Use of Sensory Nutrition to Optimize and Evaluate Food Products for Patients with Cancer

by

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Abstract

Inadequate nutrition is prevalent among patients with cancer and has a detrimental impact on prognosis. However, development of taste appealing foods targeting specific nutritional requirements of this population has been overlooked and few commercially available products can be found for that purpose. Snacks were chosen as vehicles for fortification given their potential to increase caloric and nutrient intake in a small portion size. The aim of this research was to investigate different aspects impacting the acceptance of nutrient-rich snacks for patients with cancer. A commercially available oat-based beverage was proposed as a nutrient-rich snack and its sensory acceptance and perception was evaluated before and after fortification. Additionally, a survey was conducted among patients to identify snack foods preferred as potential carriers for fortification and the influence of experienced symptoms on those preferences.

Overall liking and just-about-right (JAR) evaluation of three flavors at two different temperatures of the oat-based beverage among patients with cancer (n=92) and healthy participants (n=136) was assessed. Products were liked and no significant differences in liking were observed among them or between both consumer populations. Results of JAR evaluations highlighted some differences in perception between patients with cancer and healthy participants, and high perceived sweetness significantly decreased liking of three of the products. A chocolate flavor oat-based beverage was fortified with protein (whey, faba bean) and fish oil, and overall liking and attribute perception (JAR) of two formulations were evaluated compared to the unfortified product by 60 healthy participants. Differences in sweetness and thickness perception were found among the products but overall liking of one of the formulations was not significantly different compared to the unfortified product. Additionally, perception of oats

through a free-word association task revealed that patients' perceptions of oat food products were related to oat-based food products and health benefits. Sensory acceptance and perceived health benefits of oats confirmed potential for their use in fortified and unfortified products for patients with cancer.

A survey among 150 patients with cancer identified soup, yogurt, cheese, fruit juice, egg products and protein bars as suitable fortified snacks. Nutritious, flavorful, convenient, ready to eat, easy to chew and easy to swallow were desired characteristics of fortified snacks and vitamins, minerals and protein were nutrients of interest among the respondents. Three clusters of patients were identified according to symptom presence differing in their desired characteristics of fortified snacks and satisfaction with food-related life. Patients in the High symptom presence cluster were more likely to agree with fortification of ice cream bar and patients in High and Moderate symptom clusters were more likely to have reduced food intake and higher consumption of oral nutritional supplements.

This study contributes to gaps in knowledge around food preferences among patients with cancer, particularly related to snacks and fortified products. This research can provide insight to guide the development of fortified snacks targeted to the nutritional, sensory and consumption needs of patients with cancer.

Preface

This doctoral thesis is an original work by Blanca Enriquez Fernandez and consists of seven chapters. A version of **Chapter 2** has been published as "Sensory preferences of supplemented food products among cancer patients: a systematic review", Enriquez-Fernandez B., Nejatinamini S., Campbell S., Mazurak V. and Wismer W., Supportive Care in Cancer (2018). Sara Nejatinamini and I conducted the articles selection and critical review and wrote the manuscript draft. Sandra Campbell helped in the conduction of the literature search and edited the manuscript. Drs. Mazurak and Wismer were part of the conception of the paper and edited the manuscript. All authors revised and gave final approval of the manuscript.

Chapter 3 is presented in paper format. This paper has been published online as "Patient-reported taste change assessment questionnaires used in the oncology setting: a narrative review", Enriquez-Fernandez B., Martinez-Michel L., Thorlakson J., Wismer W., European Journal of Oncology Nursing. Lorelei Martinez-Michel conducted the initial paper selection and manuscript draft until 2013. I reassessed the papers for inclusion and rewrote the manuscript. Jessica Thorlakson helped with the literature search. The paper concept was by Dr. Wismer who also provided input on selected papers and edition of the manuscript. All authors revised and gave final approval of the manuscript.

A manuscript version of **Chapter 4** will be submitted to International Journal of Food Sciences and Nutrition, authors: Enriquez-Fernandez B, Klassen, P., Chen, L., Mazurak V., Wismer W. I collaborated with the concept design and was responsible of the participants recruitment and data collection of all studies and wrote the manuscript draft. Pamela Klassen contributed in the free-word association analysis and categorization and in the edition of the manuscript. Dr. Lingyun Chen contributed to secure funding and as the contact with the company commercializing the oat-based beverages, and with the edition of the manuscript. Dr. Mazurak collaborated with the study and the edition of the manuscript. The paper concept was by Dr. Wismer who also edited the manuscript. The initial evaluation of oat-based beverages in the clinical setting received ethics approval from the Health Research Ethics Board of Alberta (HREBA) Cancer Committee, Ethics ID HREBA.CC-17-0026 on July 2017. The sensory evaluation of the fortified products received research ethics approval from the University of Alberta Research Ethics Board, Project name "Sensory assessment of nutrient enhanced oat &

milk beverages", No. Pro00075398, November 2017. The survey study including the free-word association task for oats received ethics approval from the HREBA Cancer Committee, Ethics ID HREBA.CC-19-0210 on August 2019. A manuscript version of

Chapter 5 will be submitted to Nutrition and Cancer, authors: Enriquez-Fernandez B., Klassen P., Gosh S., Chen, L., Mazurak V., Wismer W. Dr. Wismer and I came up with the study concept and design. I completed patient recruitment and data collection (with help of two student volunteers), data analysis and interpretation of the results and writing of the manuscript. Pamela Klassen, Dr. Wismer and I conducted the categorization of data from the free-word association tasks. Sunita Gosh helped with data statistical analysis. Dr. Lingyun Chen contributed to secure funding and with the edition of the manuscript. Dr. Wismer and Dr. Mazurak provided input and edited the manuscript. The study received ethics approval from the Health Research Ethics Board of Alberta (HREBA) Cancer Committee, Ethics ID HREBA.CC-19-0210 on August 2019.

Chapter 6 is a study protocol designed by Dr. Wismer and I. I wrote the manuscript draft which was edited by Dr. Wismer. The study received ethics approval from the Health Research Ethics Board of Alberta (HREBA) Cancer Committee, Ethics ID HREBA.CC-18-0061 on August 2018 but the study could not be performed as the funder withdrew financial support.

I would like to dedicate this work to my mom, Teresa Fernández, who inspired me to conduct this research.

Over life she gave me love, spirit and direction.

In her illness, she taught me about courage, hope and the value of living in the moment.

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List of abbreviations

33-TSQ	Taste and Smell Questionnaire
AHS	Alberta Health Services
AHSP	Appetite, Hunger and Sensory Perception
ANOVA	Analysis of Variance
CiTAS	Chemotherapy Induced Taste Alteration Scale
CTCAE	Common Terminology Criteria for Adverse Events
DHA	Docohexaenoic acid
DQ	Dysgeusia questionnaire
EORTC	European Organization for Research and Treatment of Cancer
EPA	Eicosapentaenoic acid
ESPEN	European Society for Clinical Nutrition and Metabolism
HNC	Head and neck cancer
HNSC	Head and Neck Symptom Checklist
HPFO	High protein fish oil
HREBA	Health Research Ethics Board of Alberta
JAR	Just-about-right
LPFO	Low protein fish oil
NIS	Nutrition impact symptoms
ONS	Oral Nutritional Supplements
PG-SGA	Patient Generated Subjective Global Assessment
QASCC	Questionnaire for assessment of subjective chemosensory complaints

QOL	Quality of life
REDCap	Research electronic data capture
SFP	Supplemented food products
SWFL	Satisfaction with food-related life
TC	Taste changes
TCQ	Taste Changes Questionnaire
TCS	Taste Change Survey
TSA	Taste and smell alterations
TSS	Taste and Smell Survey
TSSCQ	Taste and Smell Subjective Changes Questionnaire
UHT	Ultra high temperature
UW-QOL	University of Washington Quality of life

CHAPTER 1: Introduction and Research Plan

1.1.Introduction

According to estimates from the Canadian Cancer Society, 225 800 new cancer cases will be diagnosed in Canada in 2020 (Brenner et al. 2020). Adequate dietary intake in terms of quantity and diversity of nutrients can contribute to improved patient outcomes including quality of life (QOL), treatment response and survival (Gellrich et al. 2015; Mantzorou et al. 2017; Canadian Cancer Society 2020). However, following cancer diagnosis and during and after oncology treatment, patients' relationship with food changes. The presence of symptoms, changes in food preferences, development of food aversions and the interest to avoid or consume only certain foods or nutrients, among other factors, can contribute to the changed relationship (Ravasco 2005; Danhauer et al. 2009; Wismer 2018). It is then difficult for patients with cancer to maintain a diverse and adequate dietary intake. Patients rely on food and nutrient fortified products such as liquid oral nutritional supplements (ONS) to improve their intake.

Despite the high incidence of cancer, the high prevalence of malnutrition among these patients and the detrimental effect of inadequate nutrition on patient outcomes (Aaldriks et al. 2013; Gellrich et al. 2015; Maasberg et al. 2017; Mantzorou et al. 2017), few commercially available products can be found to promote and increase nutrient intake among people with cancer (Tueros & Uriarte 2018). The development of food products targeting their specific nutritional requirements has been overlooked in the development of supplemented food products. These products must accommodate patients' nutritional needs and consider patient sensory preferences (flavor, texture, appearance and presentation), the presence of taste and/or smell alterations, and other symptoms that may interfere with eating. As in any food product development endeavor, the target consumer or final end-user must be considered and incorporated into different stages of the development process.

Sections 1.1.1 to 1.1.3 of this literature review describe why it is necessary to develop and evaluate nutrient dense food products for patients with cancer (prevalence and consequences of malnutrition, changes in food behavior and specific symptoms impacting those changes and their nutritional requirements). Next, current strategies to increase food and nutritional intake, the

rationale for developing fortified snacks, and the reasons to include patients at different stages of product development are presented in sections 1.1.4 to 1.1.6.

1.1.1. Malnutrition and weight loss in patients with cancer

Malnutrition is common among people with cancer (Arends et al. 2017), can be affected by cancer type, treatment and timepoint within the cancer trajectory (Ryan et al. 2016) and can occur among people with different body mass indices, including overweight and obese patients (Martin et al. 2020). Inadequate nutritional intake in the oncology setting has been associated with decreased QOL, lower performance status, increased toxicities, reduced response to treatment and decreased survival (Aaldriks et al. 2013; Gellrich et al. 2015; Maasberg et al. 2017; Mantzorou et al. 2017). Cancer-associated malnutrition has a multifactorial origin including metabolic derangements from the tumor-host interaction and food intake reduction (Arends et al. 2016). Reduced food intake has been associated with reduced appetite, pain, psychological distress, anxiety, depression and fatigue, and other nutrition impact symptoms (NIS) (e.g. taste and smell changes, dysphagia, nausea, vomiting, early satiety, sore mouth, treatment-induced mucositis, difficulty chewing and dry mouth) (Barbera et al. 2010; Omlin et al. 2013; Alsirafy et al. 2016) and to changes in food preferences and the development of food aversions (Kubrak et al. 2010; Sukkar 2012; Bye et al. 2013; Ravasco 2019).

Weight loss during cancer treatment is a result of the complex wasting syndrome derived from mechanisms such as inflammation, insulin resistance, anorexia and increased muscle protein catabolism (Evans et al. 2008). Additionally, the presence of NIS caused by the disease itself or its treatment can represent a barrier to oral nutritional intake and contribute, among other factors, to cancer related malnutrition (Omlin et al. 2013). The presence of NIS and the subsequent decreased dietary intake is also a factor contributing to wasting (Ravasco et al. 2004). Maintaining an appropriate level of nutritional intake is considered important in cancer management because nutritional intake has a direct effect on patient's QOL and can also decrease the presence of malnutrition, reducing complications and improving prognosis (Ravasco et al. 2004).

