergoing chemotherapy. A narrative review will be conducted in

accordance with the published Economic and Social Research Council guidance (292). This form of review is generally considered ideal where a broad overview is required that synthesises both current empirical evidence and theoretical understanding (38). This review will first summarise the potential causes of taste and smell dysfunction in cancer patients and discuss the methodology used to assess chemosensory dysfunction. The review will then summarise the prevalence of taste and smell dysfunction, assessed using both objective and subjective measures of assessment, in both patients on treatment and survivors of cancer. The review will then summarise the prevalence of taste and smell dysfunction, assessed using a variety gustatory and olfactory test, in both patients on treatment and survivors of cancer. The review will also summarise the impact that chemosensory dysfunction has on quality of life and oral intake and will also review the efficacy of interventions to improve chemosensory dysfunction in cancer patients.

7.2 Summary of gustation

An alteration in taste perception can be categorized as ageusia (reduced taste), dysgeusia (altered taste) (293), hypergeusia (increased sensitivity) or hypogeusia (decreased sensitivity) (287). Taste sensations have previously been categorized into four distinct groups: salty, sour, bitter and sweet. Recent work has also identified the taste of umami as a fifth taste quality, said to be a savoury flavour (294, 295). Fatty acids may also be a taste quality, though further work is needed to confirm this (296). Taste receptors are located on the papillae on the tongue and soft palate. These receptors regenerate regularly (49) although the time required for this in humans has not been firmly established (284, 287). The sense of taste comes from the detection of chemicals by the taste receptors. The taste receptors are innervated by three separate cranial nerves: 1) facial nerve (CNVII); 2) glossopharyngeal nerve (CN IX); 3) vagal nerve (CNX) and when activated, carry

the taste information to the cerebral cortex (297, 298). Recent work suggests that taste cells in the gut are sensitive to tastes (295).

7.2.1 Potential causes of gustation abnormalities in cancer patients

The mechanisms for taste abnormalities in cancer patients remain poorly understood. Damage to the sensory receptor cells is considered a primary cause of taste disorders in this population (274). Damage may be caused by a decrease in the number of normal receptor cells, changes on the taste receptor surface or an interruption in neural coding (274). The perception of taste sensations in the central nervous system may also be altered if chemotherapy agents cross the blood-brain barrier (299). Chemotherapy drugs may also interfere or damage sensory neurons, altering taste pathways (274). These drugs, including platinum based chemotherapy, cyclophosphamide, doxorubicin, 5-FU and methotrexate, are known to be associated with taste and smell changes (284). Cancer patients may also receive supportive care medicines, such as antibiotics and antihypertensive medication that are associated with disorders of taste and smell (300). Chemotherapy drugs, antibiotics and analgesics contain bitter tasting compounds which can diffuse into the taste, via secretion into the saliva (287) causing a bitter or metallic taste (274). A dry mouth is a common side effect from cancer therapy and can alter taste perception (301). Poor oral hygiene, gastrointestinal reflux and infections have also been associated with taste changes in cancer patients (290).

7.2.2 Assessment of gustatory function

Most methods used to assess gustatory function, either assess patients' detection thresholds, their recognition thresholds (274), or their identification ability (275). Recognition thresholds provide a measure of taste sensitivity and identification

ability, while detection thresholds do not include the classification of a basic taste (302). Electrogustometry is a measure of taste sensitivity. This method uses a mild anodal current on the tongue, (303) which causes a metallic taste (304). Detection of the taste is through direct stimulation of the gustatory nerve (304). A downside of this method is that it does not measure the ability of a person to identify tastants (305).

Taste strips, which use filter paper containing different concentrations of four tastes (salty, sour, bitter and sweet), have been used to assess gustatory function in local regions of the tongue (268). Gustatory function with these tastes has also been measured using whole mouth tests which involve liquid solutions or tablets at different concentrations of the four tastants (57). A version of the whole mouth method for children, using 10ml solutions and four concentrations of the above four tastants, has produced normative data from hundreds of children aged nine to twelve years (276, 277, 306). Tests for the detection of the taste of umami have only been established in recent years, with some work using discs of filter paper impregnated with monosodium glutamate (MSG) (307).

7.3 Summary of Olfaction

The nasal cavity contains olfactory receptors that are activated when odorant molecules bind to them (291). Olfactory receptors are located on the dendrites of olfactory neurons, leading to a direct conduit to the cortex and subcortex (308) via cranial nerve I (265). Olfactory neurons are able to regenerate (265), and the regeneration time is dependent on the extent and type of damage to the mitotic basal cells and olfactory epithelium (284). A reduction in olfactory function can be

categorized as anosmia (inability to smell); hyposmia (reduced sensitivity); hyperosmia (increased sensitivity) or dysosmia (distorted perception) (273).

7.3.1 Potential causes of olfaction abnormalities in cancer patients?

The causes of smell dysfunction in the general population may include: 1) traumatic olfactory loss; 2) viral-induced olfactory loss; 3) exposure to toxic agents (265); 4) age; and 5) chronic rhinosinusitis(307). For cancer patients, olfactory dysfunction is likely related to chemotherapy destroying the rapidly dividing olfactory basal cells in the olfactory epithelium (281), (300). Chemotherapy may also cause patients to become sensitive to odours, (265) causing food aversions and a loss of appetite (281). This may be caused by the compounds in the chemotherapy drugs diffusing from the nasal capillaries to the olfactory receptors (308). Changes in smell sensitivity in cancer patients may also relate to pseudo hallucinations of odours that others cannot sense (309). Cancer patients may also report an increase in sensitivity to smells, though the aetiology remains unknown (309).

7.3.2 Objective measures of olfaction

The most common tests of olfactory function measure odour identification ability, odour detection or odour recognition thresholds (275, 276, 306, 310, 311). Odour identification testing is performed by assessing a person's identification of common odours (275, 306, 311). The original method developed to produce normative data for odour identification was the University of Pennsylvania Smell Identification Test (UPSIT). This method uses 40 common odourants which are microencapsulated, requiring study participants to "scratch and sniff" the odour (267). A four point forced choice method is used to determine the odour presented (267). A short version of the UPSIT is The Brief Smell Identification Test (312). Both are available

commercially. Another commercially available method for measuring olfaction is the German “Sniffin sticks” test which uses smell containing felt tip pens, allowing the odour to be presented in a uniform way. Once the odour is presented to the participant, the identification of the odour is achieved using a forced choice method (311).

Another test is the Connecticut Chemosensory Clinical Research Center test which measures both threshold and odour identification, with the odour presented to one nostril at a time (313). n-Butyl alcohol is used as the stimulus in the odour threshold component of the test. For odour identification, 10 common odourants are presented to the participant and identification is done with the aid of a list of 20 examples (313). There are a number of other tests available that measure odour discrimination, memory, and suprathreshold, odour intensity and pleasantness perception (314, 315), but little if any normative data are available from these and the reliability of the data from these tests varies (315). As such, comparisons of prevalence of odour dysfunction between studies using different methods need to be interpreted with caution.

The above methods to detect odor dysfunction were not developed for use with children. One study recently used ‘sniffin’ sticks and UPSIT tests with children, however, the scores were generally lower than considered acceptable for validating a general or specific olfactory dysfunction (316). A 16 odor identification test which was developed for use with children aged over five years, at Sydney Children’s Hospital in Australia (275, 276, 306) has been used with hundreds of children at schools and in the Sydney Children’s Hospital to produce normative data. This method involves participants sniffing opaque bottles containing the odorant. Identification is with a three picture - three word forced choice task (306, 317).

7.4 Prevalence of taste and smell alterations in cancer patients

Ten studies have assessed taste function in cancer patients (Table 7-1). Eight studies reported decreased taste sensitivity (n=407) (109, 271, 318-323) and one study reported no effect on taste function (n=12) (324). Two studies found both increased sensitivity and decreased sensitivity to specific tastes. Nishijima et al, 2013 reported an increased sensitivity to sweet, salty and sour tastes and decreased taste sensitivity to bitter (325), while Caputo and colleagues reported increased sensitivity to bitter but decreased sensitivity to salty and sweet (326).

Table 7-1 Summary of studies assessing taste function in cancer patients

Hyperguesia (increased sensitivity)	No effect	Hypoguesia (decreased sensitivity)
Nishjima 2013 (filter - paper strips : sweet, sour, salty) Caputo 2012 (wholemouth: bitter)	Steinbach 2012 (taste strips)	Berteretche 2004 (electrogustometry) Nishjima 2013 (filter paper: bitter) Steinbach 2010 (taste strips: bitter) Sanchez-Lara 2010 (whole mouth: sweet, bitter) Caputo 2012 (whole mouth: salty, sweet) Strasser 2008 (whole mouth: 4% bitter, 33% sour, 35% salty, 4% sweet (% with a higher detection threshold) Steinbach 2009 (taste strips: salty, sour, bitter, sweet) Oversen 1991 (electrogustometry) Cohen 2012 (whole mouth; 40% of participants) Skolin 2006 (whole mouth: bitter)

Several objective methods have been used to assess taste and smell function in cancer patients (Table 7-3). Two studies that assessed taste sensitivity using electrogustometry found higher detection thresholds in cancer patients than in control groups (318, 320). Use of whole mouth methods to assess taste detection found higher sweet (271) and salty scores (326) compared with controls. Interestingly, Caputo et al, (2012) (326) found lower detection bitter scores compared with controls, whereas Sanchez-Lara and colleagues (2010) (271) reported the opposite. Reasons for this discrepancy in these results are unknown as both studies used similar participant groups and testing methods. Strasser and

colleagues (2008) (323) assessed the taste detection of 41 cancer patients and found a low prevalence of bitter and sweet dysfunction (4%), but higher rates of sour and salty dysfunction (33% and 35% respectively. Two studies have used taste test strips to assess taste function. In one study of 12 patients with ovarian cancer, no significant decrease in taste function during their chemotherapy treatment was found (322). However, a study of 87 breast and gynaecological cancer patients found that their taste function decreased significantly after chemotherapy infusion (322). Two studies assessed taste detection and recognition in paediatric cancer patients. One study of children undergoing a bone marrow transplant (BMT) reported that 40% of the patients experienced a taste dysfunction (319). Taste function appeared to resolve within two months post-transplant. The second study assessed 10 paediatric cancer patients during chemotherapy treatment and found higher thresholds for bitter taste than controls (109).

A total of seven studies assessed olfactory function in cancer patients undergoing chemotherapy with conflicting results (Table 7-3). One study reported decreased odour detection (n=87) (321) and another reported no effect on odour detection (n= 15) (327). The results for odour identification were mixed, with four studies reporting decreased identification (n= 130) (319, 321, 324, 328), one study reporting an increase in identification (n= 69) and three studies reporting no effect (n= 46) (322). Two studies assessed odour sensitivity with one study finding a decreased odour threshold (n= 87) (321) and two studies finding no effect (n= 120) (320, 322).

The majority of studies (Table 7-2) assessing olfactory function in cancer patients used "Sniffin sticks". Yakirevitch et al, 2005 reported a prevalence of olfactory dysfunction of 5% in patients with solid tumours (328). Two of these studies found a statistically significant decrease in olfactory function compared with controls after

chemotherapy infusion (321, 324). These findings were not repeated when the olfactory function of 69 breast cancer patients were compared with normative data and no difference in odour threshold was found (322). Olfactory function assessed using the European Test of Olfactory Capabilities also found no difference in odour detection and identification between 15 bronchial cancer patients and 15 healthy controls (327). The only study assessing olfactory function in paediatric BMT patients reported a prevalence of dysfunction of 30%, with symptoms resolving within two months (319).