1.1.2. Sensory nutrition and food behavior

'Sensory nutrition' is a research area that examines how sensations of food influence what a person chooses to eat or drink, and importantly, how these choices motivated by sensory perceptions affect health (Reed et al. 2019). In people with cancer, this area needs further research to provide a deeper understanding of the drivers of food choice and food behavior in this population.

Beliefs, attitudes and perceptions about food, and practices related to food (choice, handling, preparation, cooking and consumption), including nutrition and food safety knowledge, are all encompassed in 'food behavior' (Drareni et al. 2019). Food intake is regulated by a complex neurohormonal mechanism mainly within the hypothalamus. Food behavior is also strongly influenced by sensory properties of food (e.g. taste, smell, texture, palatability, appearance) and chemosensory signals (Sørensen et al. 2003; Drareni et al. 2019). In addition to the changes in oral perception, taste receptors expressed in the gastrointestinal tract might be affected by similar mechanisms as oral taste cells during chemotherapy treatment (Nolden & Reed 2019). Thus, changes in food behavior can be a result of taste alterations combined with gastrointestinal alterations (Nolden & Reed 2019)

Patients receiving oncological treatment tend to modify their food behavior and dietary intake to avoid particular foods, or to increase the consumption of nutrient dense foods (Danhauer et al. 2009). For example, patients with head and neck cancer (HNC) commonly eat foods characterized as easy to eat or with low potential to worsen symptoms, and avoid foods with dry texture, even at 4-10 months post-treatment (Álvarez-Camacho et al. 2016). When assessing energy, macronutrient and intake by food groups of 117 patients with breast cancer before and during chemotherapy compared to 88 healthy women, people with cancer reported lower total energy, fat and protein intake during chemotherapy treatment (de Vries et al. 2017). In particular, lower intake of pastries, cheese, legumes and meat products was observed among patients with cancer compared to healthy participants, and a decline in hunger and appetite and increased self-reported taste perception and symptoms like dry mouth, lack of energy, difficulty chewing and nausea, were associated with lower energy intakes (de Vries et al. 2017).

A recent study compared objective taste perception (detection and recognition thresholds for four basic tastes) and preferences for typical Korean dishes between patients with breast cancer

and healthy controls, before, during and after chemotherapy treatment (Kim et al. 2020). Significant differences in preference were observed for porridges, ground grains, breads, tuber crops, fish, eggs, beans, vegetables, dairy products, and soup/stew. In some cases, preference for the meal was higher among patients compared to controls, while for other dishes, it was the opposite. Overall, at baseline, patients preferred mild, soft and less greasy dishes and over treatment, meals with mild or soft texture and/or flavor were preferred (Kim et al. 2020).

The development of food aversions has also been documented in these patients; coffee, red meat, tea and chocolate are the most commonly reported food aversions during chemotherapy (Boltong & Keast 2012). The consumption of novel foods during chemotherapy treatment can also trigger food aversions (Schwartz et al. 1996). These developed or learned food aversions can limit food choices (Bernstein 1985).

1.1.2.1.Nutrition Impact Symptoms

The development of any food product focused on increasing dietary intake of oncology patients must consider the symptoms experienced and promote the consumption of products that will not worsen symptoms and create an enjoyable eating experience. A greater number and severity of NIS has been correlated with low nutritional status (Barbosa-Silva & Barros 2006), reduced QOL (Tong et al. 2009), weight loss and lower functional capacity (assessed through the patient-generated subjective global assessment) (Kubrak et al. 2010). The majority of NIS identified through the Head and Neck Symptom Checklist (HNSC©) have also been associated with reduced dietary intake and weight loss (Kubrak et al. 2013; Farhangfar et al. 2014).

Number, severity and specific NIS experienced by patients will depend on the tumor site and treatment received. For example, patients with HNC are particularly vulnerable to oral symptoms such as dysphagia, dry mouth, mouth sores, difficulty chewing and swallowing and taste changes (Kubrak et al. 2013). Among people with advanced cancer, NIS can also be very common, with taste and smell alterations (TSA), constipation, pain and dysphagia being the most commonly reported symptoms in a retrospective study (Omlin et al. 2013).

Nutrition impact symptoms can also impact food choices by creating eating limitations, disrupting the sense of taste and limiting oral intake (Bressan et al. 2017). Results of 255

questionnaires completed by a diverse population of patients with cancer (mainly breast, gastrointestinal and head and neck) indicated that fatigue, nausea, dry mouth and odor sensitivity were the main side effects and treatment-related side-effects that affected eating and drinking in over 80% of the patients, principally inducing a reduced appetite or desire to eat, food aversions or satiety (Guerdoux-Ninot et al. 2016). Similarly, reduced appetite was reported by 6-69% of patients under chemotherapy treatment (Boltong & Keast 2012). Early satiety, the desire to eat associated with a subsequent inability to eat except for small amounts due to a sense of fullness (Woodward 2010) is a commonly reported symptom and has an impact on low adherence with consumption of ONS (Fearon et al. 2003; van der Meij et al. 2012). Diarrhea and constipation can also impact eating, especially when abdominal distention and pain prevent dietary intake (Capra et al. 2001). Nausea and vomiting, common symptoms in some chemotherapy treatments, can also contribute to the development of food aversions and reduced food choices (Capra et al. 2001).

1.1.2.2.Taste and smell alterations

Taste and/or smell alterations are one of the more frequent patient-reported NIS among people with cancer (Omlin et al. 2013). Prevalence of taste alterations can range between 12-84% (Gamper et al. 2012; Nolden & Reed 2019) and smell alterations between 5 and 60% (Gamper et al. 2012). This prevalence can be influenced by clinical factors such as tumor type and treatment, and by the study design and method used to assess TSA (de Vries et al. 2018; Drareni et al. 2019; Nolden & Reed 2019). Taste and smell alterations are a unique experience for each patient and can include increased, decreased or mixed intensity sensations (Brisbois et al. 2011; Drareni et al. 2019) or the presence of bad taste in the mouth (Hutton et al. 2007), and can vary over time for the same patient (Johnson 2001).

The exact mechanisms for TSA in patients with cancer are not completely understood (Cohen et al. 2016). Different mechanisms have been suggested as the cause of changes in taste perception in this population. As chemotherapy treatment targets rapidly dividing cells including taste and olfactory cells, TSA can be a side effect of this treatment type (Boltong & Keast 2015). Chemotherapy agents can also be secreted in saliva and cause metallic or chemical tastes (Epstein & Barasch 2010). Surgery, such as the resection of portions of the oral and nasal

cavities can also impact taste and/or smell perceptions (Halyard 2009). Due to the effects (direct or indirect) of ionizing radiation, radiotherapy, particularly when applied to the head and neck can also cause TSA and other oral complications including xerostomia and mucositis (Deshpande et al. 2018). Low salivation, a treatment side effect, can reduce the intensity of taste perception by a decreased ability to dissolve food particles which reduces the number of molecules reaching the taste receptors (Epstein et al. 2016). Immunotherapy, bone marrow transplant and therapies that alter hormone levels can also cause TSA or hedonic changes (Boltong & Keast 2015).The acute inflammatory state could also affect taste perception through the action of inflammatory markers on taste buds and at brain levels (Murtaza et al. 2017).

Taste changes have particularly been shown to influence changes in food behavior. Severe taste alterations have been associated with low dietary intake and altered dietary patterns (Drareni et al. 2019; Nolden & Reed 2019; de Vries et al. 2019). However, results must be interpreted cautiously because a small number of studies and different taste changes assessment tools have been used, including objective (threshold assessments) (Nolden & Reed 2019) and subjective evaluations (de Vries et al. 2019). Standardized TSA evaluations are required to confirm any relationship between these perceptions and food behavior in patients with cancer (Drareni et al. 2019). In addition to the effect of taste changes on patients nutritional status, this symptom can also be frustrating and distressing for patients, impacting their QOL (Ravasco 2005)

Taste and smell alterations influence the acceptance of a food product and its repeated consumption (Ravasco 2005). The dietary patterns of patients with advanced cancer have been studied and it was observed that the type of foods consumed were associated with the severity of TSA; patients with mild alterations consumed more meat and potatoes whereas patients with a high burden of TSA consumed mainly liquid foods (e.g. milk, soups) (Hutton et al. 2006). Therefore, when developing products for the oncology population, it is important to consider and if possible, assess the presence of TSA. For instance, product sweetness needs to be carefully evaluated considering that some patients experience higher or lower sweetness perception; also aftertaste should be limited to avoid the perception of “metallic taste” which is a common disturbance reported by patients (Brown et al. 2013).

1.1.3. Nutritional requirements

The specific nutrient requirements of the oncology population are of importance when developing food products targeted for them. ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines for oncology patients include the following intake recommendations (Arends et al. 2016):

- Protein above 1g/kg/day and if possible 1.5g/kg/day.
- Energy similar to healthy subjects, between 25 and 30 kcal/kg/day.
- In patients with advanced cancer undergoing chemotherapy and at risk of weight loss: supplementation with fish oil to improve appetite, food intake, lean mass and weight.
- Micronutrient consumption in amounts approximately equal to the recommended dietary allowances.

However, the evidence for the recommendations is moderate for protein and low for the other nutrients (Arends et al. 2016) and actual requirements might be higher. Energy intake recommendation of 25 kcal/kg/day underestimated total energy expenditure in patients with newly diagnosed colorectal cancer (Purcell et al. 2019) and for patients with HNC, a study showed that meeting ESPEN energy recommendations was not enough to attenuate skeletal muscle loss (McCurdy et al. 2019).

Moreover, oncology patients can fail to meet the recommendations. For example, it has been reported that among patients with advanced cancer, protein intake was below 1.0g/kg in 35% (Prado et al. 2013) and intake can vary between 0.2 and 2.7g/kg for this nutrient (Hutton et al. 2006). For micronutrients, a recent study it was observed that patients with HNC did not meet recommended intakes of micronutrients without consuming fortified products (Nejatinamini et al. 2018). Energy-dense food products fortified with the recommended nutrients could promote their intake.

1.1.3.1.Protein

One of the most important factors affecting prognosis in patients with cancer is muscle wasting, and an adequate protein supply is the foundation to maintain or increase muscle mass (Prado et al. 2020). The optimal protein intake, combined with anabolic stimuli, required to prevent

muscle loss is unknown (Prado et al. 2020) but many patients fail to meet the recommended intake for healthy individuals (0.8 g/kg/day) (Hutton et al. 2006; Prado et al. 2012). Higher protein intake has been suggested as beneficial as an increased red meat consumption was associated with reduced seven-year mortality among patients with stage III colon cancer (Van Blarigan et al. 2018).

Further research is needed to clarify recommended protein intakes and the specific protein type, including the potential beneficial effect of specific amino acids (Ravasco 2019; Prado et al. 2020). Although the specific requirements for protein have yet to be established, food products with high protein could aid in meeting protein consumption recommendations, especially given that red meat, a main source for protein intake is avoided among some oncology patients (Salminen et al. 2004; Velentzis et al. 2011).

1.1.3.2. Fish oil and Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is a polyunsaturated long-chain fatty acid that is a component of fatty fish and their oils. Fish oils have been applied in interventions aiming to prevent muscle or weight loss, reduce inflammation markers, diminish side effects and improve treatment response among people with cancer (Murphy et al. 2011; Arends et al. 2016; Klassen et al. 2020). Not all studies have reported a benefit of fish oil supplementation for cachexia, probably due to differences in adherence, study designs and patient body composition measurements (Prado et al. 2020). Nevertheless, trials have shown a beneficial role of n-3 fatty acids in preventing muscle and weight loss and improvements in chemotherapy response, reduced toxicities and improved performance status among patients undergoing active treatment (Murphy et al. 2012; de Aguiar Pastore Silva et al. 2015; Morland et al. 2016; Klassen et al. 2020). Docosahexaenoic acid (DHA), another polyunsaturated fatty acid has also been studied for the improvement of the tumor response to cytotoxic treatments (Klassen et al. 2020).

Eicosapentaenoic acid is mostly well tolerated with minimal side effects and a number of studies report positive outcomes with EPA supplementation, thus fish oil has been suggested as a practical intervention to stabilize or improve appetite, food intake, muscle mass and body weight in patients with advanced cancer undergoing chemotherapy and at risk of weight loss (Arends et al. 2016). Moreover, studies have found low concentrations of plasma n-3 fatty acids among

patients with cancer compared to healthy people (Zuijdgeest-Van Leeuwen et al. 2002). Thus, its addition to fortified foods for this population could be beneficial.

Specific recommended intake has not been established, best evidence supports doses of 2-2.5 g of EPA + DHA, with recent research studies prescribing daily doses between 608 and 3200mg of combined EPA and DHA (Klassen et al. 2020). Given that the addition of fish oil or EPA into a food might result in fishy taste or aftertaste, acceptance testing of fortified foods containing these n-3 fatty acids is necessary. Moreover, the exact amount and proportions of EPA and DHA can vary among fish oils which will impact the amount of fish oil required to reach a target EPA and DHA content (Calder & Yaqoob 2015).

1.1.4. Current strategies to increase intake

There is no consensus on the best way to treat malnutrition among patients with cancer. However, nutritional interventions aiming to identify, prevent and treat this condition accompanied or not by the use of ONS, have been recommended as part of the multidisciplinary approach (Arends et al. 2016; Arends et al. 2017; Ravasco 2019). Nutritional counselling by a health professional is recommended as the first line of nutrition therapy (Arends et al. 2016) but is unfortunately not widely accessible to all patients at nutritional risk (Ravasco 2019).

1.1.4.1.Oral nutritional supplements

Dietary counselling with or without ONS has been effective to increase body weight and nutritional intake among malnourished patients (Ravasco et al. 2005; Baldwin & Weekes 2011; Baldwin & Weekes 2012). However, the use of ONS has to be considered carefully because it may substitute voluntary dietary intake, causing caloric or nutrient intake to remain the same or even be reduced (Fearon et al. 2003).

Conventional ONS available commercially include formulations “nutritionally complete” that provide macro and micronutrients in the required amounts such that no other nutritional source is required if sufficient quantities of the supplement are consumed (Woodward 2010). The most common ONS are milk-, soy-, yogurt or juice- based liquids available in different flavor varieties (mostly sweet). Ice cream, a nutritious jelly and puddings, have also been evaluated, mostly

developed for patients with HNC (Woodward 2010; Trinidade et al. 2012; Trachootham et al. 2015; Valmorbida et al. 2019).

The success of a product designed to increase nutrient and caloric intake depends on the product's acceptability and long-term adherence with its consumption. Among older adults, those who disliked the product´s taste had the greatest wastage of ONS (Gosney 2003). Consumption of ONS over time can be limited by factors such as:

a) Patient preference to consume food products over ONS (Danhauer et al. 2009; Prado et al. 2012). The tendency to select ONS has been found to be favored by a specific subset of patients whose food choices were clustered with the consumption of other liquid foods (soups, juices) (Hutton et al. 2006; van der Meij et al. 2012). In previous research 70% of patients with advanced cancer did not select available commercial supplements for consumption (Hutton et al. 2006); among patients with advanced lung or colorectal cancer (Prado et al. 2012), only 5% consumed ONS. Similarly, when questioned about their preferred type of snacks, only 30% of oncology patients with diverse tumor types indicated a preference for ONS (Danhauer et al. 2009).
b) Low acceptance of the product´s taste, color, flavor, aftertaste, texture or palatability (Bolton et al. 1992; Rahemtulla et al. 2005; Brown et al. 2013) or development of taste fatigue (Bolton et al. 1990; Ravasco 2005). Supplements offering a variety of flavors are likely to prevent taste fatigue (Ravasco 2005).
c) Presence of NIS such as nausea, vomiting, anorexia and early satiety can impact the acceptability of ONS (van der Meij et al. 2012).
d) Patient perception of the required consumption volume as 'excessive' and a perceived reduced intake of food when consuming the ONS (Hogan et al. 2019).
e) Taste and/or smell alterations. Few studies have focused on the effect of taste changes on the acceptability of ONS and the results are contradictory. Some studies have not found associations between ONS liking or preference and the presence of TSA (Bolton et al. 1990; Bolton et al. 1992; Baldwin & Weekes 2011). On the other hand, in one study specific changes in taste thresholds reflected variations in liking of different ONS (IJpma et al. 2017). Alterations in taste and smell along the chemotherapy treatment trajectory were also shown to affect liking and prevalence of "metallic taste" perceived after tasting ONS (IJpma et al. 2017).

A study reported greater weight loss with ONS consumption compared to food consumption at similar intakes in the absence of nutritional counselling (Giles et al. 2016). The recommendation when using ONS is that their consumption should not substitute traditional food intake, which is preferred and more likely to be maintained in the long term (Ravasco et al. 2005).

1.1.4.2. Fortified foods

When developing products to improve the nutritional status of patients with cancer, key factors contributing to food behavior such as appearance, texture, emotions, and food hedonics must be considered in addition to nutritional requirements (Tueros & Uriarte 2018). Currently, food options available in the market for nutrition support of patients with cancer are mainly limited to ONS. Oral nutritional supplements fail to address the pleasure of eating by not considering possible changes in sensory perception and patients' food preferences, impacting their QOL (Tueros & Uriarte 2018). To my knowledge, there is only one brand commercializing products targeted to aid in the treatment and recovery of patients with cancer (Hormel Vital Cuisine®) (Hormel Health Labs 2020). This brand is currently not available in Canada.

As stated by Arends and others (2016), "the best way to maintain or increase energy and protein intake is with normal food". Food goes beyond nutrition by contributing to the social, cultural and psychological QOL (Bernstein & Munoz 2012). The consumption of food can contribute to patient autonomy, be a significant part of the routine and represents an opportunity to spend time with family or others and thus positively impact patient QOL (Arends et al. 2016; Ravasco 2019). The use of taste appealing nutrient-enhanced or fortified foods with high energy density and/or containing nutrients of interest may represent an alternative to improve nutrient intake among patients with cancer. However, access to palatable and varied food products is limited for these patients (Wismer 2018; Tueros & Uriarte 2018). Innovative food products considering nutritional requirements, the pleasure of eating, sensory preferences, taste and/or smell alterations, capacity to alleviate symptoms and food preferences/aversions in the cancer context are needed (Tueros & Uriarte 2018).

1.1.4.2.1. Fortified foods designed for and evaluated by patients with cancer

Few food products have been developed specifically for people with cancer and the focus has been primarily on HNC patients. An easy to swallow semi-solid food gel was developed and evaluated among HNC patients (Trachootham et al. 2015). Most patients liked the texture and flavor of the product and continuous supplementation with the jelly resulted in improvement in the psychological and physiological aspects of health related QOL (Trachootham et al. 2015). Fortified ice cream formulations have been developed for patients with cancer (Casas et al. 2012; Trinidade et al. 2012; Vieira et al. 2018). Designed to help HNC patients with swallowing and nutritional concerns, a fortified soft ice cream was liked by a majority (77%) of patients, particularly its texture and temperature (Trinidade et al. 2012). High protein ice cream in four different flavors has also been developed for people with cancer undergoing chemotherapy with good acceptability of all flavors. Specific details about demographics and clinical factors such as tumor site and chemotherapy regimen were not disclosed in the latter study (Vieira et al. 2018).

1.1.5. Rationale for the development of fortified snacks for patients with cancer

Several definitions of snacks exist. According to the American Heart Association (St-Onge et al. 2017), a snack may be anything eaten outside the timeframe of main meals or food products that provide less than 15% of daily recommended energy intake. Other considerations to define a snack may be the type of food or eating location (Hess et al. 2016). In the following studies, "snacks" will refer to any food or beverage consumed in between main meals.

Distributing intake into 5-6 eating occasions can help promote food consumption and improve nutritional status among individuals with difficulty tolerating large quantities of food in one sitting. To improve nutritional status, snacks should provide specific nutrients, be highly energy dense and be appealing (Marangoni et al. 2019). In a study evaluating 24-hour dietary recalls from over 2000 older adults, it was observed that those consuming snacks presented with significantly higher energy, protein, carbohydrate and fat intakes, with snacks contributing 22.5% of their daily energy intake (Zizza et al. 2007). In the same way, when older adults and orthopedic patients consumed fortified meals and between meal snacks, 82% achieved their required energy consumption recommendation (Gall et al. 1998). Energy and protein fortification

and supplementations has been recommended as a well-tolerated and cost-effective intervention among older inpatients to improve intake (Mills et al. 2018).

This strategy of offering between meal snacks may also improve the caloric and nutrient intake in people with cancer where low appetite and early satiation can be present. When the pattern of food intake of patients with advanced cancer was characterized (Hutton et al. 2006), meat, desserts, fruit, milk and white bread were the greatest contributors to caloric intake. Moreover, a significant relationship was found between the frequency of eating and total caloric intake, which promoted the use of snacks or smaller meals frequently along the day to achieve higher caloric intakes (Hutton et al. 2006).

Collectively, the evidence described above highlights the opportunity to provide nutritious products in the form of snacks to people with cancer. The American Cancer Society recommends the consumption of easy to prepare protein-rich snacks in between meals throughout the day to meet the caloric needs of patients losing weight (The American Cancer Society editorial content medical team 2019).

1.1.6. Consumer-oriented food product development and use of sensory science

Successful food product development needs to incorporate the final consumer or end user into the product development process. New product development strategies must be consumer driven (O'Sullivan 2016). The development of successful nutrient-enhanced snack products targeted for the oncology population must consider their specific nutrient requirements, symptoms and sensory preferences (Tueros & Uriarte 2018). However, there is a lack of research about the specific format or products that patients would like to consume as snacks.

As most patients with cancer are older adults and some symptoms such as low appetite and changes in taste and smell perception have also been reported in this population, studies with older adults can help guide studies in the oncology population. Song and others (Song et al. 2019) conducted a survey to identify older adults' attitudes towards food products for protein enrichment. Older consumers in the study were most willing to try traditional, healthy and part of their main meals (opposed to snacks) (Song et al. 2019).

Specifically, for people with cancer, a picture-aided questionnaire to study between-meal food desires was completed by 112 hospitalized patients with hematological cancer. Fresh-fruit, ice cream, cheese and mashed potatoes with bacon were the most desired food items (Okkels et al. 2016). A high influence of texture on food desire was observed (Okkels et al. 2016). However, the study was conducted only within a specific cancer population and among inpatients and it was not focused on products to be fortified or nutrient-enhanced.

As evidenced by the information presented, the development of innovative food products for people with cancer is needed. This would address not only patient nutritional requirements, but also sensory preferences and symptoms impacting food intake and behavior, including TSA. Nutrients of interest that can potentially be incorporated into a nutrient-enhanced food product are proteins and EPA. The development and evaluation of these products should incorporate patient evaluation and feedback, preferably from early stages of the development process. Moreover, research to understand patient food preferences and their desired attributes in such products is lacking. Snacks were chosen as a vehicle for a nutrient-enhanced food product given their potential to increase caloric and nutrient intake and their small portion size to accommodate symptoms like early satiety and anorexia.

Research Plan

The overall thesis research objective was to study nutrient-rich snacks as an option to promote nutrient intake among patients with cancer. As shown in Figure 1.1, through these studies (chapters), different factors that can impact the acceptance of nutrient-enhanced snacks were considered.