Table 7-1 Summary of findings of taste and smell dysfunction

Author, year	N (age range)	Cancer Type	Chemotherapy	Measures	Findings
Joussain et al, 2013 (327)	15 cancer patients (63.46 ± 6.16 yrs) 15 control (65.9 ± 4.93 yrs)	Bronchial	Cisplatin	European Test of Olfactory Capabilities (ETOC)	No difference in odour detection ($p > 0.05$) and identification ($p > 0.05$) between patients and controls
Berteretche et al, 2004 (318)	110 cancer patients (58.5±11 yrs) 170 controls (60.5±11.6 yrs)	Not specified	Alkylating agents, antimetabolites, Antispindle agents, Intercalating agents, other	Electrogustometric detection threshold	Cancer patients had significantly higher taste detection thresholds than controls ($p=0.02$)
Steinbach et al, 2012 (324)	12 (56.5 ± 9.8 yrs)	Ovarian	Carboplatinum (plus taxol)	Smell: "Sniffin Stick"; Taste: Taste strips	Cancer patients had a significant decrease in olfactory identification ($p = 0.019$) after chemotherapy; olfactory function had recovered after 3 months No significant decrease in taste function after chemotherapy
Nishijima et al, 2013 (325)	23 (58.0± 11.5 yrs)	Gynecological	Taxane, carboplatin	Subjective assessment using the Common Terminology Criteria for	48% self-reported taste disturbances Electrogustometry:

				Adverse Events Electrogustometry; Filter paper disc testing	Decreased taste sensitivity in the chorda tympani nerve field. Increased taste sensitivity in the greater petrosal nerve field Filter paper testing: Increased taste sensitivity for sweet, salty, and sour & decrease taste sensitivity for bitter
Steinbach et al, 2010 (322)	69 (52.4±10.4 yrs)	Breast	NS#	Taste strips; “Sniffin Sticks”	Smell Compared with normative data, no significant difference in odour threshold, but better scores for odour identification and odour discrimination. Taste A significantly decreased taste sensitivity value compared with controls for sour only
Sánchez-Lara et al, 2010 (271)	30 cancer patients (56.0 ± 15 yrs) 30 controls (49.4 ± 11 yrs)	Breast, lung, prostate, multiple myeloma and lymphoma	NS	Whole mouth method using solutions (sweet, bitter and umami)	Cancer patients had a higher sweet detection (p=0.03) and bitter recognition thresholds (p=0.04) than controls
Caputo et al, 2012 (326)	29 cancer patients (50.1± 11.7 yrs)	Breast, uterus, prostate and	NS	Whole mouth detection method using single	Cancer patients had higher detection scores for salty,

	44 controls (49.5 ± 16.3 yrs)	head and neck cancer		concentration of bitter, salty, sour and sweet.	sweet, (p< 0.05) and lower bitter detection scores than controls (p< 0.05)
Strasser et al, 2008 (323)	41 cancer patients	Breast, prostate, lung and other	Docetaxel Paclitaxel	Self-reported taste (VAS *scale) Whole mouth detection for salty, sour, sweet and bitter at a single concentration	85% self-reported taste alterations After chemotherapy, a number of patients had higher detection thresholds: 4% bitter; 33% sour; 35% salty; 4% sweet.
Steinbach et al, 2009 (321)	87 (53.5 ± 10.5 yrs)	Breast and gynaecological	CMP: (Cyclophosphamide, methotrexate, fluorouracil) Anthracycline Anthracycline & taxane Platinum	"Sniffin sticks"; Taste strips (sweet, sour, salty & bitter)	Higher detection thresholds after chemotherapy infusion A decrease in the smell threshold, discrimination and identification score after chemotherapy infusion
Yakirevitch et al, 2005 (328)	21 (mean: 53.6yrs)	Solid tumours	Cisplatin	"Sniffin Sticks"	Only 5% of patients had decreased smell identification after chemotherapy infusion
Ovesen et al, 1991 (320)	51 cancer patients (mean: 64 yrs) 29 controls (mean: 62yrs)	Lung, ovarian, breast	Lung cancer: Cisplatin, vindesine, etoposide, vincristine, doxorubicin, tenoposide, cyclophosphamide, CCNU, and hexamethylamine, or monotherapy with tenoposide or etoposide	Electrogustometric detection threshold Olfactory detection threshold	Higher electrical taste threshold in cancer patients than controls (P< 0.001) No difference in smell thresholds between the cancer and control group

			Ovarian: Carboplatin, cisplatin, and etoposide or with cyclophosphamide, Adriamycin (doxorubicin), and 5-flu-orouracil Breast: cyclophosphamide, epirubicin, and 5-fluorouracil or monotherapy epirubicin		
Cohen et al, 2012 (319)	10 (mean: 12.5yrs)	Bone marrow transplant patients	NS	16 odour identification test Taste detection and identification test (bitter, salty, sweet, sour)	40% of cancer patients had a taste dysfunction 30% of cancer patients had a smell dysfunction
Skolin et al, 2006 (109)	10 cancer patients (mean: 14.5yrs) 10 controls	Leukaemia, solid tumour, lymphoma, central nervous system tumour	NS	Taste recognition thresholds (bitter, salty, sour and sweet).	Patients had higher thresholds for bitter taste than controls. Patients had more taste recognition errors compared with control

* VAS: Visual Analogue Scale; #NS: Not specified

7.5 Assessment of taste and smell dysfunction in cancer patients

Table 4 shows the results of eight studies that assessed taste and smell function. Unfortunately, there are no validated methods for assessing self-reported taste and smell function (302). Fifty percent of the studies used a 16-item taste and smell questionnaire which measures self-reported taste and smell alteration (329-332). One study indicated that 60% of general cancer patients had taste and/or smell alterations (n=192) (330), while others reported that 69% of lung cancer patients (n= 89), 86% of lung, gastrointestinal, breast and prostate cancer patients (n= 66)(331) and 75% of lung, breast, gastrointestinal and general patients (n= 518)(333) experienced taste and smell alterations. Self-reported smell changes alone was reported in 3% of general cancer patients (n= 192), 5% of lung, gastrointestinal, breast and prostate cancer patients (n=66) and 10% of breast, gastrointestinal and gynaecological cancer patients (n=518).

Using a two item scale, two studies assessed taste function in breast and gynaecological patients (n= 109)(299) and lung, colorectal and pancreatic cancer patients (n= 197) (334) and found approximately 70% of patients surveyed reported changes in taste. Patients receiving Irinotecan appeared to have a higher report of taste changes than those receiving Gemcitabine and a platinum containing chemotherapy (334). The results were in contrast to another study of breast and gynaecological cancer patients, with less taste changes occurring for those receiving gemcitabine (299). In another breast cancer study (n=45), 84% of patients complained of taste alterations (335). A total of 68% of colon, breast, lung, lymphoma and ovarian cancer patients reported taste changes assessed via a 41-item taste change questionnaire (284).

Table 7-3 Summary of studies assessing olfactory function in cancer patients

	Decreased	No effect	Increased
Odour detection	Steinbach 2009 (sniffin sticks)	Joussain 2013 (ETOC)*	
Odour identification	Steinbach 2012 (sniffin sticks) Steinbach 2009 (sniffin sticks) Yakrevitch 2005 (sniffin sticks: 5% of participants) Cohen 2012 (odor identification: 30% of participants)	Joussain 2013 (ETOC)* Yakrevitch 2005 (sniffin sticks: 95% of participants) Cohen 2012 (odor identification: 70% of participants)	Steinbach 2010 (sniffin sticks)
Odour threshold	Steinbach 2009 (sniffin sticks)	Steinbach 2010 (sniffin sticks) Oversen 1991 (detection threshold method)	

* ETOC: European test of olfactory capabilities

Table 7-2 Summary of findings of taste and smell alteration

Author, year	N (age)	Cancer Type, age range	Measures	Findings
Brisbois et al, 2011(330)	192 (64.3 ±12.4 yrs)	Lung, breast, genitourinary, gastrointestinal, neuroendocrine system , hematological conditions	Taste and smell survey	60 % taste and smell alteration 26% taste only 3% smell only
McGreevey et al, 2014 (332)	89 (69± 9 yrs)	Lung cancer	Taste and smell survey	69% taste and smell alteration
Hutton et al, 2007 (331)	66 (65.4 ± 12.4 yrs)	Lung , gastrointestinal, breast & prostate	Taste and smell survey	86% taste and smell alteration 52% taste and smell 30% taste only 5% smell only
Jensen et al, 2008 (335)	45 cancer patients (mean age: 45yrs)	Breast cancer	Subjective assessment using standardized questions of perceived taste disturbances	84% self-reported taste changes
Bernhardson et al, 2008 (333)	518 (58.71 ± 10.77yrs)	Breast, gastrointestinal, gynecological and other	Taste and smell survey	75% taste and smell alteration 10% smell only 35% taste only
Gamper et al, 2012 (299)	109 (61.0 ±12.8)	Breast and gynecological	Taste alteration scale	71% taste alteration
Zabernigg et al, 2010	197 (65.2 ±10.4)	Lung, pancreatic and colorectal	Taste alteration scale	70 % taste alteration

(334)				
Wickham et al, 1999 (336)	284 (58 ± 15 yrs)	Colon, breast, lung, lymphoma, ovarian	41-item taste change questionnaire	68% taste alteration

QoL: Quality of life

7.6 Chemosensory dysfunction in cancer survivors

Taste and smell receptors in cancer patients are said to regenerate within a finite time with some studies indicating a time-scale of 10-30 days (281, 284). For this reason, researchers hypothesize that chemosensory dysfunction should not affect patients once they have recovered from their cancer therapy. Steinbach et al, (2009) (321) assessed chemosensory function in 87 breast and gynaecological cancer patients before, during and after their chemotherapy. This study reported olfactory and gustatory function returned to normal three months after completion of therapy (321). In a study of 12 patients with ovarian cancer, olfactory function returned to normal after three months from completion of chemotherapy (324). Two other studies assessed paediatric haematopoietic stem cell transplant (HSCT) patients after treatment completion and found chemosensory function normalized after two months (319, 337).

Much of the work assessing taste and smell function in adult cancer survivors has focused on patients who had undergone HSCT using self-report measures. In an assessment of 50 haematological cancer patients, 20% of the patients reported taste or smell changes 100 days post-HSCT (293). In contrast, Mattson et al, (1992) found that taste and smell dysfunction continued up to one year after HSCT (338).

7.7 Chemosensory dysfunction and effect on oral intake in cancer patients

Food aversions can occur if an unpleasant experience occurs in conjunction with food ingestion (271). Studies exploring the influence of taste changes and food intake during chemotherapy remain inconclusive (339). However, some evidence

suggests that there is an association between chemosensory dysfunction and changes in oral intake in cancer patients. For example, in an assessment of 192 advanced cancer patients, those with a self-reported change in taste function consumed 20-25% fewer calories per day, had greater weight loss and had a poorer quality of life than those who reported no taste and smell alteration (330). A similar trend was seen in lung cancer patients, with those reporting taste and smell alterations having decreasing energy intake (332). Furthermore, Sanchez-Lara et al, (2010) (271) found that in a group of 30 adult cancer patients, those with a higher sweet detection threshold or a higher bitter recognition threshold had a lower energy and nutrient intake (271). One assessment of 42 cancer patients reported an association between those with self-reported taste changes and decreased appetite (340). Taste and smell alterations were also associated with a decreased appetite in breast and gynaecological cancer patients (299) and lung, colorectal and pancreatic cancer patients (334). Importantly, when assessed separately, taste and smell dysfunction is associated with a decreasing energy intake (331).

Not all patients however, report that taste and smell changes influence their intake. A qualitative study of 21 adult cancer patients with chemosensory loss showed that for several of the patients interviewed, their oral intake did not change as a result of this dysfunction (341). Bernhardson et al, (2009) (309) compared patients who had self-reported smell dysfunction alone, with those who reported both a taste and smell dysfunction. Those with a smell dysfunction alone appeared to have fewer difficulties with weight loss, appetite and oral intake. This study provides some early data that taste and smell dysfunction in combination may be a stronger driver of the dietary intake of cancer patients, than smell dysfunction alone. Since the flavor of food is comprised of smell and taste stimuli, this finding is not surprising.

7.8 Chemosensory changes and quality of life

For many cancer patients, taste changes can affect their quality of life (274, 336). In a study of 45 breast cancer patients, 10% of those with a self-reported taste dysfunction indicated that this was their most distressing oral symptom (335). Another study involving 314 cancer patients with self-reported taste and smell alteration, found that over 50% reported high distress as a result of their chemosensory symptoms. Almost 30% of this group also reported that it impacted their daily life (342). In a study of 284 cancer patients, 40% reported that taste changes were moderately distressing and 18.6% reported that their taste changes affected their lives (336). A similar finding was seen in a cohort of breast and gynaecological cancer patients, with those with a self-reported chemosensory dysfunction being more likely to report a depressed mood (333). Taste and smell dysfunction may be associated with fatigue in breast and gynaecological cancer patients (299) and lung, pancreatic and colorectal cancer patients (334). Taste alterations during chemotherapy can also affect activities of daily living such as grocery shopping, cooking meals and socializing with friends (340).