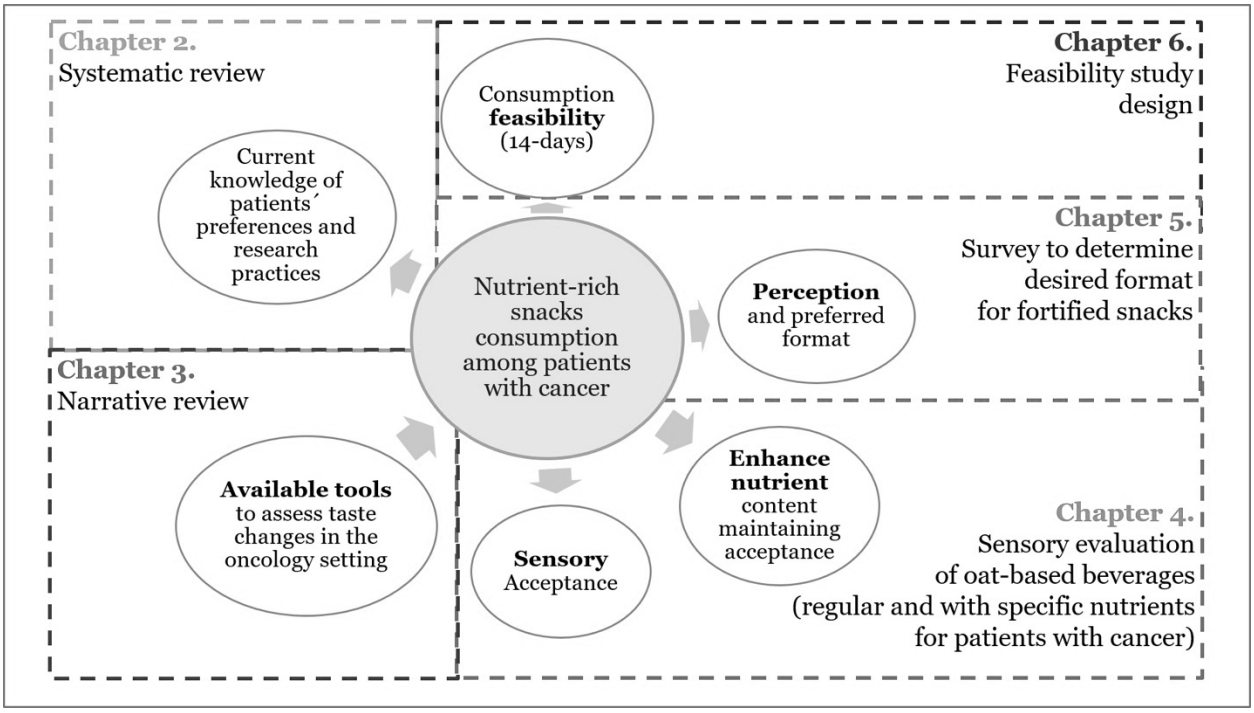

Figure 1.1. Overview of thesis chapters and research objectives.

The specific thesis objectives and sub-objectives with their rationale are described as follows:

Objective 1 (Chapter 2): Identify sensory preferences for fortified foods and/or ONS among patients with cancer through a systematic review.

Sub-objective 1.1: Evaluate and compare the appropriateness of sensory evaluation methods used in published studies.

Sub-objective 1.2: Identify the types of products that have been developed and evaluated.

Rationale: Some studies evaluating fortified food products by patients with cancer have been published, mostly for ONS. However, the results, products evaluated, and sensory evaluation methods used have not been previously summarized and analyzed. This exploratory review aimed to do that summary and serve as a basis by identifying what has been published in this research area, the types of products assessed and what could be improved.

Objective 2 (Chapter 3): Describe and analyze self-reported tools (questionnaires) used to assess taste alterations in patients with cancer using a narrative review format.

Sub-objective 2.1. Analyze the specific domains of taste assessed through the questionnaires to profile the aspects of taste alterations that have been assessed.

Rationale: The prevalence and relevance of self-reported taste alterations in patients with cancer has been reported, showing high diversity in the specific items and domains assessed. To study the impact that taste alterations might have on the sensory preferences and food choices of people with cancer, it is first necessary to investigate what is being assessed and reported as "taste alterations". As an exploratory review, no hypothesis was framed.

Objective 3 (Chapter 4): Assess acceptance of oat beverages for fortification among patients with cancer.

Sub-objective 3.1: Assess liking and appropriateness of attributes intensities (using just-about-right scales) of three flavors of commercially available oat-based beverages at two different temperatures among patients with cancer and compare to healthy participants.

Sub-objective 3.2: Develop two formulations of an oat-based beverage fortified with protein and fish oil and assess liking and Just-about-right of the fortified products compared to the unfortified one.

Sub-objective 3.3: Understand and analyze perception of oat food products among using a free-word association method.

Rationale: Few food products to improve nutrient intake have been developed and evaluated among patients with cancer. Real food products with added nutrients represent an alternative to traditional nutritional supplements. Oat-based beverages were selected as a potential vehicle for nutrient enhancement in this population because of their nutritional and sensory characteristics. However, it is necessary to confirm acceptance of the products and of oats in general.

Hypothesis: It was hypothesized that oat products would be accepted and show potential as fortification carriers. Hypothesis for sub-objective 3.1 was that the product would be liked by patients with cancer (liking over 7 in 9-points hedonic scale), and perception of attributes does

not change between patients with cancer and healthy participants. For sub-objective 3.2, it was hypothesized that there is no difference in liking between the fortified products and the unfortified one.

Objective 4 (Chapter 5): Identify through a survey of 150 patients with cancer the preferred snack product to be used as a vehicle for fortification.

Sub-objective 4.1. Identify desired attributes and nutrients or ingredients of interest in a fortified snack.

Sub-objective 4.2. Explore if symptoms presence influence snack product preferences, desired nutrients and snack product characteristics.

Sub-objective 4.3. Understand and analyze perceptions of ONS through a free-word association task.

Rationale: The incorporation of consumer perceptions into the product development process can aid in the creation of successful food products. Identification of consumer needs and desires of a food product can guide the development of new food products. By identifying desired and preferred foods to be fortified as a snack, future projects/studies and researchers can more easily create and evaluate these products.

Hypothesis: It was hypothesized that patients would show preference for one or a few snack products and the experienced symptoms will have an impact on that preference and the desired attributes. It was also hypothesized that symptoms presence would have an influence on snack preferences and desired attributes.

Objective 5 (Chapter 6): Design an intervention trial to evaluate the feasibility of 14-day consumption of oat-beverages as a snack to increase nutrient intake.

Sub-objective 5.1. Assess if liking over time influences overall product liking, amount consumed and QOL of HNC patients.

Rationale: The successful use of a nutrient-enhanced snack for patients with cancer will depend on its long-term consumption. Home-use tests provide a more realistic context of the actual

consumption of food products. The trial received ethics approval but could not be completed. However, the trial study protocol could be used in the future to assess another food product.

Hypothesis: It was hypothesized that adherence with consumption of the beverage daily was feasible and mean overall liking will be maintained and an improvement in satisfaction with food-related life will be observed.

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CHAPTER 2. Sensory preferences of supplemented food products among patients with cancer: a systematic review.

2.1. Introduction

The prevalence of cancer-related malnutrition is frequent, ranging from 9 to 55% depending on the type of cancer and how malnutrition is assessed (Baldwin & Weekes 2011). Cancer-related malnutrition is associated with poor response to treatment, increased treatment toxicity, reduced QOL (Van Cutsem & Arends 2005), increased mortality, morbidity and length of hospitalization (Kubrak & Jensen 2007). Therefore, detection and treatment of malnutrition or inadequate nutrition in patients with cancer must occur as early as possible.

Currently there is no consensus on the best way to treat malnutrition among patients with cancer. However, ESPEN guidelines recommend nutrition counselling as 1st line nutrition therapy to maintain or increase nutrient intake in patients with cancer (Arends et al. 2016). Similarly, the Academy of Nutrition and Dietetics recommends nutritional therapy for patients undergoing chemotherapy or radiotherapy (Thompson et al. 2017). In addition to nutrition counseling, fortified foods (foods containing added nutrients), and/or ONS (commercially available homogeneous and usually nutritionally complete nutrient mixtures for oral consumption) are recommended to achieve the required amount of nutrients and calories (Arends et al. 2016). In this review, the term "supplemented food products" (SFP) will be used to refer collectively to both fortified foods and ONS.

Clinical outcomes expected from SFP consumption are limited by patients´ failure to achieve the recommended ONS intake (Fearon et al. 2003). Successful increase in patient nutrient and caloric intake through SFP depends on long-term adherence and acceptability of the product (Ravasco 2005). Although commonly recommended for patients with cancer at risk for malnutrition, ONS are not habitually consumed by patients with advanced cancer (Hutton et al. 2006; Prado et al. 2012). Many symptoms known to impact oral intake are prevalent among oncology patients (e.g. nausea and vomiting, mucositis) (Van Cutsem & Arends 2005), including TSA which are common among patients receiving cancer treatment (McGreevy et al. 2014; Cohen et al. 2016), and may affect sensory preferences and general acceptability of the product.

Lack of acceptability can present a barrier to long-term adherence and effective use of ONS (Bolton et al. 1992; Rahemtulla et al. 2005; Ravasco 2005; Brown et al. 2013). The extent to which TSA and sensory preferences influence ONS adherence of patients with cancer remains relatively unknown. Greatest wastage of ONS was observed among a group of elderly patients who disliked the product´s taste (Gosney 2003). Moreover, when ONS are consumed regularly over long periods, "taste fatigue" occurs (Rahemtulla et al. 2005). Supplements offering a variety of flavors are more likely to prevent taste fatigue (Ravasco 2005).

Understanding the sensory preferences of SFP of patients with cancer is necessary to improve their consumption. Sensory evaluation can be used to assess sensory preferences. The use of sensory evaluation, a scientific discipline "used to evoke, measure, analyze and interpret those responses to products as perceived through the senses of sight, smell, touch, taste, and hearing" (Anonymous 1975) is commonly applied to optimize chemosensory characteristics in the food and beverage industry. This discipline can be applied in the development, improvement and assessment of preferences for SFP by patients with cancer.

Although sensory characteristics such as taste, flavor, aroma, color and consistency will impact the acceptance of short and long-term consumption, literature assessing the sensory preference of SFP is limited. Furthermore, the methods used to assess sensory characteristics and preferences are rarely based on established sensory evaluation methods. The aim of this systematic review is to identify sensory preferences for SFP among patients with cancer as well as to evaluate and compare the methodologies employed in the assessment of those sensory preferences.

2.2. Methods

2.2.1. Search strategy

A systematic review was conducted. Searches were conducted in several databases (OVID MEDLINE, OVID EMBASE, OVID PsycInfo, WOS CABI, EBSCO CINAHL, EBSCO AGRICOLA, SCOPUS, Proquest Dissertations and Theses GLOBAL, PROSPERO and OVID All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED) by an expert searcher (SC) between July and August, 2016, and updated in September

2017. Searches employed both controlled vocabularies (eg: MeSH, EMTREE, etc) and key words representing concepts such as: (cancer or neoplasms) AND (palatability or adherence) AND (food supplements). Search strategies were adapted for each database. No limits were applied. References were exported to RefWorks citation manager. Search strategies are presented in Appendix A.

Articles were considered for evaluation if they were published in peer-reviewed journals and were retrievable through the University of Alberta Library Services including interlibrary loan. Studies were included if they assessed taste preference, liking or ranking evaluations of ONS and fortified foods among patients with cancer irrespective of patient age, tumor type or tumor stage. Studies were excluded if the main focus was on developed food intake patterns (aversions or preferences), the supplements/foods were not assessed for taste quality (food records only), or only adherence and/or nutritional outcomes after the consumption of SFP were assessed. Publications in form of reviews, communications, editorials, letters, abstracts or expert opinions were also excluded. Additionally, a hand search through reference lists of relevant articles was performed.

2.2.2. Data extraction

Duplicate papers retrieved within the searches were deleted. The first and second authors evaluated the retrieved articles for inclusion, obtaining full text of those identified as meeting inclusion criteria. The third and fourth authors confirmed that the chosen publications met the inclusion criteria. Any disagreement about a publication was discussed and resolved by consensus. On occasion, authors of publications were contacted to request details of the methods employed.

The first and second authors independently extracted data from the selected studies. The following details were extracted from each study: authors; year, country and journal of publication; patient population characteristics (diagnosis, demographic information (age mean and range, number of males/females), treatment); details of the evaluations (sensory method, assessments, and when applicable, details of the control group used for comparisons); supplements or fortified foods assessed (number, characteristics); results.

The systematic review of the literature presented in this paper is the result of a thorough search of databases and references in peer-reviewed journals to be captured. We believe that our search strategy captured all sensory evaluations of SFP among patients with cancer. However, as is the case with any review, these searches may fail to cover all relevant published papers. Moreover, some companies and researchers might assess sensory preferences for SFP among patients with cancer without publication in international journals because they do not consider the studies relevant or prefer to keep them as part of the company expertise.

2.3. Results

2.3.1. Literature search findings

The search criteria were met by 1,056 articles. After exclusion of 138 duplicates, the titles and abstracts of 918 publications were reviewed; 884 of the potentially relevant studies did not meet the inclusion criteria, the remaining 34 articles were extracted for full review (Fig. 2.1). Studies in a different language extracted for full review were translated to English by bilingual volunteers. A further 16 papers were eliminated for a variety of reasons (Fig. 2.1). After the search, one additional article was retrieved and included. Nineteen studies were included in the final review (Garofolo et al.; De Wyes et al. 1977; Gallagher & Tweedle 1983; Brown et al. 1986; Parkinson et al. 1987; Bolton et al. 1990; Morris et al. 1990; Bolton et al. 1992; Rahemtulla et al. 2005; McGough et al. 2006; de Luis et al. 2007; Martin et al. 2008; Cohen et al. 2011; Gómez-Candela et al. 2011; Trinidade et al. 2012; Brown et al. 2013; Baik et al. 2014; IJpma et al. 2016; Petersen & Andersen 2016).

2.3.2. Description of patients and SFP included in the review

A high variability in cancer type, treatment received and SFP products evaluated was found among the different studies; no two studies evaluated the same patient group. Most studies included a mixed population of two or more tumor types (n=14), some focusing on a specific area [pelvic (n=1), thoracic (n=1)], stage [metastatic (n=1), advanced (n=1)], or age group [pediatric (n=1)]. The remaining studies included only one cancer type [hematological (n=2), testicular (n=1), head and neck (n=1), or gastrointestinal (n=1)].

The majority of SFP evaluated in the studies were ready-made ONS and liquids. Supplements evaluated were diverse; 14 studies evaluated different formats (e.g. milk-based, juice-based, powdered, hospital prepared) and/or brands of commercially available supplements either with the same flavor (n=4) or a variety of flavors (n=10), 3 studies assessed the effect of powdered supplement addition into food recipes, 1 study assessed homemade supplements and 1 paper evaluated a fortified soft ice cream.

2.3.3. Description of comparisons used in the review

The final 19 articles were categorized into 3 formats of sensory preference assessment; studies comparing the sensory preferences for SFP of patients with cancer with those of a control group (n=9) (De Wyes et al. 1977; Gallagher & Tweedle 1983; Brown et al. 1986; Rahemtulla et al. 2005; McGough et al. 2006; Martin et al. 2008; Cohen et al. 2011; Brown et al. 2013; Baik et al. 2014), studies assessing the sensory preferences of patients with cancer over time (n=6) (Bolton et al. 1990; Bolton et al. 1992; Rahemtulla et al. 2005; McGough et al. 2006; Gómez-Candela et al. 2011; IJpma et al. 2016) and studies assessing the presence of TSA in patients with cancer and its influence on sensory preferences (n=5) (De Wyes et al. 1977; Gallagher & Tweedle 1983; Brown et al. 1986; Baik et al. 2014; IJpma et al. 2016).

Diversity in choice of sensory methodologies and validity of their application to assess sensory preferences and/or acceptance was documented among the studies. Standard sensory evaluation methodologies and practices were not commonly employed. Moreover, the control of study variables known to influence the evaluation of a product's sensory characteristics (e.g. testing location, product and presentation format), and thus the sensory preferences of the products, was not consistently reported. Therefore, following the presentation of the data, we present a comparison and analysis of sensory evaluation methods used in the reviewed studies and discuss the control of study variables that influence sensory evaluation outcomes.

Sensory science is a scientific discipline incorporating reliable and validated methods. A brief overview of affective sensory tests is presented to clarify the terms used in this review. Affective testing is a class of sensory tests used to determine the degree of liking/disliking, acceptance, preference or emotions for a product (ASTM international 2009). Preference and acceptance

tests are the two principle categories that exist within affective testing, defined by the task performed and research question of the test (Table 2.1).

2.3.4. Sensory preferences and/or acceptance of SFP comparing patients with cancer and a control group.

Nine studies compared the preference or acceptance of supplements by patients with cancer to healthy participants (control groups; Table 2.2). Five studies combined a preference ranking test (ranking in order of liking) with an acceptance rating (rating degree of liking), while the remaining studies focused only on the acceptance of taste and/or other attributes. Although acceptance and preference sensory tests ask participants to assess different affective aspects, in this review acceptance and preference ranking results were similar when both were used within a study; those supplements that were rated significantly higher were also ranked as preferred.

The presence of TSA among patients with cancer, such as alterations in taste intensity and/or the perception of metallic taste without an external stimulus, is well documented (McGreevy et al. 2014; Cohen et al. 2016). TSA impact sensory perception and preferences, and contribute to differences in preferences between patients with cancer and healthy individuals. Age-related decrements in smell and taste perception are also well documented (Boyce & Shone 2006; Doty & Kamath 2014). As the mean age in all studies with adult patients was over 57 years, the use of an age-matched control group provided the appropriate comparison to accommodate age-related changes in taste and smell. However, only 3 of 9 studies used age and sex matched individuals and one study used an age-matched control group. In all studies where the control group was not matched, no significant differences were found between the two groups for the supplement´s ratings. In contrast, all studies using a sex- and -age or age-matched control group, observed differences in the acceptance and/or preference for at least one of the supplements. Collectively, these studies suggest that the liking for SFP by patients with cancer may differ from those of healthy participants and highlights the importance of selecting a control group matched for key characteristics known to influence sensory preferences.

2.3.5. Sensory preferences of patients with cancer over time

Impaired taste perception and altered food preferences have been observed during and post-treatment. Four studies assessed changes in taste preferences after cancer treatment (Table 2.3). Three studies with diverse patients with different cancer treatments (chemotherapy, radiotherapy or combined) showed no effect of cancer treatment on SFP preferences. Conversely, one study showed increased preference for powdered supplements after treatment except two flavors (vegetable and chocolate). However, other studies using qualitative methods revealed that taste preferences of patients with cancer change over the course of treatment and tastes that are well tolerated before treatment may no longer be tolerable (Bernhardson et al. 2007).

Most studies used one-sip assessments in a 'taste and rate' format, a common and practical approach as participants provide a single liking score. However, this approach does not reflect changes in liking during consumption of a complete serving of product. As confirmed by Methven and others (Methven et al. 2010) and Thomas and others (Thomas et al. 2016) working with healthy participants in multi-sip assessments of SFP, dynamic changes in the perception of negative mouthfeel and taste attributes (e.g. dry, mouthdrying, metallic) build up over consecutive sips, decrease the liking of SFP and thus lead to reduced consumption. In both studies, the most liked products were consumed in higher volumes, showing the influence of acceptance on overall consumption.

SFP will successfully improve patient nutritional status only if products are consumed over a period of weeks. Hence longitudinal assessment of both the volume of product consumed and its acceptance are required to reflect potential intake and subsequent improvement of nutrient intake. Of the studies reviewed, only two evaluated the relation between taste preferences and adherence to ONS consumption over time. Bolton et al. (Bolton et al. 1990) allowed patients to taste and preference rank six ONS to determine each patient's most preferred product for a home use test. The researchers then assessed the adherence of the preferred supplement over the 3-week study and observed that the majority of patients consumed their preferred supplement over the 21 days. The average acceptance rating over the 21 days was above 7.3cm (on a 10 cm visual analogue scale) except for two cases (5cm and 0cm). Although 16.7% of patients stopped drinking their preferred product due to a decrease in palatability or disliking of the product, most patients consumed their preferred flavor chosen at the beginning of the trial over the 21 days. In

another study by Bolton et al. (Bolton et al. 1992), patients were randomized to one of three supplement groups and patient adherence was assessed over time. The median time patients were on supplement was 60 days. Initial taste dislike and flavor fatigue caused shorter supplement consumption compared to other reasons (e.g. side effects, back to normal eating, disease progression) and was the stated cause of discontinued supplement intake by 54% of patients. 'Flavor fatigue' was greater among patients who found the supplements unpalatable from the onset. The three supplements were not offered in identical flavors and the authors suggested product acceptance may have been negatively influenced by the novel flavors of one product (orange and banana versus chocolate and strawberry of other products). These two studies highlight the influence of sensory preferences on SFP compliance. The opportunity to taste SFP and choose the preferred product can increase adherence in a longitudinal evaluation and may have direct application in the clinical setting. In these adherence studies the volume of SFP consumed by the patients is not presented. In addition to recording the amount of time patients are able to consume SFP, the ability of patients to consume prescribed quantities should be assessed, as this may also be affected by taste fatigue and palatability.

As presented previously in this review, product acceptance by healthy participants is not consistent with that of patients with cancer. Therefore, the study of temporal changes in liking and perception of SFP among patients with cancer could help elucidate the reasons for a lower than anticipated adherence in this setting. However, these types of assessments are difficult to conduct because they require longer tasting sessions and could represent an extra burden for patients.

2.3.6. The influence of TSA on sensory preferences of patients with cancer

TSA are commonly reported among patients with cancer and may lead to changes in sensory preferences over the course of cancer treatment. Five of 19 studies assessed TSA and their association with SFP acceptability (Table 2.4). In three studies TSA were measured objectively by threshold assessments (Henkin technique, concentration range of test solutions, and commercially available taste strips and 'Sniffin' Sticks' for taste and smell thresholds assessment) while in two studies TSA were measured subjectively (patient reported alterations in

taste since onset of cancer). Thresholds are commonly used in research and clinical settings mainly because they provide numeric values suitable for comparisons, however, their assessment can be time consuming and prone to errors if factors such as subject adaptation and subject fatigue are not considered (Snyder et al. 2006). Self-reported TSA rather than clinical measures have been suggested as a more appropriate predictor of food intake behavior since sensory perception encompasses more complex concepts such as flavor and food enjoyment that clinically assessed thresholds fail to capture (Wickham et al. 1999; Brisbois et al. 2011).

In a mixed population of patients with cancer with different treatment regimens, 40% of patients reported experiencing TSA after cancer onset, which may explain the significant differences in taste preferences of supplements between patients with cancer and healthy controls in the study (Baik et al. 2014). Only one study (IJpma et al. 2016) assessed TSA and palatability of products before and after treatment; TSA were reported after treatment without changes in palatability of the tested products. However in two studies (De Wyes et al. 1977; IJpma et al. 2016), basic taste thresholds were correlated with the preference score of SFP, indicating that taste and smell function of patients influences palatability of SFP. One study observed higher sensitivity to bitter taste and lower sensitivity to sweet taste among patients with cancer compared to healthy controls resulting in significant differences in taste preferences between them (Gallagher & Tweedle 1983).