7.9 Intervention studies and strategies to improve/ prevent taste and smell dysfunction

There are few therapeutic options for the treatment of chemosensory dysfunction (298). Although zinc deficiency may be associated with taste disorders (343), there is little evidence to suggest that zinc supplementation improves taste function for people with taste disorders in the general population (344). As regards to cancer patients, a double-blind, placebo controlled randomized controlled trial of 58 patients found that zinc supplementation did not prevent taste and smell dysfunction (345). Glutamine, a branched-chain amino acid, is thought to play a role in the prevention

of chemotherapy-induced neurotoxicity (346). However, a randomized controlled trial of glutamine in 52 patients undergoing cancer treatment, found no impact on the incidence of taste disorders in an adult cancer population (323).

Encouragingly, the cannabinoid, delta-9-tetrahydrocannabinol (THC) may be effective in improving appetite and oral intake in cancer patients (347). Brisbois et al, (2011) assessed the effect of THC on taste and smell, appetite and food intake in 46 patients with cancer in a randomized controlled trial (24 controls) (294) and found that compared with placebo, THC patients exhibited significantly improved chemosensory perception, appetite, food intake and quality of life (294). In another approach, miraculin, a protein in a West African fruit, was tested for its ability to mask unpleasant flavors in a cross-over trial. Although the sample size was small and the trial was not blinded, there was some suggestion that consumption of this protein improved the taste of food for all participants while undergoing chemotherapy. For some participants, this improvement in taste translated to an improvement in oral intake (348). Further testing is required to confirm these results.

Patients use multiple strategies to manage chemosensory dysfunction and to improve oral intake. In a qualitative study of 12 patients with taste and smell alteration, patients described several strategies, including: 1) Trial and error to determine tolerable foods; 2) Having a selection of quick and easy foods available to consume; 3) Limiting social interactions; and 4) Working through the symptoms (349). It appears that strategies to cope with chemosensory dysfunction, such as the use of herbs and spices and avoidance of cooking smells, are not very effective (342). In a qualitative study of 21 patients with cancer, participants were unable to report any strategies that could alleviate their taste and smell changes (350). When cancer patients were provided with an educational intervention on strategies to

manage taste changes, only 16% of participants felt that the intervention helped “a lot” (340). There is only one study providing data suggesting that a nutritional intervention can improve intake. In that study, a combination of flavour enhancers in food and nutritional education was used with 107 adult cancer patients (54 intervention: 53 control)(351). The intervention group received 13 bottles of food flavour enhancers in combination with food preparation information. The intervention group had improved nutritional status and physical functioning compared with controls, though there was no difference in macronutrient intake or quality of life between the two groups (351).

7.10 Discussion

This review summarizes studies that have assessed taste and smell dysfunction in cancer patients undergoing chemotherapy. Overall there was some suggestion of lower taste sensitivity in adult and child cancer patients in 80% of the studies reviewed. The results were not as clear for studies that assessed olfactory function. Nevertheless, there appeared to be a higher incidence of odor identification dysfunction in patients with cancer undergoing chemotherapy when compared with the general population. Overall, the results for changes in odor detection and identification for patients with cancer were inconclusive. Eight studies assessed taste and smell function using self-reported measures. The incidence of taste and smell function, assessed by such imprecise methods ranged from 60% in general cancer patients (330) to 86% in lung, gastrointestinal, breast and prostate cancer patients (331).

There were methodological limitations in the studies in this review. For example, there was little consistency in the assessment methods used, making cross-study comparisons difficult. Of the included studies, four different methods were used to assess taste function: 1) whole mouth testing; 2) filter paper discs; 3) taste strips and 4) electrogustometry. Similarly, four methods were used to assess odor function: 1) “Sniffin sticks”; 2) ETOC; 3) odor identification; and 4) odor detection. In addition, a variety of self-report tools were used that did not compare results with a control group. Our review concurs with that of Gamper et al, 2012 and Bolton and Keast, 2012, who were unable to make firm conclusions regarding the occurrence of chemosensory dysfunction in cancer patients due to methodological limitations in many of the studies (302, 339).

Very few studies have assessed the prevalence of chemosensory dysfunction in paediatric cancer patients undergoing chemotherapy. The limited studies suggest that taste and smell dysfunction is prevalent during chemotherapy treatment and BMT. There is a dearth of literature assessing the association of taste and smell dysfunction with appetite, oral intake and QoL in childhood cancer patients. A recent systematic review of symptom experiences of children and adolescents with cancer reported nausea and vomiting to be one of the most commonly identified symptoms (10). Taste and smell alterations were not a key symptom identified by paediatric patients in the review. The varying cognitive abilities of children of differing ages makes it difficult to standardize chemosensory testing (276). What remains unclear from the systematic review of cancer symptoms is whether it is difficult for children to articulate taste and smell alterations. Recent work has shown that many cancer patients have poor dietary habits after cancer treatment, especially those who have survived a diagnosis of childhood cancer (202, 352). There remains a dearth of

literature regarding taste and smell function in survivors of childhood cancer and whether this is contributing factor the survivor's poor nutritional intake.

Overall, this review provides evidence that chemosensory dysfunction may be associated with a poor appetite, potentially leading to a poor nutritional intake and weight loss. The data were predominantly derived from self-reports of taste alterations and appetite by patients. The senses of taste and smell are an integral part of the experience of eating, but only represent part of the sensations experienced (349). A person's dietary habits and food intake are driven by their enjoyment of the food (353). It may be that severe chemosensory dysfunction reduces food enjoyment leading to reduced oral intake (331, 336). The tests used to assess chemosensory function are not necessarily in line with the patient's experience of eating (333). Food texture, temperature (349), touch and emotional state of mind (354) may be just as important as taste and smell for driving a patient's food intake and preferences (344). Most studies of chemosensory function in cancer patients assess taste and smell in isolation. Other factors contributing to food intake and food preferences in cancer treatment have not been assessed.

Despite the conflicting evidence for changes in the senses of smell and taste, this review also provides evidence for a relationship between chemosensory dysfunction and its effect on quality of life in patients undergoing treatment for cancer. Self-perceived taste alterations appear to affect mood and can increase fatigue (299, 333, 334). Taste alterations are also associated with a higher level of distress for cancer patients (309, 335), leading to changes in their daily activity (284, 309). Unfortunately, despite these important effects, this review demonstrated that the available chemosensory interventions are largely ineffective. It may be that interventions are ineffective because they aim to improve perceived taste or smell of

food, but have not considered flavour or texture. Given that taste and smell changes are often unique to each individual cancer patient, it may be that future interventions might be more effective if tailored to the needs of individual patients, rather than offering a generalized intervention to all affected patients.

7.11 Conclusion

This review summarizes the available evidence for the role of taste and smell dysfunction and on the food intake, appetite and quality of life of patients undergoing chemotherapy treatment for cancer. Both adult and child cancer patients should be counselled about the potential impact that taste and smell dysfunction could have on their appetite and oral intake during their cancer therapy. Further work is required to ascertain the taste and smell function of both adult and child survivors of cancer.

7.11.1 Implication

This chapter summarised the available literature on taste and smell changes during and after chemotherapy treatment for both adult and child cancer patients. There appears to be a high incidence of self-reported taste and smell alterations occurring during chemotherapy treatment. It also appears that taste and smell changes are altering the dietary intake of cancer patients. There is some suggestion that taste and smell changes may persist well after the cancer therapy is completed in adult cancer patients. The next chapter is a study on the taste and smell function in a cohort of survivors of childhood cancer.

8 TASTE AND SMELL DYSFUNCTION IN CHILDHOOD CANCER SURVIVORS⁶

Chapter 7 identified that taste and smell dysfunction is seen in cancer patients undergoing chemotherapy treatment. Taste and smell alteration was shown to be associated with an increase in distress, a reduction in appetite and may be contributing towards poor nutritional status in cancer patients. There is also some suggestion that taste and smell alteration may continue to be an issue well after cancer therapy has been completed. This chapter describes the findings from a study assessing taste and smell function in a cohort of survivors of childhood cancer. This study was published in *Appetite*.

8.1 Introduction

One potential side-effect of cancer therapy is reduced or altered taste and smell function (265). Both taste and smell receptor cells rapidly turn over and are produced from dividing basal cells (282, 283). The division mechanism is sensitive to the effects of chemotherapy and/or radiotherapy (284). The senses of taste and smell are integral in motivating a person's food preferences (270, 288) and both child and adult cancer patients commonly attribute difficulties maintaining food intake to the altered taste developed during treatment (127, 265, 289). Altered taste

⁶ This chapter has been published in the following peer reviewed journal:

Cohen J, Laing DG, Wilkes FJ, Chan A, Gabriel M, Cohn RJ. Taste and smell dysfunction in childhood cancer survivors. *Appetite*. 2014;75:135-40

JC & RC designed the study, JC & AC undertook data collection, JC, DL & AC contributed to data analysis, FW provided statistical support and JC, DL, FW & RC contributed to manuscript development

The key findings have been peer reviewed and presented by JC at ANZCHOG ASM, 2014.

in cancer patients has also been associated with decreased energy and nutrient intake (271), potentially leading to nutrient deficiencies (290).

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 (290). Long-term taste and smell dysfunction has been documented in the adult oncology population (182, 355). 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. (287, 355)

Survivors of childhood cancer have been shown to have poor dietary habits (16, 17, 202) and preferences for high fat foods (153). 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 (271, 331). Taste dysfunction has also been associated with obesity in both adults and children (356, 357) 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.

8.2 Methods

8.2.1 Study 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

8.2.2 Demographics

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

8.2.3 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 (276) 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 (276). This criteria was established from normative data for children (n=232) and adults (n= 56) older than five years, using the same test procedure (276). The same criteria for taste impairment has been used with participants with cystic fibrosis (317), chronic kidney disease (358) and healthy school children (306).

8.2.4 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 (276). 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 (276). 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 (277). In addition, it has been shown to have a test-retest reliability of 0.98 (306) 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 (276).

8.2.5 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 (359, 360) 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.

8.2.6 Food liking

A 94-item food liking questionnaire was used to elicit participant's food preferences (361, 362). 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.

8.2.7 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 (306, 317, 319). 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 (363). 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 (363). 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.

8.3 Results

8.3.1 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 8-1).

Table 8-1 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
Cranial Radiotherapy	6
Abdominal Radiotherapy	2
Head and Neck Radiotherapy	1

<i>Other sites</i>	8
<i>HCST#</i>	7
<i>Total Body Irradiation</i>	4

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

8.3.2 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 ± 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.

8.3.3 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 9.1).

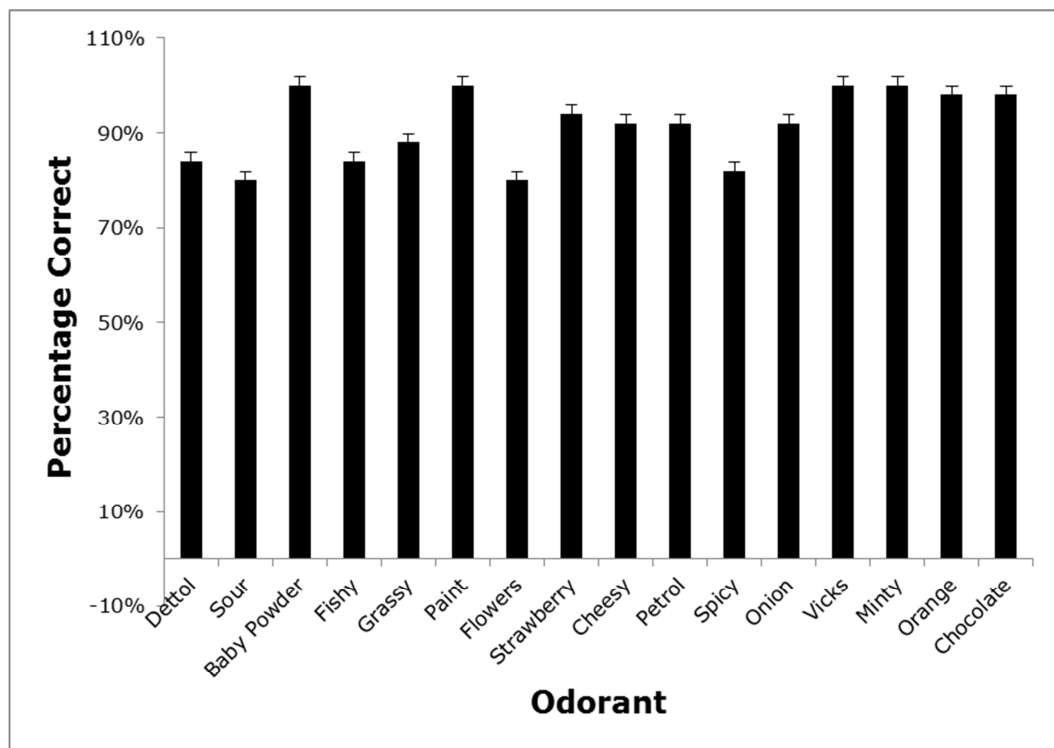


Figure 8-1 Percentage of participants who correctly identified each odorant

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 which two received total body irradiation (TBI) as part of their treatment. No other significant differences were found when comparing the treatment groups.