TSA were reported separately for males and females in one study. Sex could affect TSA and sensory preferences as females may be more prone than males to increased taste sensitivity during cancer treatment (Epstein et al. 2002; Coa et al. 2015). As studies are heterogeneous in cancer sites, treatment and method used to assess TSA it is difficult to compare results. In addition, only one of these studies report confounding factors for TSA such as smoking and patient use of dentures (Baik et al. 2014), while no studies reported other symptoms known to impact oral intake.

2.3.7. Comparison and analysis of sensory evaluation methodologies

The discipline of sensory science comprises a set of methodologies and standards to reduce potential bias from the sample itself or the surroundings that may influence consumer perception

(Lawless & Heymann 2010). By following these standards, the sensory properties of a product can be isolated to provide informative, valid and reliable results (Meilgaard et al. 2016).

This review highlights the need for thorough reporting and control of study variables in product sensory testing; standards should be incorporated and reported such as product serving size and temperature, presentation order and product identity details (ingredients, manufacturer, flavor), as well as external factors such as tasting area conditions and location (e.g. cafeteria, home, clinic, quiet room), time of day, number of products evaluated in one session, and use of palate cleansing before and between sample evaluations to avoid taste carry-over effect. The results of this review revealed that food industry sensory evaluation standards are not consistently translated into the clinical setting, reducing the reliability of study results. For future studies of SFP evaluation, standards organizations such as the American Society for Testing and Materials (ASTM international 2009) and the International Organization for Standardization (International Organization for Standardization 2017) as well as sensory evaluation textbooks (Stone & Sidel 2004; Lawless & Heymann 2010; Meilgaard et al. 2016) can be consulted to guide product evaluation and study design.

In the 19 papers reviewed, rating scales to assess acceptance or liking (n=15), either alone (n=8) or combined with preference ranking (n=7) were most commonly used (Table 2.5). Among the studies, scales used were highly variable and inconsistent with the reliable and validated scales commonly used in sensory science to rate acceptance (Pimentel et al. 2015).

In most studies samples were presented in a randomized presentation order (14 out of 19) and sample identity was blinded (12 out of 19). As confirmed by Cohen and others (Cohen et al. 2011), the acceptance and preference of the supplements can be influenced by the brand, appearance or any previous information about the products. The use of blinded samples, identified by three-digit codes, is a common practice in sensory science to reduce bias. Moreover, sample presentation order will influence results and a balanced or randomized presentation design is essential to reduce presentation order bias (Lawless & Heymann 2010).

Sample serving size should be sufficient for participants to evaluate all product attributes and re-taste if necessary. For products similar to ONS (e.g. flavored milk), consumption of a normal serving size of the product is recommended because factors such as sweetness or satiety can be

liked or accepted at low volumes, while overall acceptability is reduced by an increased volume. Eleven of 19 studies reported the product serving size used. However, 5 of those 11 studies used serving sizes smaller than 30mL, which is concerning especially when more than one attribute is assessed. For example, Petersen and Andersen (Petersen & Andersen 2016) provided only 4 mL of product to assess eight attributes in two different tests, while Brown and others (Brown et al. 1986) provided 15mL samples and asked participants to rate six different attributes.

Only six studies reported product serving temperature. The sensory science recommendation is to serve products at the temperature at which they are normally consumed (Kemp et al. 2009). Additionally, the number of products evaluated in one session differed among the studies, ranging from 1 to 24. The number of samples evaluated depends on the sensory and mental fatigue of the participants (Meilgaard et al. 2016), and especially in the cancer setting, the presence of other symptoms such as pain or fatigue can represent a barrier to the number of samples that can be assessed.

In some studies included in this review, the terms preference and acceptance (liking) are used interchangeably. However, as mentioned previously, both tests assess different outcomes. While in preference measurement the participant chooses one product over one or more other products, acceptance assessments do not require direct comparison to another product and the participant rates their liking or acceptance on a scale (Lawless & Heymann 2010). Thus, in acceptance ratings, the participant may like or dislike two products equally, while in preference ranking the participant must compare and choose one product over another.

2.3.8. Commonalities in patient sensory preferences for SFP

A synthesis of the results of the papers in this review reveal low patient acceptance for ONS in 6 (De Wyes et al. 1977; Gallagher & Tweedle 1983; Bolton et al. 1992; Rahemtulla et al. 2005; McGough et al. 2006; de Luis et al. 2007) out of 9 papers reporting ‘average ratings’ (e.g. below mildly good taste, 2.5/5 points, etc.). In contrast, studies of food products (n=3) (Garofolo et al.; Rahemtulla et al. 2005; Martin et al. 2008) showed good product acceptance. Despite the variability in sensory methodologies and patient populations among the studies, a preference for fresh milk-based supplements when compared to other supplement types and a general low

acceptance of ONS were reported. Comparing sensory preferences of ONS and supplemented foods with similar flavors is worthy of investigation in future studies.

Six of 19 studies compared acceptance and/or preference of fresh milk-based products to fruit juice-based, UHT (Ultra High Temperature) milk and powdered milk-based products. These studies revealed that patients with cancer prefer fresh milk-based supplements (De Wyes et al. 1977; Bolton et al. 1990; Bolton et al. 1992; Rahemtulla et al. 2005; Cohen et al. 2011; IJpma et al. 2016). A previous published systematic review (Hubbard et al. 2012) including 46 studies (mostly patients with cancer) found greater adherence with liquid ONS than solids when patients have poor appetite as liquid ONS are less satiating. Liquid fresh milk-based supplements could be a good choice as a base matrix to create new supplements for patients with cancer. Chilled and frozen products such as ice cream can also enhance palatability and acceptability of SFP among patients with cancer (Trinidade et al. 2012).

2.4. Conclusion

The effectiveness of SFP for nutrition support depends on its consumption, which is directly influenced by its sensory acceptance. This review highlighted the need for the use of existing reliable and validated scales and methodologies for the assessment of sensory preferences and product acceptance, and consistent reporting and control of variables that influence the sensory characteristics of the SFP when product sensory preferences are assessed in the clinical setting. Future research in this field would benefit from the application of sensory evaluation standards and facilitate analysis and comparisons among different studies.

In general patients expressed a preference for fresh milk-based supplements when compared to other supplement types. The acceptance and preference for SFP by patients with cancer differs from healthy age-matched controls. For future studies it will be beneficial to report other symptoms known to impact oral intake as well as smoking and patient use of dentures.

Adherence is often an issue with SFP due to taste fatigue, the lack of flavor varieties and taste alterations. Since sensory preferences are variable among patients, providing SFP that meet patients' sensory preference needs and expectations can improve SFP adherence and patient

nutritional status. The opportunity to taste SFP and select the preferred product can increase adherence in a longitudinal evaluation.

Three studies in this review showed no effects of cancer treatment on taste preferences, which is inconsistent with the findings of many other studies. Patient heterogeneity of site and stage of tumor, variation in study methodologies and type of treatment have made it difficult to draw conclusions regarding the effects of cancer treatment and TSA on taste preferences of patients with cancer. Moreover, considering major advances in cancer treatment such as targeted therapy and immunotherapy, future studies to evaluate the effects of these therapeutic alternatives on TSA are worthy of further evaluation.

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Table 2.1. Characteristics and aims of affective sensory test categories (adapted from Meilgaard et al. 2016).

Test Category	Task	Example questions	Characteristics and results obtained
Preference tests	Choice	Which sample do you prefer / like better?	• Forces a choice of one product over other(s). • Indicates whether a product is preferred over another(s). • Does not indicate whether the products are liked/disliked. • The obtained results are ordinal and can be analyzed using non-parametric statistics to detect a significant difference in preference (Lawless & Heymann 2010).
Acceptance tests	Rating	How much do you like this product? How acceptable is this product?	• Indicates the magnitude of the level of liking/disliking of each product. • Parametric statistical analysis can then be used to determine if significant differences exist between products (Lawless & Heymann 2010).

Table 2.2. Comparison of sensory preferences and/or acceptance for SFP between patients with cancer and control group.

Reference	Patients characteristics*	Control group characteristics	Sensory evaluation procedure	SFP evaluated	Comparison of sensory preference and/or acceptance between patients and control group
De Wys et al. (1977); USA	Metastatic neoplasia, n= 25; NR; Age= 57(25-81)	NR (n=25)	Taste rating using 7-point rating scale ["very bad taste" (-3) to "very good taste" (3)]	5 commercial ONS (4 milk-based and 1 semisynthetic product, all vanilla flavored)	One product was rated significantly lower by controls compared to patients. Range of average scores for each product is broader for controls.
Gallagher and Tweedle (1982); England	Variety of sites (n= 50); NR; Age= NR; Before treatment, Metastatic (n=15)	Age and sex matched (n=50)	Taste rating using 7-point scale (very bad taste to very good taste)	8 commercial supplements, each unflavored and in two alternative flavors	Patients with cancer and controls differed in their ratings for the supplements. Three supplements received significantly higher ratings from patients compared to controls.
Brown et al. (1986); USA	Breast and lung n=39; 19M; Age=56; CT (n=28), RT (n=3), Metastatic (n=16), ≥1 week since last CT	Age and sex matched (n=37)	Rating using modified wine tasting scale assessing appearance, body, flavor, aroma, sweetness, aftertaste. Higher scores reflect more pleasing elements	11 nutritional supplements: polymeric and elemental (n=NR), flavored and unflavored (n=NR)	One ONS was rated significantly higher by female patients compared to female controls. There was no significant difference in rating for the remaining ONS or between male patients and controls.
Rahemtulla et al. (2005); United Kingdom	GI, initial n=60, after treatment n=47; 35M; Age= 64(23-84); Before and six weeks after initial CT	Friends/relatives of patients or hospital staff. Initial n=63 (22M); After treatment n=47. Significantly more females and older.	a) Liking rating using 10cm visual analogue scale from "Definitely dislike" (0) to "Definitely like" (10) b) Preference ranking	3 commercial ONS: one strawberry flavored UHT milk-based, one forest fruit flavored juice-based and one strawberry flavored fresh milk-based.	No significant differences in ONS ratings between control and patient groups, before or after CT. Fresh milk product was preferred by both groups.
McGough et al. (2006);	Pelvic, initial n=50 (5M) after treatment n=	Friends/relatives of patients.	a) Liking using 7-point Likert scale ("Definitely	5 supplements (3 elemental, 1 polymeric	No significant differences in mean ONS liking ratings

United Kingdom	38; Age= 61 (34-89); Before and after 5 weeks of external beam pelvic RT	Initial n=50 (19M); After treatment n=46. Significantly older and smaller proportion of males.	dislike" (1) to "Definitely like" (7)) b) Preference ranking	and 1 peptide formula) in similar flavors (4 lemon/lime and 1 orange/pineapple)	between patients and controls before and after RT, all rating the peptide formula significantly lower. The peptide supplement was the least preferred supplement by patients and controls.
Martin et al. (2008); Canada	Any type, n=86 , NR; Age= NR	Patients´ family/friends and hospital staff. Smoothie n=88 (NR); Oatmeal n=57 (NR); Tomato pasta sauce n=64 (NR)	Rating of aroma, taste/flavor and liking of the products using 7-point hedonic scale ("Dislike extremely" (1) to "Like extremely" (7)).	A n-3 PUFA supplement added into three different foods: instant oatmeal, mixed berry smoothie, tomato pasta sauce	No significant differences between patient and non-patient ratings for each of the foods.
Cohen et al. (2011); Australia	Any pediatric cancer, n=21; 14M; Age= 12.9(±3.9); Receiving CT	Pediatric orthopedic patients or healthy. n=38 (16M). Slightly younger	a) Liking rating on 10cm CAS from "I don´t like the taste at all" to "I like the taste a lot" b) Preference ranking. Both assessments done in two conditions (blinded and branded)	5 chocolate flavored ONS. Three commercial drinks (two UHT, one fresh milk based), and two hospital-based (one UHT, one fresh milk based).	No significant difference in the ONS ratings between control group and patients, although patients gave lower ratings to all supplements compared to controls. In both groups, ratings were significantly higher for commercially available supplements over hospital-prepared. A higher number of children from both groups preferred the commercial fresh milk product. The UHT hospital supplement was ranked as least preferred by both groups, especially controls.