8.3.4 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 9.2). 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).

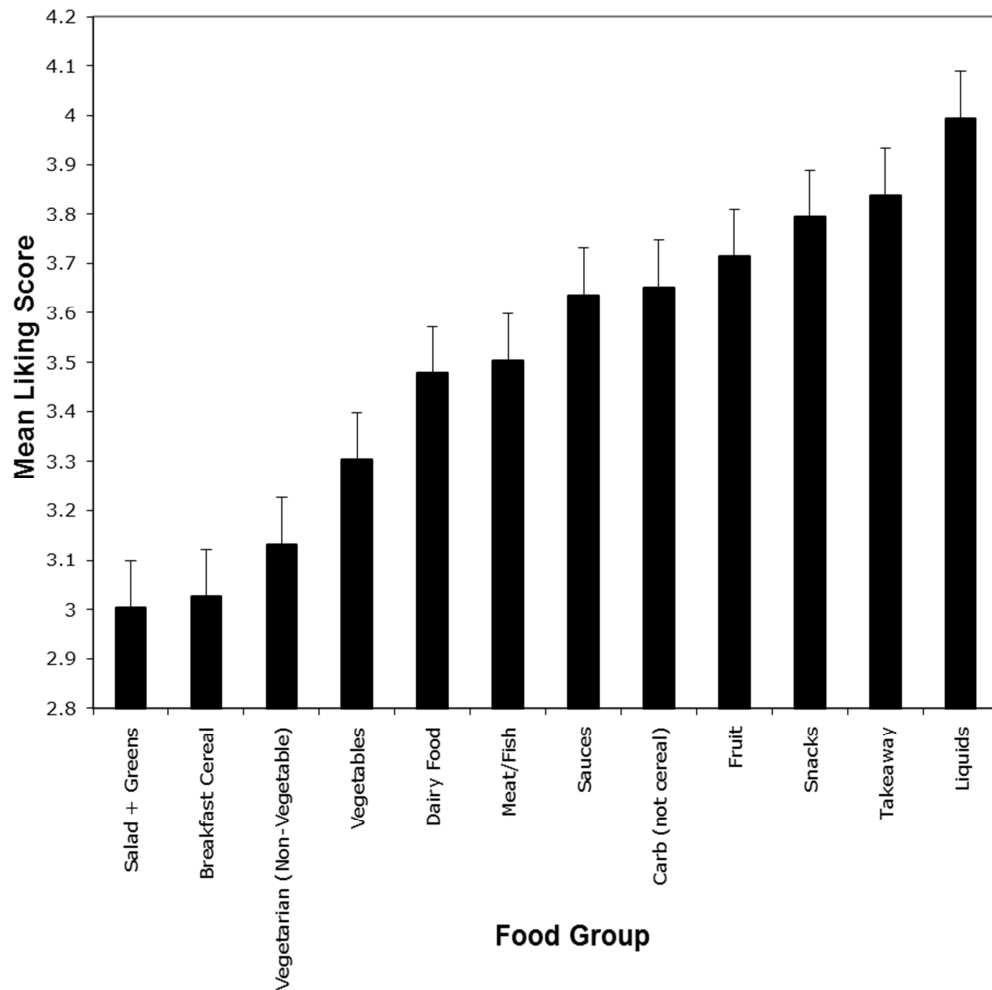


Figure 8-2 Mean liking scores for each food category

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.

8.3.5 Quality of life

Results from the additional concerns section of the QoL tool indicated that the participants had no significant food related concerns (Table 8-2).

Table 8-2 Mean score for questions in additional concerns section of the Functional Assessment of Anorexia/Cachexia Treatment QoL scale

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

* Possible values: 0 = Not at all; 1 = A little bit; 2 = somewhat; 3 = Quite a bit; 4 = very much

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.

8.4 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% (271) using objective measures or 86% using subjective measures such as self-report (331). 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 (127, 337). A taste dysfunction during the more intensive paediatric HSCT has been reported to be around 40% (319).

The findings in this study show a high prevalence of some degree of taste dysfunction in survivors of childhood cancer. Some studies have suggested that taste dysfunction continues well after treatment completion (182, 355) 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 (277).

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 (270).

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 (277). 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, 17, 202). 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 (364). 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 (290, 339). 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 (218)

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 (365, 366). It may be that a similar phenomenon occurs with taste dysfunction.

8.5 Conclusion

It is concluded that a degree of 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. Future work should compare taste and smell function of childhood cancer patients and survivors with appropriate healthy controls. 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.

8.5.1 Implications

The final study in the thesis provides evidence that taste and smell dysfunction is an issue in survivors of childhood cancer. This study provides one piece of the puzzle in determining the aetiology behind the permanent changes seen in the dietary habits of survivors of childhood cancer. The next chapter is the final chapter in this thesis.

Chapter 9 provides a summary of the findings from this thesis and provides recommendations that have implications for both clinical practice and for future research.

9 DISCUSSION

Over the last 50 years survival rates for children with cancer have improved. For the majority of patients, childhood cancer is no longer considered an acute disease with high short term morbidity and mortality, but a chronic disease with the potential for long term poor outcomes. The goals of the medical treatment for paediatric cancer patients is to maximise cure rates while trying to prevent the risk of long term deleterious effects of cancer therapy. Nutritional support is an important part of the management of paediatric oncology patients. The goal of nutritional therapy has been to prevent under-nutrition, ensuring adequate growth and development. Results from this thesis are providing the first evidence that the nutritional management of paediatric cancer patients needs to change. It needs to follow the goals of the medical treatment particularly with regard to preventing long term deleterious effects from the cancer therapy period. Childhood cancer survivors have inadequate nutrient intake early after treatment completion and it appears that young childhood cancer survivors' dietary habits do not return to what they were pre-diagnosis, often to their detriment. Poor nutritional intakes and obesity are emerging as longer term problems. Clinicians may need to alter the aims of the nutritional management of cancer patients being mindful that any decisions made during cancer therapy may affect the nutritional intake of patients' long term. At present there are no effective evidence-based interventions available that aim to improve the nutritional intake of survivors of childhood cancer.

9.1 Summary of findings

This thesis has confirmed the central hypothesis that the nutritional management decisions made during treatment for childhood cancer are primarily about the short term goal of promoting an adequate energy intake to prevent under nutrition. The research undertaken was grounded in clinical practice, using an in depth case study of a specialist paediatric oncology clinic in Sydney, Australia. A number of separate but related investigations took place to address specific questions (and related sub-hypotheses) and highlight the way forward for improved practice. The first part of the thesis aimed to identify and articulate the problem of childhood nutrition in the cancer acute care and survival (Figure 9-1).

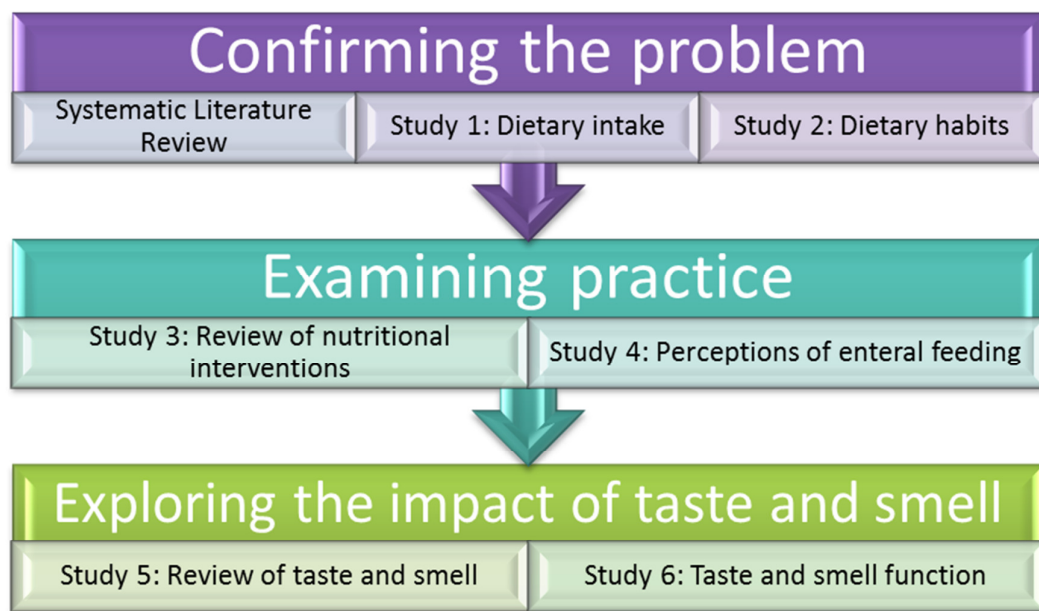


Figure 9-1 Schema of hierarchy of studies used within the context of research in practice

9.1.1 Confirming the problem

The first part of the thesis examined the hypothesis that there is a significant nutrition related problem in childhood cancer survivors. The first study (Chapter 3) showed that young childhood cancer survivors did appear to have a poor dietary intake, similar to that seen in the literature for adult survivors of childhood cancer. Fifty-four percent of young childhood cancer survivors were consuming above their estimated energy requirements. Fifty, 32 and 44 percent of children did not meet requirements for folate, calcium, and iron respectively. There was a significant trend for increasing BMI percentiles from diagnosis to time of assessment (56.29 vs. 67.17, $P = 0.01$). Results from the child feeding questionnaire showed that parents were more likely to monitor and use a restrictive form of parenting to control their child's food intake rather than pressure their child to eat ($P = 0.001$). This study indicated the extent and nature of the nutritional problem in this clinical group.

The results from chapter 4 showed that the majority of parents of childhood cancer survivors found their child's nutritional intake changed dramatically during the active treatment phase. This result was not unexpected as poor dietary intake during treatment has been well document in the literature. Of concern was that some of the dietary habits established during treatment appeared to continue once treatment had been completed. Three main themes emerged regarding parental perceptions of young childhood cancer survivors' current intake as compared with their pre-diagnosis eating habits: (1) decreased fruit and vegetable intake, (2) increased consumption of "junk food," and (3) increased portion sizes. The eating habits seen in the young cancer survivors were substantively different to that described by parents of the control group.

Many parents also appeared to shift their concerns about their child's weight. Prior to their child's cancer illness most of the parents reported their child's weight had not been a concern. During treatment their focus had been prevention of weight loss but on completion of treatment their focus shifted towards concern about their child being overweight. Although most of the children who participated in the study were not yet considered overweight, their rising BMIs indicated that the parents' concern was justified. The dietary habits and higher than recommended energy intake, would likely be one of the contributing factors in young cancer survivor's rising BMIs. This, in turn, will be putting them at greater risk of long term cancer side effects such as metabolic syndrome, cardiovascular disease and obesity. This second study qualified the nature of the problem in terms of the social context in which the nutritional intakes become a major concern.

9.1.2 Examining practice

The second part of this thesis hypothesised that clinicians may not be accounting for the potential long-term impact of nutrition decisions on survivors of childhood cancer, specifically related to actual feeding practices during and following treatment completion.

The first study in this section (Chapter 5) involved a systematic review that delivered a total of three studies on nutritional interventions of all childhood cancer survivors, both adult and child. The studies were heterogeneous in regards to the methods of the interventions and a meta-analysis was unable to be performed. One study found an improvement in calcium intake and calcium supplementation in an intervention in adult survivors of childhood cancer aimed at osteoporosis prevention. The second study found that a single group intervention improved the self-reported improvement in health food intake, though there was no improvement in self-

reported junk food intake. Overall the quality of these studies was poor, there was no focus on improving dietary intake and none of the studies focused on young cancer survivors early after treatment completion. The results indicated a need to research practice in more detail.

Research done by our research team has shown that parents are using many negative feeding practices to ensure their child consumes adequate food to prevent under nutrition during their cancer therapy. This study also indicated that a significant part of these negative practices involved threatening their child with enteral tube feeding (known as instrumental feeding) if they consuming an adequate oral intake. Long term child feeding practices and food preferences are established when children are young and parent practices such as instrumental feeding, have been associated with poor dietary intake in adults in the non-cancer population. As demonstrated in the introductory review for the thesis (chapter 2), under-nutrition is a significant issue during cancer therapy and nutritional supplementation in the form of enteral tube feeding is an important part of this management.

The second study in this section (Chapter 6) found there appeared to be common perceptions of the purposes and impact of ETF among patients, parents and healthcare workers. Both positive (good nutrition, weight gain and decreased anxiety) and negative (physical appearance, invasive insertion procedure and comfort) aspects of EN were discussed. There were some discordant perceptions regarding the timing and type of information provided on the use of ETF, as well as the decision making process used. Decision making in the healthcare setting is complex and information provision alone does not necessarily help with timely and appropriate decisions for families. This research found that by standardizing and improving the methods used for the commencement of ETF, family distress surrounding the use of ETF with paediatric oncology patients may be reduced.

9.1.3 Exploring the impact of taste and smell

The final section of this thesis hypothesised that taste and smell may be implicated in the problem of developing healthy eating habits in childhood cancer survivors. The first study in this section (Chapter 7) found self-reported taste and smell alterations are prevalent in upwards of 86% of cancer patients. There was also some evidence for decreased taste sensitivity in cancer patients when assessed using objective tests. In some patients, taste and smell alterations continued well after their cancer treatment had been completed. Taste and smell alterations in patients with cancer appeared to increase their distress, reduce appetite and contribute towards a poor nutritional status.

In light of this review the second study in this section, and the final study in the thesis, found that survivors of childhood cancer do have a greater incidence of taste and smell changes, compared to the general population. Twenty-seven percent of survivors of childhood cancer had some form of smell dysfunction. This was considerably higher than the 10% of smell dysfunction reported in the literature for the general population, using similar methods of assessment. The incidence of smell dysfunction was 10% of the cancer survivors studied which again is higher than the one to two percent smell dysfunction reported in the general population. The childhood 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". Thus it appears that taste and smell may contribute substantially to the problem of assuring adequate nutrition in childhood cancer and survival, and further research is warranted in this area.

9.2 Limitations

As stated earlier, this thesis is presented as a case study of clinical practice in a defined setting. The data collected for these studies, focused on a specialist paediatric oncology site in Sydney, Australia. With the exception of study 8 which recruited participants across two paediatric oncology units within Sydney, Australia, all the data were collected from this site. The demographics of the participants in this thesis may not be representative of the childhood cancer population within Australia and internationally, especially those from developing countries. Further case studies, such as the one conducted here would add to this knowledge. In addition the studies conducted in the thesis can be repeated with a wider demographic representation of childhood cancer patients.

From a methods perspective, the response rate for both the dietary intake study and the enteral feeding study were low. This may relate to the use of mail-out surveys to recruit the participants or due to the burden of using three-day food diaries to collect dietary intake data (367). Since the completion of the dietary intake study, a food frequency questionnaire (FFQ), the Australian Child and Adolescent Eating Survey (ACAES), has been validated for use among Australian children and adults (368). There is a lower responder burden associated with the FFQ compared with food records (367) and its use in future studies may improve response rates. The ACAES provides a measure of both nutrient intake and food variety scores. Food variety scores are positively associated with good health outcomes (369). This is advantageous for determining which food groups may need targeting in future interventions (369). Recent literature has shown that multiple 24-hour recalls may be more accurate in determining energy intake than FFQs in survivors of childhood cancer. For future interventions, in which weight loss and

subsequently energy intake, is the primary outcome, 24 hour recalls could be used as a measure of dietary intake.

The empirical component of the thesis involved discrete primary data collection and analysis (Chapters 3, 4, and 8) which employed a cross-sectional study design. As discussed in chapter one, a cross-sectional study limits the ability to determine a causal relationship (370) . Using a cross-sectional methodology does provide an assessment of the prevalence of the outcome and information for the generation of hypothesis on causal relationships (33). The results from the cross-sectional studies in this thesis have provided evidence of the need for a focus on the nutritional intake of childhood cancer survivors early off treatment. It has also provided targets for intervention in this patient cohort. Future studies could assess the changing dietary patterns during treatment and into survival using a prospective longitudinal study design. This will also provide the researchers with the opportunity to assess the mechanism involved with this permanent change in dietary habits.

9.3 Conclusions

As childhood cancer is no longer an acute condition with poor outcomes and high morbidity and mortality, it should be treated as a chronic condition. The results from my research confirm my hypothesis that dietary habits of childhood cancer patients developed during cancer therapy are continuing once treatment has completed. In addition, the poor dietary intake seen in adult survivors of childhood cancer is likely manifesting itself early after treatment completion. There now needs to be greater awareness of the link between the nutrition decisions made during the cancer therapy and how they may be affecting the child's nutritional intake well after cancer therapy is completed. At the very least, nutritional interventions to improve the

dietary habits of survivors of childhood cancer need to be initiated soon after treatment completion. Ideally a focus on long-term healthy dietary habits may need to occur during cancer therapy.

9.4 Implications for clinical practice

This research was grounded in changing clinical practice. The following recommendations are for dietitians and clinicians working with childhood cancer patients:

9.4.1 Models of care

The current standard of dietetic care in paediatric oncology is to provide funding for a dietitian to see patients during the acute phase of cancer therapy. This thesis highlights the need for the health service to recognise that paediatric oncology no longer just about treating disease but is about health protection. Paediatric oncology centres should be considering enhancing funding models for the provision of long-term dietetic follow-up as part of standard care. Medical conditions such as cystic fibrosis and type I diabetes are considered chronic conditions and their care model provides significant funding for a dietitian to review and manage patients on a regular basis. Cancer centres may need to utilise the same model of care as other such chronic paediatric diseases, providing regular nutritional assessment and follow-up to paediatric cancer patients once treatment is complete.

The referral criteria for nutritional interventions may need to be altered. The current model is reactive, where referrals are made to a dietitian once weight loss or a reduction in oral intake is seen in the patient. This model is used because the current funding model is not adequate to allow all patients to be assessed early in

their cancer journey. This thesis provides early evidence that the poor dietary habits and parenting practices seen during treatment are continuing once therapy is completed. This has implications for survivors who are at a high risk of early-onset chronic health conditions. The dietetics model should be changed to a proactive model in which all patients are counselled on good nutritional practices early on in their cancer journey.

9.4.2 Dietetic practice

As the prevention or treatment of under-nutrition has been the focus of the dietary management of childhood cancer patients, recommendations for nutritional support have been based on increasing the energy intake of a patient's diet. This has been to the detriment of good nutritional practices. The mantra of "eat whatever you like" has been recited among both dietitians and clinicians for many years. In light of the shift towards childhood cancer being considered a chronic disease, these practices need to also change. Dietitians should no longer focus on improving a patient's energy intake in isolation. Parents and carers should be counselled on the use of healthy high energy diets in combination with maintaining intake as close to the dietary guidelines as possible.

Dietitians could consider providing education and counselling to parents and patients on using positive feeding practices to encourage their child to consume an adequate intake during their child's cancer treatment. The constant pressure to get a child to consume an adequate intake may be causing long term issues with food aversions. Parents should avoid using the threat of the insertion of a nasogastric tube to get their child to eat. Parents and clinicians need to view nasogastric tube insertion as part of standard practice of care rather than something that is used as a last resort. The practice of prophylactic nasogastric tube insertion may reduce

parental stress surrounding their child's food intake, thereby potentially avoiding these negative feeding practices. If a child has a nasogastric tube in to ensure an adequate nutritional status is maintained throughout treatment then parents may feel more comfortable encouraging a healthy diet when their child does eat. Constant exposure to a greater food variety on treatment has the potential to improve the dietary habits of childhood cancer patients once their treatment is complete.

9.4.3 Food service

At present, the meals and snacks provided to the patients in the hospital environment, do not necessarily reflect good nutritional practices. Many of the foods are heavily processed, the vegetables are inedible, and the mid-meal snacks provided include items such as chocolate and sweet biscuits, high sugar yoghurts and flavoured milks and high sugar muffins. In light of the results from the thesis, a review of the food service system in paediatric oncology units is required. The foods provided to the patients, especially mid-meal snacks should complement the education regarding healthy high energy foods. The snacks should be low in saturated fat and sugar but high in energy and provide other nutritional benefits. The paediatric oncology unit currently provides patients and families with fruit for consumption, and could consider providing vegetables as well. This may encourage families to cook healthier meals to provide to their child when an inpatient. Funding for a nutrition assistant could also allow cooking demonstrations on the wards to also encourage childhood cancer patients to have a positive relationship with food.

Commercially prepared oral nutritional supplements and some of the supplements used for enteral tube feeding may not represent good nutritional practices. Many of the oral supplements are very high in sugar to help with palatability, but if used as a sole source of nutrition, are likely increasing the patient's intake of sugar above that

recommended in the dietary guidelines. The use of commercially prepared supplements is an important part of dietetic practice to provide the patient with additional energy and nutrients. To enable a continuation with the practice of using a healthy high energy diet to prevent weight loss, the nutritional supplements should reflect this. The paediatric oncology unit could provide blenders and high energy healthy drink recipes for the parents to make for their children while they are an inpatient. Use of healthy high energy drinks provides an opportunity for the patient to consume a greater amount of fruit and vegetables in an easy to consume format.

Although consumption of non-processed food is preferable, supplying freshly cooked meals and snacks to patients in the hospital may not be practical. Parents have a limited capacity to cook meals due to the time constraints involved with looking after a sick child as well as a lack of resources available in the hospital to cook for their child. Many patients also find it difficult to consume hot meals due to a hypersensitivity to smells. Many families rely on highly processed packaged food to ensure their child consumes an adequate energy intake though these foods don't usually provide any other nutrients. Clinicians and dietitians could partner with the food industry to develop more appropriate snacks which are not only high in energy and palatable but be based on fruit and vegetables as a way to reinforce this concept of healthy high energy.

9.4.4 Dietetic education

Childhood cancer is not the only paediatric condition in which improvements in treatment have meant that diseases which were once associated with early mortality are now considered chronic disease. Clinicians who work with paediatric patients with conditions such as Cystic Fibrosis, renal disease and HIV are also finding their patients are at a higher risk of chronic disease, such as cardiovascular disease, than

their peers. Dietitians are also becoming aware of the importance of promoting good nutritional practices (not just high energy) in young patients with these conditions and are starting to change their practice accordingly. Clinical based nutrition research should not only focus on nutrient intake but food variety and dietetic education given to the patient should reflect this.

The education of dietetic students must also start to reflect this change in dietetic practice. Many students are still being educated on the use of commercially prepared snacks and supplements as well as sugar-sweetened beverages as the first line of dietetic practice. Although these will still remain an important part of dietetic practice they should not be considered the first option in dietetic practice. Dietetic students should be educated in providing and trialling food based recommendations with their patients first, before the use of commercially snacks and supplements.

9.5 Directions of future research

A number of research questions have been proposed as a result of this thesis and have provided a focus for nutritional interventions for young cancer survivors early after treatment completion. Our research team has commenced the development of an intervention (ReBoot-kids) which aims to improve fruit and vegetable intake and reduce non-core food intake in young cancer survivors early after their treatment completion. The aim of this study is to determine whether dietary habits of childhood cancer survivors can be improved early after treatment completion. The long-term aim is reducing the incidence of chronic health conditions in adult survivors of childhood cancer.

The prevention of poor dietary habits in childhood cancer patients should ideally be a focus during treatment. To reflect the recommendations from this thesis on the importance of focusing on healthy high energy diet education, a need assessment will be undertaken with parents and carers on the paediatric oncology ward, to clarify their views on the current dietetic care model. There is a dearth of research assessing the dietary intake of cancer patients during treatment as focus has been on energy intake alone. An assessment of the nutritional intake of childhood cancer patients should also be undertaken to provide targets for interventions on treatment. The results of this research will be used to design education materials reflecting the use of a healthy high energy diet, and to improve the food service model.

The thesis has also provided a focus for an intervention for improving the information provision regarding nutritional support options during cancer therapy. Results from this thesis as well as previous work completed at our centre show that uptake of nutritional support such as ETF can be delayed. Parents are using poor feeding practices such as forcing their child to eat to prevent their need for ETF. These feeding practices also have the potential to cause long-term oral aversions and poor dietary habits after treatment completion. Research has begun on developing and pilot testing a decision aid for use with childhood cancer patients regarding decisions on nutrition supplementation. The aim is to provide adequate education to parents about the benefits and risks of all nutrition support options in a timely manner. The long-term goal is to ensure parents are adequately informed about their child's nutrition choices. This may reduce the poor parent feeding practices seen in this patient cohort thereby preventing poor dietary habits from developing during and after cancer therapy.