Brown et al. (2013); United Kingdom	Thoracic cancer, n= 31; 18M; Age= 69(±9) ; Variety of palliative treatments	Age-matched healthy volunteers (n=32). Smaller proportion of males.	a) Rating evaluation using 7-point Likert scale ("definitely like" (1) to "definitely dislike" (7)) b) Preference ranking	4 supplement types: Juice, milk, yoghurt and skimmed milk powder based, in different flavors. Participants selected flavor of each supplement type before tasting.	Patients with cancer rated the skim milk powder product significantly higher. Controls rated the yogurt product significantly higher. For ranking, most patients preferred the skim milk powder product and most controls preferred the yogurt style product (least preferred among patients).
Baik et al. (2014); Korea	Variety of solid tumors, n= 30; 11M; Age= 59(±15;19-89); Current treatment or ≤ 6 months	Age- and sex-matched (n=30). Smaller number of controls smoking and drinking alcohol.	a) Rating of color, flavor, viscosity and taste on 5-point Likert scale ["very bad" (1) to "very good" (5)] b) Preference ranking	3 powdered cereal base trial supplements mixed with milk, all compared to commercial liquid isolated soy protein supplement.	Taste of cereal product and viscosity of fruit product received significantly lower ratings by cancer group compared to controls. No significant difference in overall preference rating for the supplements by both groups. Patients showed significant preference for the fruit and commercial supplements while there was no significant difference in preference for the supplements by control group.

NR= Not reported; M= males; CT= Chemotherapy; RT= Radiotherapy; GI= Gastrointestinal; SCLC= Small Cell Lung Cancer; UHT= Ultra high temperature; CAS= Colored Analogue Scale; PUFA= Poly unsaturated fatty acids; ***** Diagnosis, n=size, (# of males), Age= mean or median age (y) + range, treatment status.

Table 2.3. Studies evaluating changes in sensory preferences over time.

Reference	Country	Patients characteristics*	SFP	Comparison	Results
Bolton et al., 1990	UK	n=30 (18M); Age=NR; variety of sites (mostly SCLC); active treatment for all or part of the study	6 ONS: Three containing protein and energy and three supplying energy only	Short-term *vs.* long-term palatability (after 21 days)	Over the 3-week study the majority of patients consumed the ONS preferred at the first visit
Bolton et al., 1992	UK	n=60 (NR); Age=59; variety of patients with advanced cancer; variety of treatment	3 ONS: One milk-based product and two "synthetic"	Length of time the ONS can be consumed	Flavor related issues were the main reason for discontinuation of ONS. The median time for supplement intake was 60 days
Rahemtulla et al., 2005	UK	Initial n=60 (35M). After treatment n=47; 64(23-84); GI cancer; six weeks CT	3 ONS: UHT milk-based, fruit juice-based and fresh milk-based	Change in taste preferences following a 6-week of CT	There were no changes in taste preferences after 6-week CT
McGough et al., 2006	UK	Initial n=50 (5M). After treatment n= 38; Age= 61(34-89); Pelvic cancer; 5 weeks of pelvic RT	5 ONS (3 elemental, 1 polymeric and 1 peptide formula): Similar flavors of each ONS	Change in preferences after radical pelvic RT	There were no changes in ONS preferences after RT
Gómez-Candela et al., 2011	Spain	Powdered supplement (n=31; Age=61.3(±12); liquid ONS n=30, Age=63.6(±11.3); variety of cancer; Variety of treatments	2 ONS: Hypercaloric powder with 1.5g of EPA and hypercaloric liquid supplement	Sensory preferences of ONS enriched by EPA over a month	Preference for ONS was higher at the end of treatment except for two flavors (powdered product with vegetables and with chocolate flavor)
Ijpma et al., 2016	Netherlands	n=21 (21M); Age=32(27-36); Disseminated testicular cancer; CT	6 ONS: Two high protein milk-based, two juice-based and two yogurt based	Palatability of six ONS at multiple time point during treatment	There were no changes in palatability in five out of six ONS after CT

NR= Not reported; M= males; CT= Chemotherapy; RT= Radiotherapy; SCLC= Small Cell Lung Cancer; UHT=Ultra High Temperature;* n= sample size, (# of males), Age= mean or median age (y) + range, cancer type, treatment status

Table 2.4. Assessment of taste and smell alteration (TSA) influencing sensory perception among patients with cancer.

Reference	Country	Patients characteristics*	TSA assessment method	Results
De Wys et al., 1977	USA	n= 25 (NR); 57 (25-81); Variety of metastatic cancers	Taste recognition threshold using Henkin technique (urea and sucrose recognition threshold)	SFP preference scores statistically correlated with urea and not sucrose recognition thresholds. Negative SFP preference scores were more common among patients with a low urea recognition threshold than among those with a normal threshold.
Gallagher et al., 1983	UK	n= 50 (NR); Age= NR; Variety of cancer sites; Before treatment	Single drop taste recognition thresholds (urea for bitter, sucrose for sweet, sodium chloride for salt, and hydrochloric acid for sour).	Patients with cancer showed lower sensitivity to sweet and higher sensitivity to bitter tastes compared to age and sex matched healthy subjects.
Brown et al., 1986	USA	n=39 (19M); Male with lung cancer: age=57.3(±7.4; 42-72), female with breast cancer: age=56.4(±8.5;41-70); CT (n=28), RT (n=3); ≥1 week since last CT	Subjective taste/food aversions since onset of cancer	11M and 16 F reported the development of changes in the sense of taste since illness onset, including hypogeusia (n=6M/6 F), meat aversion (n=4M/6F), and excessive sweet taste of food (n=1M/4F).
Baik et al., 2014	Korea	n= 30 (11 M); 59(±15;19-89); Variety of cancers; Receiving treatment or ended treatment ≤ 6 months	Self-assessment of taste change since the diagnosis of cancer.	40% of patients reported taste changes after diagnosis of cancer.
Ijpma et al., 2016	Netherlands	n=21 (21M); Age=32(27-36); Disseminated testicular cancer; CT	Taste recognition and detection thresholds for sweet, sour, salty and bitter using taste strips; composite smell function (thresholds, discrimination and	Compared to baseline the salt taste threshold increased after treatment. Some taste and smell thresholds were statistically correlated with liking or disliking of specific supplement flavors.

			identification) using 'Sniffin' Sticks'. Self-assessment of taste change and 'foods taste differently' since start of treatment; presence and identification of continuous bad taste in the mouth.	Metallic taste of supplement was associated with lower liking of the supplements. The metallic taste of the juice-based apple ONS increased over treatment.

NR= Not reported; M= males; F= females; CT= Chemotherapy; RT= Radiotherapy

* n= sample size; (# of males); Age= mean or median age (y) + range; cancer type; treatment status

Table 2.5. Comparison and analysis of sensory evaluation methodologies.

Authors (year)	Stated aim	Number of patients (n); Age (mean ± standard deviation)	Sensory evaluation methodology							
			# of products evaluated	Type of sensory evaluation*	Scale	Sample serving size and temperature (T)	Sample blinded	Samples randomized among	Palate cleansing	Control of other external factors
Studies assessing the supplement´s acceptance rating for one or more attributes.										
DeWys et al. (1977)	Evaluate patient preferences for several supplements	n= 25; Age= 57 (25-81)	5	Taste acceptance rating	7-points (-3=”very bad taste”, 3=”very good taste”)	5mL; T=NR	✔	✔	✔	
Gallagher and Tweedle (1982)	Evaluate taste thresholds and palatability of ONS among patients with cancer and control group	n= 50; Age= NR	24 (8 in three flavors)	Taste acceptance rating	7-points (-3=”very bad taste”, 3=”very good taste”)	20 mL bottles; T=NR		✔	✔	✔
Brown et al. (1986)	Compare quantitative evaluations of ONS by patients with cancer and matched controls.	Male lung cancer: n=19; Age=57.3(±7.4 ; 42-72) Female breast cancer: n=20; Age=56.4(±8.5 ;41-70)	11	Acceptance rating of appearance, body, flavor, aroma, sweetness, aftertaste	Modified wine scale	15mL; T=cold	✔	Same order for all patients	✔	✔
De Luis et al. (2007)	Evaluate acceptability of 3 commercial ONS by hematological patients with cancer	n=32; Age=47.6(±16. 8)	3	Rating of color, smell, taste, texture and temperature	VAS (1=”very good”, 5 “very bad”)	NR		✔		

Martin et al. (2008)	Determine overall acceptability of three food products fortified with n-3 polyunsaturated fatty acid (PUFA)	Smoothie n=38; Oatmeal n=22; Tomato pasta sauce n=26; Age=NR	1 of 3 (1 supplement into 3 recipes)	Rating of aroma, taste/flavor and liking	7-point hedonic scale (1="Dislike extremely", 7="Like extremely").	Sample=30mL; T=NR				Test at time of day when typically eaten
Trinidade et al. (2012)	Investigate if introduction of fortified soft ice-cream increases compliance with oral-feeding regimes in post-operative HNC patients.	n=30; Age=NR	1	Acceptance rating of taste, temperature, consistency and ease of eating	10 point scales with end anchors (1= "not at all enjoyable", 10="extremely enjoyable" or 1="very difficult to swallow", 10= "extremely difficult to swallow" for ease of eating).	200g	Only one product evaluated			
Gómez-Candela et al. (2011)	Evaluate and compare efficacy and acceptance of an oral powdered supplement enriched with EPA, compared to standard liquid ONS	Powdered supplement (n=31; Age=61.3(±12); liquid ONS n=30, Age=63.6(±11.3)	1 out of 2	Liking rating of taste, smell, consistency and consumption willingness.	Percentage scale (0-100%)	Product evaluated in patient homes				
Ijpma et al. (2016)	Investigate palatability of six ONS in testicular patients with cancer before, during and after chemotherapy	n=21; Age=32(27-36)	6	Liking rating of appearance, smell, taste, sweetness, thickness, texture, aftertaste, mouthfeel	7-point hedonic scale; 16 attributes assessed on 7-point Likert type scale (1="dislike very much", 7= "like very much")	Sample=30mL; T=cold	✔	✔	✔	✔
Studies assessing preference ranking										

Parkinson et al. (1987)	Develop standard recipes using natural protein and energy supplements and determine the most acceptable	n=60; Age=NR	40 (10 recipes, in four levels each)	Preference ranking		NR	✔	✔		
Morris et al. (1990)	Compare palatability and ability to increase energy of two supplements when added to common recipes	n= 10 in each panel; Age=NR	30 (10 recipes in three supplement levels)	Preference ranking		NR	✔	✔		
Studies using both acceptance rating and preference ranking										
Bolton et al. (1990);	Evaluate extent of loss of palatability among patients with cancer using six commercial ONS	n= 30; Age=NR;	6	Preference ranking		NR	✔	✔		
			ONS chosen in preference ranking	Acceptance rating	10cm VAS for "how acceptable is this product?" (end points not reported)	Product evaluated at home				
Rahemtulla et al. (2005)	a) Examine short-term preferences of GI patients with cancer and controls for milk- and non-milk-based supplements	Initial n=60. After treatment n=47; Age= 64(23-84)	4	Liking rating	10cm visual analogue scale (0="Definitely dislike", 10="Definitely liked")	30mL; T= room T	✔	✔	✔	
	b) Assess reliability of VAS to assess preferences for ONS.			Preference ranking						
McGough et al. (2006)	Identify if elemental peptide and polymeric ONS are acceptable to patients and compare preferences with healthy controls	Initial n=50. After treatment n= 38 ; Age= 61(34-89)	6	Liking rating	7-point Likert type (1= "Definitely dislike", 7="Definitely like")	30mL; T=cold	✔	✔	✔	✔