The results from this thesis will inform a longitudinal study assessing the change in childhood cancer patient's dietary habits during their cancer therapy and beyond. The longitudinal study will focus on assessing nutrient intake, food variety and dietary habits of childhood cancer patients. This study will also assess potential predictors and of the changing dietary habits and intake. Such predictors will include:

- Taste and smell changes
- Parental feeding practices
- Development of learned aversions
- Lack of repeated exposure
- Change in appetite regulation

The longitudinal study will aim to confirm the hypothesis generated from this thesis that the dietary habits of childhood cancer patients permanently change as a result of their cancer therapy. A secondary aim will be to determine the aetiology and predictors of the change in dietary habits. The results from the longitudinal study will then drive future dietary interventions for children while on cancer therapy with the long-term aim to reduce their risk of long-term metabolic conditions associated with survivors of childhood cancer.

I hope that results from this thesis combined with future research on dietary habits and dietary practice will ensure that survivors of childhood cancer will have a QoL equal, if not better than their peers.

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APPENDIX A – CHILD FEEDING QUESTIONNAIRE

The Child Feeding Questionnaire (CFQ)

**An Instrument for Assessing
Parental Control in Child Feeding**

**Leann L. Birch, Ph.D.
Susan L. Johnson, Ph.D.
Karen Grimm-Thomas
Jennifer O. Fisher, Ph.D.**

The Pennsylvania State University

INSTRUCTIONS:

Using the scale below, please circle one number for each question which best corresponds to your answer. **Please answer about your child who is in our study.**

	never	seldom	half of time	most of time	always
1. When your child is at home, how often are you responsible for feeding her?	1	2	3	4	5
2. How often are you responsible for deciding what your child's portion sizes are?	1	2	3	4	5
3. How often are you responsible for deciding if your child has eaten the right kind of foods?	1	2	3	4	5

Using the scale below, please indicate how you would classify your own weight at each of these 4 time periods listed below (Please circle ONLY ONE number for each time period)

	markedly underweight	underweight	average	overweight	markedly overweight
4. Your Childhood (5 to 10 years old)	1	2	3	4	5
5. Your Adolescence	1	2	3	4	5
6. Your 20's	1	2	3	4	5
7. Currently	1	2	3	4	5

Using the scale below, please indicate how you would classify
your child's weight at each of these 4 time periods listed below.
(Please circle ONLY ONE number for each time period)

	markedly underweight	underweight	average	overweight	markedly overweight
8. Your child during the first year of life	1	2	3	4	5
9. Your child as a toddler	1	2	3	4	5
10. Your child as a pre-schooler	1	2	3	4	5
11. Your child kindergarten through 2 nd grade	1	2	3	4	5
12. Your child from 3 rd through 5 th grade	1	2	3	4	5
13. Your child from 6 th through 8 th grade	1	2	3	4	5

Using the scale below, please circle one number for each question which best corresponds to
your answer. Please answer about your child who is in our study.

	unconcerned	slightly unconcerned	neutral	slightly concerned	concerned
14. How concerned are you about your child <i>eating too much</i> when you are not around her?	1	2	3	4	5
15. How concerned are you about your child having to diet to maintain a desirable weight?	1	2	3	4	5
16. How concerned are you about your child becoming over weight?	1	2	3	4	5

INSTRUCTIONS:

Using the scale below, please circle one number for each question which best corresponds to your answer. **Please answer about your child who is in our study.**

	disagree	slightly disagree	neutral	slightly agree	agree
17. I have to be sure that my child does not eat too many <i>sweets (candy, ice cream, cake or pastries)</i> .	1	2	3	4	5
18. I have to be sure that my child does not eat too many <i>high fat foods</i> .	1	2	3	4	5
19. I have to be sure that my child does not eat too much of her <i>favorite foods</i> .	1	2	3	4	5
20. I intentionally keep some foods out of my child's reach.	1	2	3	4	5
21. I offer <i>sweets (candy, ice cream, cake, pastries)</i> to my child as a reward for good behavior.	1	2	3	4	5
22. I offer my child her <i>favorite foods</i> in exchange for good behavior.	1	2	3	4	5
23. If I did not guide or regulate my child's eating, she would eat too many <i>junk foods</i> .	1	2	3	4	5
24. If I did not guide or regulate my child's eating, she would eat too much of her <i>favorite foods</i> .	1	2	3	4	5
25. My child should always eat all of the food on her plate.	1	2	3	4	5
26. I have to be especially careful to make sure my child eats enough.	1	2	3	4	5
27. If my child says "I'm not hungry," I try to get her to eat anyway.	1	2	3	4	5
28. If I did not guide or regulate my child's eating, she would eat much less than she should.	1	2	3	4	5

INSTRUCTIONS:

Using the scale below, please circle one number for each question which best corresponds to your answer. **Please answer about your child who is in our study.**

	never	rarely	sometimes	mostly	always
29. How much do you keep track of the sweets (<i>candy, ice cream cake, pies, pastries</i>) that your child eats?	1	2	3	4	5
30. How much do you keep track of the snack food (<i>potato chips, Doritos, cheese puffs</i>) that your child eats?	1	2	3	4	5
31. How much do you keep track of the high fat foods that your child eats?	1	2	3	4	5

APPENDIX B – 3 DAY FOOD DIARY

Parental Attitudes to Nutrition Study 3-day food diary



Instructions

1. Pick three days to keep your child's food diary-one of these days should be **1 weekend and 2 weekdays**
2. Do not change your child's eating habits during this time
3. Record everything your child eats and drinks over those three days
4. Please be as accurate as possible including brands, amounts (weighed if possible) and how it was cooked.
5. Please indicate if the food is made at home or is bought at a store
6. Try and include individual ingredients i.e. a ham sandwich is 2 slices white bread & 2 slices of primo ham & 1 tsp margarine

Example

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc)
Breakfast	6.15am	Rice bubbles	½ cup	
Breakfast	6.15am	Shape milk	½ cup	2 tsp sugar
Recess	10.30am	UncleTobys muesli bar	1 bar	
Recess	10.30am	Orange Juice-freshly squeezed	200ml	
Lunch	12.10pm	White bread	2 slices	
Lunch	12.10pm	Tomato	4 slices	
Lunch	12.10pm	Cheese	1 Kraft cheese slice	
Lunch	12.10pm	Lettuce	1 leaf cos lettuce	2 tsp margarine
Afternoon Tea	3.30pm	Apple-Granny Smith	1 small	
Afternoon tea	3.30pm	Chips-salt & vinegar	25g packet	
Dinner	6.30pm	Lamb chop-grilled	2 x 60g	2 tsp tomato sauce
Dinner	6.30pm	Broccoli-boiled	3 rosettes (30g)	
Dinner	6.30pm	Carrots-steamed	¼ cup	
Dinner	6.30pm	Chips-fried-McCain	½ cup	

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

Name: _____
Date: _____

Day of Week: _____

Meal	Time	Food Item	Serving Size	Extras (salt, mayo etc

APPENDIX C – ETHICS APPROVAL LETTER (CHAPTER 3 & 4)

	<p>SOUTH EASTERN SYDNEY ILLAWARRA</p> <p>NSW HEALTH</p> <p>HUMAN RESEARCH ETHICS COMMITTEE – Northern Hospital Network</p> <p>Room G71, East Wing Edmund Blacket Bldg Prince of Wales Hospital Cnr High & Avoca Streets RANDWICK NSW 2031 Tel: (02) 9382 3587 Fax: (02) 9382 2813</p>
<p>9 November 2010</p>	
<p>Ms Jennifer Cohen Department of Nutrition & Dietetics Sydney Children's Hospital RANDWICK NSW 2031</p>	
<p>Dear Ms Cohen</p>	
<p>HREC Reference Number: 08/059 Project Title: Parental attitudes to nutrition and physical activity after their child's cancer treatment and its relationship the risk of obesity and the metabolic syndrome</p>	
<p>Thank you for your correspondence dated 1 November 2010 to the Human Research Ethics Committee (HREC) responding to questions which arose at the Executive Committee meeting on 18 October 2010.</p>	
<p>Authority to grant final approval was delegated to the Executive Officer and I am pleased to advise that ethical approval has been given for the following:</p>	<ul style="list-style-type: none">• Protocol dated 23 September 2010• Interview discussion guide version 3, dated 1 November 2010• Classified advertisement version 3, dated 1 November 2010• Generic web/magazine/pin board advertisement version 3, dated 1 November 2010
<p>Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website:</p>	<p>http://www.sesiahs.health.nsw.gov.au/Research_Support/NHN/.</p>
<p>Please quote HREC ref no 08/059 in all correspondence.</p>	<p>We wish you every success in your research.</p>
<p>Yours sincerely</p>	
<p>Deborah Adrian Executive Officer, Human Research Ethics Committee</p>	
<p>This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) <i>National Statement on Ethical Conduct in Human Research (2007)</i>, NHMRC and Universities Australia <i>Australian Code for the Responsible Conduct of Research (2007)</i> and the CPMP/ICH Note for Guidance on Good Clinical Practice.</p>	
<p>O:\Correspondence\2008\059\9.11.10 EO approval of amendments after responses.doc</p>	<p>South Eastern Sydney and Illawarra Area Health Service Locked Mail Bag 8808 South Coast Mail Centre NSW 2521 Level 4 Lawson House Wollongong Hospital Tel (02) 4253 4888 Fax (02) 4253 4898 A8N 78 390 886 131</p>

APPENDIX D – SEARCH STRATEGY FOR COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (CENTRAL)

1. For **Population** the following text words were used:

(infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR young adult OR young adults OR young adult*)

AND (post treatment OR off treatment OR treatment complet* OR treatment termin* OR follow up OR follow-up OR followup OR survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term survivor OR survivo* OR surviving)

2. For **Nutrition** the following text words were used:

patient education OR practice guideline OR practice guidelines OR dietary guideline OR dietary guidelines OR practice guideline* OR dietary guideline* OR diet OR diets OR diet* OR diets* OR dietetic OR dietetics OR diet therapy OR health diet OR healthy food OR health promoting behaviour OR health promoting behaviour OR (diet* AND intervent*) OR (diet* AND advic*) OR diet* AND counsel* OR (diet* AND therap*) OR (diet* AND treatment*) OR (diet* AND educat*) OR (nutriti* AND intervent*) OR (nutriti* AND advice*) OR (nutriti* AND counsel*) OR (nutriti* AND therap*) OR (nutriti* AND treatment*) OR (nutriti* AND educat*) OR (nutriti* AND support) OR supportive therapy

3. For **Outcome** the following text words were used:

food OR foods OR food* OR foods* OR food intake OR eating OR ingestion OR nutrition OR nutrition* OR (health* AND diet*) OR (health* AND food*) OR energy intake OR caloric intake OR kilojoule OR kilojoules OR calorie OR calori* OR caloric restriction OR vitamin OR vitamins OR vitamin* OR minerals OR minerals* OR mineral OR mineral* OR micro-nutrient OR micro-nutrients OR macro-nutrient OR macro-nutrients OR nutrient OR nutrients OR calcium OR folate OR folic acid OR iron OR ferric OR ferrous OR protein OR proteins OR fat intake OR fat reduced OR dietary fat restriction OR low fat OR low calorie OR low energy OR reduced energy OR calorie controlled OR fatty foods OR high fat OR fruit OR fruits OR vegetable OR vegetables OR dietary composition OR carbohydrate intake OR obesity OR obese OR adiposity OR body weight OR overweight OR body mass index OR BMI OR body mass OR body fat distribution OR body composition OR "bioelectrical impedance analysis" OR health behavior OR health behaviors OR health behaviour OR health behaviours OR health behaviour* OR health behaviour* OR health promotion OR behaviour change OR behavior change OR behaviour change* OR behavior change* OR health behaviour change OR health behavior change OR health behaviour change* OR health behavior change* OR life style OR life style* OR weight gain OR weight gains OR weight gain* OR body weight OR weight loss OR weight change OR weight changes OR weight change* OR overnutrition OR overeating OR hyperphagia OR Metabolic syndrome OR Waist hip ratio OR Waist height ratio OR Skinfold thickness OR Skinfold thicknesses OR Skinfold thickness* OR DEXA OR Diabetes OR type 2 diabetes OR glucose metabolism OR insulin metabolism OR insulin resistance OR hyperinsulinemia OR hyperinsulinaemia OR cardiomyopathy OR myocardial Infarction OR fat metabolism OR cardiovascular risk factor OR cardiovascular risk factors OR cardiovascular risk factor* OR cardiovascular disease OR cardiovascular diseases OR blood pressure OR hypertension OR blood lipid OR blood lipids

OR blood lipid* OR hyperlipidemia OR hyperlipidaemia OR dyslipidemia OR dyslipidaemia
OR cholesterol metabolism OR hypercholesterolemia OR osteoporosis OR bone mineral
density OR dual energy x-ray absorptiometry OR malnutrition OR undernutrition OR
Nutritional Deficiency OR Nutritional Deficiencies OR ideal body weight OR body image OR
eating disorder OR eating disorders OR eating disorder* OR disordered eating OR fussy
eating OR food refusal OR quality of life OR QoL

4. For **Cancer** the following text words were used:

cancer OR oncology OR oncolog* OR neoplasms OR neoplas* OR carcinoma OR carcinom*
OR tumor OR tumour OR tumor* OR tumour* OR cancer* OR malignan* OR
hematooncological OR hemato oncological OR hemato-oncological OR hematologic
neoplasms OR hematolo* OR bone marrow transplantation OR bone marrow transplant* OR
leukemia OR leukaemia OR lymphoma

The search was performed in title, abstract or keywords
Final search 1 and 2 and 3 and 4

[* = zero to many characters]

APPENDIX E – SEARCH STRATEGY FOR MEDLINE (PUBMED)

1. For **Population** the following MeSH headings and text words were used:

(infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn OR young adult[mh] OR adult[mh] OR young adult)

AND (post treatment OR off treatment OR treatment complet* OR treatment termin* OR follow up OR follow-up OR followup OR survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving)

2. For **Nutrition** the following MeSH headings and text words were used:

patient education OR practice guideline OR practice guidelines OR dietary guideline OR dietary guidelines OR practice guideline* OR dietary guideline* OR diet OR diets OR diet* OR diets* OR dietetic OR dietetics OR diet therapy OR health diet OR healthy food OR health promoting behaviour OR health promoting behaviour OR (diet* AND intervent*) OR (diet* AND advic*) OR diet* AND counsel* OR (diet* AND therap*) OR (diet* AND treatment*) OR (diet* AND educat*) OR (nutriti* AND intervent*) OR (nutriti* AND advice*) OR (nutriti* AND counsel*) OR (nutriti* AND therap*) OR (nutriti* AND treatment*) OR (nutriti* AND educat*) OR (nutriti* AND support) OR supportive therapy

3. For **Outcome** the following MeSH headings and text words were used:

food OR foods OR food* OR foods* OR food intake OR eating OR ingestion OR nutrition OR nutrition* OR (health* AND diet*) OR (health* AND food*) OR energy intake OR caloric intake OR kilojoule OR kilojoules OR calorie OR calori* OR caloric restriction OR vitamin OR vitamins OR vitamin* OR minerals OR minerals* OR mineral OR mineral* OR micro-nutrient OR micro-nutrients OR macro-nutrient OR macro-nutrients OR nutrient OR nutrients OR calcium OR folate OR folic acid OR iron OR ferric OR ferrous OR protein OR proteins OR fat intake OR fat reduced OR dietary fat restriction OR low fat OR low calorie OR low energy OR reduced energy OR calorie controlled OR fatty foods OR high fat OR fruit OR fruits OR vegetable OR vegetables OR dietary composition OR carbohydrate intake OR obesity OR obese OR adiposity OR body weight OR overweight OR body mass index OR BMI OR body mass OR body fat distribution OR body composition OR "bioelectrical impedance analysis" OR health behavior OR health behaviors OR health behaviour OR health behaviours OR health behaviour* OR health behaviour* OR health promotion OR behaviour change OR behavior change OR behaviour change* OR behavior change* OR health behaviour change OR health behavior change OR health behaviour change* OR health behavior change* OR life style OR life style* OR weight gain OR weight gains OR weight gain* OR body weight OR weight loss OR weight change OR weight changes OR weight change* OR overnutrition OR overeating OR hyperphagia OR Metabolic syndrome OR Waist hip ratio OR Waist height ratio OR Skinfold thickness OR Skinfold thicknesses OR Skinfold thickness* OR DEXA OR Diabetes OR type 2 diabetes OR glucose metabolism OR insulin metabolism OR insulin resistance OR hyperinsulinemia OR hyperinsulinaemia OR cardiomyopathy OR myocardial Infarction OR fat metabolism OR cardiovascular risk factor OR cardiovascular risk factors OR cardiovascular risk factor* OR cardiovascular disease OR cardiovascular diseases OR blood pressure OR hypertension OR blood lipid OR blood lipids OR blood lipid* OR hyperlipidemia OR hyperlipidaemia OR dyslipidemia OR dyslipidaemia OR cholesterol metabolism OR hypercholesterolemia OR osteoporosis OR bone mineral

density OR dual energy x-ray absorptiometry OR malnutrition OR undernutrition OR Nutritional Deficiency OR Nutritional Deficiencies OR ideal body weight OR body image OR eating disorder OR eating disorders OR eating disorder* OR disordered eating OR fussy eating OR food refusal OR quality of life OR QoL

4. For Cancer the following MeSH headings and text words were used:

cancer OR oncology OR oncolog* OR neoplasms OR neoplas* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR cancer* OR malignan* OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo* OR bone marrow transplantation OR bone marrow transplant* OR leukemia OR leukaemia OR lymphoma

5. For RCTs and CCTs the following MeSH headings and text words were used:

(randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) AND (humans[mh])

Final search 1 and 2 and 3 and 4 and 5

[pt = publication type; tiab = title, abstract; sh = subheading; mh = MeSH term; * = zero to many characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

APPENDIX F – SEARCH STRATEGY FOR EMBASE (OVID)

1. For **Popuation** the following Emtree terms and text words were used:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant\$ or newborn\$ or (new adj born\$) or baby or baby\$ or babies or neonate\$ or perinat\$ or postnat\$).mp.
6. (child\$ or (school adj child\$) or schoolchild\$ or (school adj age\$) or schoolage\$ or (pre adj school\$) or preschool\$).mp.
7. (kid or kids or toddler\$ or adoles\$ or teen\$ or boy\$ or girl\$).mp.
8. (minors\$ or (under adj ag\$) or underage\$ or juvenil\$ or youth\$ or young adult or young adults or young adult\$).mp.
9. (puber\$ or pubescen\$ or prepubescen\$ or prepubert\$).mp.
10. (pediatric\$ or paediatric\$ or peadiatric\$).mp.
11. (school or schools or (high adj school\$) or highschool\$ or (primary adj school\$) or (nursery adj school\$) or (elementary adj school) or (secondary adj school\$) or kindergar\$).mp.
12. or/5-11
13. 4 or 12

AND

1. (survivor or survivors or (long adj term survivor) or (long adj term survivors) or survivo\$).mp.
2. survivor/ or cancer survivor/
3. survivi\$.mp.
4. (post treatment or off treatment).mp.

5. (treatment complet* or treatment termin*).mp.
6. (follow up or followup or follow-up).mp. or exp follow up/
7. or/1-6

2. For Nutrition the following Emtree terms and text words were used:

1. patient education.mp. or exp patient education/
2. (practice guideline or practice guidelines or practice guideline\$).mp.
3. exp practice guideline/
4. (dietary guideline or dietary guidelines or dietary guideline\$).mp.
5. exp DIET/ or diet.mp.
6. (diets or diet\$ or diets\$ or dietetic or dietetics).mp.
7. diet therapy.mp. or exp diet therapy/
8. (health diet or healthy food).mp. or exp health food/
9. exp health behavior/
10. (health promoting behaviour or health promoting behavior).mp.
11. (diet\$ and intervent\$).mp.
12. (diet\$ and advic\$).mp.
13. (diet\$ and counsel\$).mp.
14. (diet\$ and therap\$).mp.
15. (diet\$ and treatment\$).mp.
16. (diet\$ and educat\$).mp.
17. (nutriti\$ and intervent\$).mp.
18. (nutriti\$ and advice\$).mp.
19. (nutriti\$ and counsel\$).mp.
20. (nutriti\$ and therap\$).mp.
21. (nutriti\$ and treatment\$).mp.
22. (nutriti\$ and educat\$).mp.

23. (nutriti\$ and support).mp.

24. supportive therapy.mp.

25. or/1-24

3. For Outcome the following Emtree terms and text words were used:

1. (food or foods or food* or foods* or food intake).mp.

2. exp FOOD INTAKE/ or exp FOOD/

3. eating.mp. or exp EATING/

4. ingestion.mp. or exp INGESTION/

5. exp NUTRITION/

6. (nutrition or nutrition\$).mp.

7. (health\$ and diet\$).mp.

8. (health\$ and food\$).mp.

9. (energy intake or carbohydrate intake or caloric intake).mp. or exp caloric intake/

10. (kilojoule or kilojoules or calorie or calori\$ or caloric restriction).mp.

11. vitamin/

12. (vitamin or vitamins or vitamin\$).mp.

13. exp MINERAL/

14. (minerals or minerals\$ or mineral or mineral\$).mp.

15. exp trace element/

16. (micro-nutrient or micro-nutrients).mp.

17. exp MACRONUTRIENT/

18. (macro-nutrient or macro-nutrients or nutrient or nutrients).mp.

19. (calcium or 7440-70-2).mp.

20. (folate or folic acid or 59-30-3).mp.

21. (iron or 7439-89-6 or ferric or ferrous).mp.

22. protein/

23. (protein or proteins).mp.
24. exp low fat diet/
25. (fat reduced or dietary fat restriction or low fat or fat intake).mp.
26. (low calorie or low energy or reduced energy or calorie controlled).mp.
27. (fatty foods or high fat).mp.
28. (fruit or fruits or vegetable or vegetables).mp.
29. exp dietary intake/ or dietary composition.mpp.
30. exp OBESITY/
31. (obesity or obese).mp.
32. adiposity.mpp.
33. body weight.mpp. or exp body weight/
34. overweight.mpp.
35. exp body mass/
36. (body mass index or BMI or body mass).mp.
37. body fat distribution.mpp. or exp body fat distribution/
38. bioelectrical impedance analysis.mpp.
39. body composition.mpp. or exp body composition/
40. exp health behavior/
41. (health behavior or health behaviors or health behaviour or health behaviours or health behaviour\$ or health behaviour\$).mp.
42. health/
43. (health knowledge or health attitude\$).mp.
44. health promotion.mpp. or exp health promotion/
45. exp behavior change/
46. (behaviour change or behavior change or behaviour change\$ or behavior change\$ or health behaviour change or health behavior change or health behaviour change\$ or health behavior change\$).mp.

47. exp lifestyle/
48. (life style or life style\$ or lifestyle or lifestyle\$).mp.
49. (weight gain or weight gains or weight gain\$).mp.
50. exp weight gain/
51. exp weight reduction/
52. (weight loss or weight change or weight changes or weight change\$).mp.
53. exp OVERNUTRITION/
54. exp HYPERPHAGIA/
55. (overnutrition or overeating or hyperphagia).mp.
56. Metabolic syndrome.mp. or metabolic syntrome X/
57. Waist hip ratio.mp. or exp waist hip ratio/
58. Waist height ratio.mp.
59. exp skinfold thickness/
60. (Skinfold thickness or Skinfold thicknesses or Skinfold thickness\$).mp.
61. DEXA.mp. or exp dual energy X ray absorptiometry/
62. (Diabetes or type 2 diabetes).mp. or exp diabetes mellitus/
63. glucose metabolism.mp. or exp glucose metabolism/
64. insulin metabolism.mp. or exp insulin metabolism/
65. exp hyperinsulinemia/ or (hyperinsulinemia or hyperinsulinaemia).mp.
66. exp CARDIOMYOPATHY/ or cardiomyopathy.mp.
67. myocardial Infarction.mp. or exp heart infarction/
68. fat metabolism.mp. or exp lipid metabolism/
69. exp cardiovascular risk/
70. (cardiovascular risk factor or cardiovascular risk factors or cardiovascular risk factor\$).mp.
71. exp cardiovascular disease/ or (cardiovascular disease or cardiovascular diseases).mp.
72. blood pressure.mp. or exp blood pressure/

73. exp hypertension/ or hypertension.mp.
74. exp lipid blood level/
75. (blood lipid or blood lipids or blood lipid\$).mp.
76. cholesterol metabolism.mp. or exp cholesterol metabolism/
77. exp hypercholesterolemia/ or hypercholesterolemia.mp.
78. exp hyperlipidemia/ or (hyperlipidemia or hyperlipidaemia).mp.
79. exp dyslipidemia/ or (dyslipidemia or dyslipidaemia).mp.
80. osteoporosis/co, dt, rt, si, th [Complication, Drug Therapy, Radiotherapy, Side Effect, Therapy]
81. Osteoporosis.mp.
82. bone mineral density.mp. or exp bone density/
83. malnutrition.mp. or exp MALNUTRITION/
84. undernutrition.mp.
85. exp nutritional deficiency/
86. (Nutritional Deficiency or Nutritional Deficiencies).mp.
87. ideal body weight.mp. or exp body weight/
88. body image.mp. or exp body image/
89. exp eating disorder/
90. (eating disorder or eating disorders or eating disorder\$ or disordered eating or fussy eating).mp.
91. exp food refusal/ or food refusal.mp.
92. exp "quality of life"/ or (quality of life or QoL).mp.
93. or/1-92

4. For **Cancer** the following Emtree terms and text words were used:

1. (cancer or cancers or cancer\$).mp.
2. (oncology or oncolog\$).mp. or exp oncology/

3. (neoplasm or neoplasms or neoplasm\$).mp. or exp neoplasm/
4. (carcinoma or carcinom\$).mp. or exp carcinoma/
5. (tumor or tumour or tumor\$ or tumour\$ or tumors or tumours).mp. or exp tumor/
6. (malignan\$ or malignant).mp.
7. (hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo\$).mp. or exp hematologic malignancy/
8. (leukemia or leukaemia).mp. or exp LEUKEMIA/
9. lymphoma.mp. or exp LYMPHOMA/
10. or/1-9

5. For RCTs and CCTs the following Emtree terms and text words were used:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. Human/
11. 9 and 10

Final search 1 AND 2 AND 3 AND 4 AND 5

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title or abstract; / = Emtree term; \$= zero to many characters; co = complication; dt = drug therapy; rt =

radiotherapy; si = side effect; th = therapy; RCT = randomized controlled trial; CCT = controlled clinical trial]

APPENDIX G – ETHICS APPROVAL LETTER FOR CHAPTER 6

**SOUTH EASTERN SYDNEY
ILLAWARRA**

NSW HEALTH

HUMAN RESEARCH ETHICS COMMITTEE – Northern Hospital Network

Room G71, East Wing
Edmund Blacket Bldg
Prince of Wales Hospital
Cnr High & Avoca Streets
RANDWICK NSW 2031
Tel: (02) 9382 3587
Fax: (02) 9382 2813

14 December 2010

Ms Jennifer Cohen
Department of Nutrition and Dietetics
Sydney Children Hospital
High St
RANDWICK NSW 2031

Dear Ms Cohen

HREC ref no: 10/156

Project title: Patient, parent and healthcare worker attitudes towards enteral nutrition in a paediatric oncology setting

Thank you for submitting the above application for ethical and scientific review. The application was first considered by the Human Research Ethics Committee (HREC) at a meeting on 26 October 2010 at which further information was requested.

The Executive Committee on 2 December 2010 reviewed your response and provided feedback, delegating authority to approve the application to the Executive Officer upon receipt of a satisfactory response. The requested information and modifications were received with your correspondence dated 14 December 2010.

I am pleased to advise that ethical approval has been granted for this project to be conducted at Sydney Children's Hospital.

The following documentation has been approved for this study:

- NEAF, locked code AU/1/4227010
- Study Protocol, version 1, dated 31 August 2010
- Participant Information Sheet and Consent Form – Healthcare Workers, Version 3, dated 12 November 2010
- Participant Information Sheet and Consent Form – Parent for Child, Version 3, dated 12 November 2010
- Participant Information Sheet and Consent Form – Parent for Self, Version 3, dated 12 November 2010
- Participant Information Sheet and Assent Form – Child/Young Person, Version 5, dated 14 December 2010
- Invitation Letter - Adolescent, Version dated 13 December 2010
- Invitation Letter – Parent/Carer/Healthcare Worker, Version dated 13 December 2010
- Opt-in card, Version 1, dated 17 November 2010

South Eastern Sydney and Illawarra Area Health Service
Locked Mail Bag 8808 South Coast Mail Centre NSW 2521
Level 4 Lawson House Wollongong Hospital
Tel (02) 4253 4888 Fax (02) 4253 4878

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- Interview Discussion Guide – Patient, Version 2, dated 29 September 2010
- Interview Discussion Guide – Parent, Version 2, dated 29 September 2010
- Interview Discussion Guide – Healthcare Worker, Version 2, dated 29 September 2010

Conditions of approval

1. This approval is valid for 5 years from the date of this letter.
2. Annual reports must be provided on the anniversary of approval.
3. A final report must be provided at the completion of the project.
4. Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the Committee.
5. The Principal Investigator will immediately report matters which might warrant review of ethical approval, including unforeseen events which might affect the ethical acceptability of the project and any complaints made by study participants.

Optional It is the responsibility of the sponsor or the principal (or co-ordinating) investigator of the project to register this study on a publicly available online registry (eg Australian New Zealand Clinical Trials Registry www.anzctr.org.au).

For NSW Public Health sites only: You are reminded that this letter constitutes ethical approval only. You must not commence this research project until you have submitted your Site Specific Assessment (SSA) to the Research Governance Officer of the appropriate institution and have received a letter of authorisation from the General Manager or Chief Executive of that institution.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: http://www.sesiahs.health.nsw.gov.au/Research_Support/NHN/.

Please quote **HREC ref no 10/156** in all correspondence.

We wish you every success in your research.

Yours sincerely

Deborah Adrian
Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

APPENDIX H – ETHICS APPROVAL LETTER FOR CHAPTER 8

the
children's
hospital at Westmead

Research and Development

Karen Steinhoff

KarenS10@chw.edu.au

Phone: (02) 9845 3017

Facsimile: (02) 9845 1317

23 June 2011

Ms Jennifer Cohen
Nutrition & Dietetics

Dear Ms Cohen,

HREC reference number: 11/CHW/24
You must quote this number for all future correspondence

Project title: Assessment of taste and smell function in long-term survivors of childhood cancer

NSW Sites listed: Sydney Children's Hospital
The Children's Hospital at Westmead

Thank you for submitting the above project for single ethical and scientific review. This project was first considered by The Children's Hospital at Westmead's lead Human Research Ethics Committee (HREC) at its meeting held on 1 April 2011. This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review.

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the HREC Committee has granted ethical approval of this research project.

Document	Version	Date
NEAF Application AU/1/D288019	1	28 February 2011
Protocol	2	11 May 2011
Food Preference Questionnaire	-	-
Participant Information Sheet	2	11 May 2011
Parent Information Sheet	2	11 May 2011
Child Participant Information Sheet	2	11 May 2011
Consent Form: Participant	2	11 May 2011
Consent Form: Parent	2	11 May 2011
Assent Form	2	11 May 2011

Please note the following conditions of approval:

1. The co-ordinating investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
 - Unforeseen events that might affect continued ethical acceptability of the project.
2. Proposed changes to the research protocol, conduct of the research, or length of HREC approval, will be provided to the HREC for review in the specified format.
3. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
4. The co-ordinating investigator will provide an annual report to the HREC and at completion of the study. The annual report form is available on the Hospital's intranet and internet or from the Secretary.
5. Your approval is valid for 5 years from the date of the final approval letter. If your project extends beyond five years – at the 5 year anniversary you are required to resubmit your protocol, according to the latest guidelines, seeking the renewal of your previous approval. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the Ethics Committee will be required.

Should you have any queries about the HREC's consideration of your project please contact Ms Karen Steinhoff, Secretary of the Ethics Committee on 9845 3017.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully,

Ms Eleanor Thackray
Secretary, Human Research Ethics Committee

APPENDIX I – FOOD LIKING QUESTIONNAIRE

FOOD PREFERENCE QUESTIONNAIRE

Please indicate how much you like each food by ticking in the appropriate box

IF YOU HAVE NEVER TRIED A FOOD, TICK THE 1ST BOX ONLY

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Beef	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Beefburger, hamburger	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lamb	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pork	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chicken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turkey	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Veal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ham	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sausages / Frankfurts	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Liver	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Liver sausage /Liverwurst	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bacon	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mortadella / Devon / Salami	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fish: fried in batter or breadcrumbs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Fish: plain, white (Snapper, Bream, Flounder)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High fat fish (Mullet, Gemfish, Herring)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tuna / Salmon - tinned	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Baked beans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lentils, chickpeas etc	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tofu	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soya meat eg Nutolene,	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TVP (textured vegetable protein)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vegeburger, Vegesausage eg Sanitarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nuts, eg peanuts, nut dishes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eggs: boiled, poached	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eggs: scrambled	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eggs: fried	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lasagne	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Spaghetti Bolognaise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Meat pies / Party Pies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pizza	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Quiche	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sausage rolls	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shepherd's pie	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bread, Bread Rolls	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lavash / Lebanese bread / Pitta bread	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Saos/ Water crackers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ryvita / Vita Weats/ Salada etc	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Savoury snacks eg Ritz / Jatz/ Shapes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cheese (processed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cheese (hard), eg cheddar	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cheese (soft), eg cottage cheese, Ricotta	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cheese: (cream) eg Philadelphia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Cheese (soft): eg Brie, camembert	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bran cereals: e.g. All Bran	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muesli:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Porridge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rice or corn cereal, eg Cornflakes, Rice Bubbles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sugared cereal, eg Frosties, Coco Pops, Froot Loops	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wheat cereal, eg Weetbix, Shredded Wheat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Potatoes: boiled, mashed or jacket	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Potatoes: chips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Potatoes: roast, fried	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Broccoli	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cabbage, Bok Choy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Carrots	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cauliflower	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Egg Plant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pumpkin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Green beans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Leeks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Zucchini	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mushrooms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Onions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Parsnips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peas	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Salad greens, eg lettuce	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Capsicum	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tomatoes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Brussel Sprouts	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cucumber	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Olives	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Celery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spinach	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Yams	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Pumpkin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sweetcorn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Avocado	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Apricots	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Apples	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bananas	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oranges	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mandarins	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grapes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Melon – Honeydew / Cantaloupe Watermelon	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peaches, Nectarines	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pears	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plums	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kiwi Fruit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dried fruit eg Sultana, Prune, Apricot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cherrys	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Strawberries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mango	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pineapple	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tinned fruit eg two fruits, fruit salad	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soup: vegetable or meat-based	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Milk (skimmed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Milk (semi-skimmed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Milk (full fat)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soft drinks eg Coca Cola, Fanta, Lemonade	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fruit juice:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cordial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Butter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Margarine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cream	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Biscuits: plain, eg Morning Coffee, Milk Arrowroot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Biscuits sweet eg cream biscuits, Monte Carlo,	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Biscuits: chocolate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cakes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pavlova, Cheese cake	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buns/pastries, eg scones, Danish pastries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fruit pie / tarts / crumbles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sponge pudding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ice cream	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ice blocks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Custard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blancmange	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dairy desserts, eg mousse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Yogurt, Fruche	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Doughnuts , Krispy Creams	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Packet chips / Twisties / Burger Rings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jam / Honey	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never tried it	I hate it	I don't like it	It's OK	I quite like it	I love it
Chocolate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lollies eg boiled / jelly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lollies eg mints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lollies: toffee, fudge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sauces: BBQ, Tomato, Soy, HP, Teryaki etc	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sauces: Salad Dressing, Mayonnaise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sauces: warm, savoury eg gravy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pasta	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peanut Butter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vegemite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dried peas, beans or lentils	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Baked beans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tinned spaghetti	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you very much for helping us with our research.

APPENDIX J – THE FUNCTIONAL ASSESSMENT OF ANOREXIA/CACHEXIA TREATMENT QOL SCALE (FAACT)

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
O6	I have a good appetite.....	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight.....	0	1	2	3	4
ACT3	Most food tastes unpleasant to me.....	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat.....	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT1 0	When I eat, I seem to get full quickly	0	1	2	3	4
ACT1 1	I have pain in my stomach area	0	1	2	3	4
ACT1 3	My general health is improving.....	0	1	2	3	4