				Preference ranking						
Cohen et al. (2011)	Examine taste preferences for ONS in children undergoing cancer treatment. Determine if preference is influenced by source of the product (commercial vs hospital)	n=21; Age= 12.9(±3.9)	10 in 2 blocks of 5	Liking rating	10 cm colored analogue scale (CAS) (0="I don´t like the taste at all", 10="I like the taste a lot")	Sample=10mL; T=NR;	✔	✔	✔	
				Preference ranking						
Brown et al. (2013)	Assess initial liking and preferences of patients with thoracic cancer for ONS and compare those preferences with age-matched healthy volunteers	n= 31; Age= 69(±9)	5	Liking rating	7-point Likert agree-disagree scale (1="definitely like", 7="definitely dislike")	Sample=30mL (drink as much as desired); T=cold	✔	✔	✔	✔
				Preference ranking						
Baik et al. (2014)	Compare sensory assessments of trial ONS and a top seller. Examine possible differences between patient and control groups.	n= 30; Age= 59(±15;19-89)	4 (3 trial and control)	Rating of color, flavor, viscosity and taste	5-point Likert scale (1"very bad" (1), 5="very good")	Sample=30mL; T=NR	✔	✔	✔	✔
				Preference ranking						
Petersen and Andersen (2015)	Examine taste perception of ONS in patients with malignant hematological disease	n= 41; Age=53(34-70)	4 (one repeated)	Intensity rating for sweet, sour, salt, bitter, thickness, gritty, metal and ability to drink	10cm VAS	Sample= 4mL; T=room	✔	✔		

	and assess reproducibility of VAS.			150mL ("palatability").						
				Preference ranking						
Studies using other sensory evaluation methods										
Bolton et al. (1992)	Randomized trial to evaluate long-term palatability of three ONS over indefinite timeframe	n=60 (20 on each group); Age= 59(30-79), 58.5(22-75) and 58(31-80)	One randomly assigned	Comments regarding the supplement and reasons to quit were documented		Product evaluated at home				
Garofolo et al. (2010)	Describe the development of eight formulations of hypocaloric homemade supplements to increase supply of energy, protein and micronutrients	n=312; Age=NR	8	Questionnaire with closed question about the flavor (good/regular/bad) and open ended questions for opinion						

T=temperature; NR= not reported; VAS= Visual Analogue Scale; EPA: eicosapentaenoic acid

* For papers with several assessments, only those involving sensory acceptance/preference are presented.

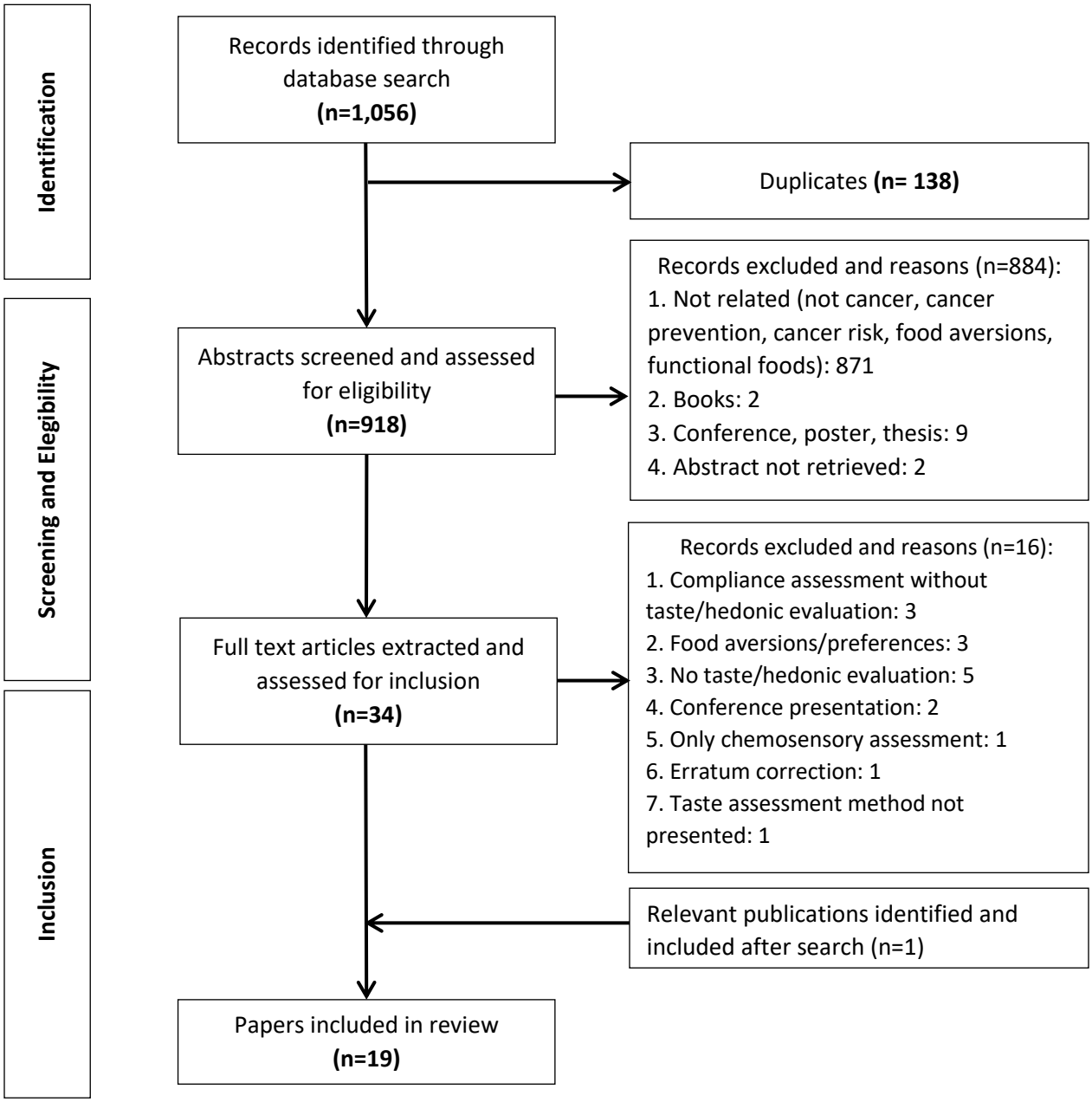

Figure 2.1. PRISMA diagram.

CHAPTER 3: Patient-reported taste change assessment questionnaires used in the oncology setting: a narrative review

3.1. Introduction

Taste changes (TC) are one of the most prevalent and distressing symptoms experienced by patients with cancer during and after treatment (Bernhardson et al. 2009). They are associated with a variety of causes including location and type of malignancy, oncological treatment, comorbidities and other conditions such as the psychological state of the patient (Bromley & Doty 2003; Wismer 2008; Boltong et al. 2012).

Taste changes are a complex phenomenon that include changes in perceived intensity (stronger, weaker or absence of taste), detection of unpleasant and/or lingering tastes (e.g. metallic), dysgeusia or changes in food hedonics (Bartoshuk 1990; Brisbois, De Kock, et al. 2011; Boltong & Keast 2012; Epstein et al. 2016). Severity, character and intensity of TC vary among and within patients on a daily basis (Johnson 2001; Belqaid et al. 2016). Alterations in the sense of taste are idiosyncratic and can be classified as any or all changes stronger, weaker or as mixed intensity sensations (Brisbois, De Kock, et al. 2011). As TC are not life-threatening, they may receive little attention when considered as an unavoidable transitory side effect of cancer treatment (Comeau et al. 2001; Zabernigg et al. 2010). However, TC are a nutrition impact symptom and affect patients' ability to enjoy meals and ultimately affect food choices, leading to loss of appetite, development of food aversions, and reduction of dietary intake. These challenges negatively affect patient quality of life (QoL) and social interactions, and impact survival through weight loss and malnutrition (Comeau et al. 2001; Wismer 2008; Baharvand et al. 2013). Therefore, it is important to detect TC as early as possible.

Reported prevalence of TC among patients with cancer varies between 38-100% (Ripamonti et al. 1998; Gamper et al. 2012). This variation can be attributed to the range of treatments, cancer types and evaluated patients, as well as the method used to assess TC (Spotten et al. 2017). TC can be evaluated through objective or patient-reported assessments. Objective methods (clinical methods), evaluate oral taste sensitivity to tastants through thresholds to the five primary taste qualities (sweet, sour, salty, bitter, umami). Numerical results of objective methods facilitate comparison of taste perception capabilities among populations (Snyder et al.

2006) but they do not reflect the "real-world" taste experience (Boltong & Keast 2012) as they do not capture dimensions of taste important to patients such as flavor, food enjoyment or hedonic changes (Boltong et al. 2012) which may be the first sign of a change in taste noted by a patient. Consequently, the use of patient-reported questionnaires and qualitative research methods are recommended to capture the individual subjective experience comprising the taste perception of these patients (Bernhardson et al. 2008; Wismer 2008; Brisbois, De Kock, et al. 2011).

Appropriate taste change assessment is needed to detect and manage this symptom during and after a patient's disease course. A growing body of oncology literature has documented TC; however, their management remains a challenge in part because of inconsistent terminology to address TC problems (Boltong et al. 2011; Boltong et al. 2012) and a poor understanding of the exact nature of each patient's complaints (Bernhardson et al. 2008). Changes to the sense of smell have also been reported (Gamper et al. 2012). While the words taste and flavor are often used interchangeably by patients and clinicians, for sensory scientists they have different meanings (Boltong et al. 2011; Boltong et al. 2012). Taste is one of the five senses and refers to the perception provoked when chemical molecules stimulate taste receptor cells in the tongue, within the oral cavity and in the throat (Breslin & Spector 2008). Flavor comprises the sensory combination of taste, smell, texture, temperature, irritation or pain and mouthfeel (Prescott 1999; Delwiche 2004). In general, smell and taste are not well differentiated by the general population (Spence 2015). Studies in the oncology setting do not consistently assess smell changes with TC yet most TC are accompanied by smell changes (Bernhardson et al. 2007). The focus of the current review is on patient-reported questionnaires used to assess TC among patients with cancer. Questionnaires that assess only smell changes were not included in the review.

A variety of patient-reported TC questionnaires can be found in the literature (Comeau et al. 2001; Bromley & Doty 2003; Brisbois, De Kock, et al. 2011). Nonetheless, no "gold standard" tool is available to assess subjective TC (Spotten et al. 2017). Prior literature reviews have documented TC prevalence associated with treatment (e.g. chemotherapy) (Boltong & Keast 2012; Gamper et al. 2012), TC management (Munankarmi 2017), mechanisms of TC (Altundag & Cayonu 2016; Epstein et al. 2016), or have focused solely on objective assessments (Mclaughlin 2013). A narrative review by Spotten et al. (2017) evaluates the prevalence,

assessment and clinical consequences of taste and smell changes in the oncology population and includes a critical evaluation of objective and subjective assessment questionnaires. Previous reviews have described TC assessment questionnaires; the TC domains (i.e. specific approaches or aspects) evaluated by the patient-reported questionnaires, such as description of TC, factors impacting or causing TC, effect of TC on eating, or other areas impacted by TC, have not been documented. Therefore, the aims of this review were to 1) provide an overview and description of questionnaires that have been used to assess patient-reported TC among patients with cancer and 2) identify the most common TC domains assessed in TC assessment questionnaires.

3.2. Methods

A narrative approach was chosen for this study as it covers "a wide range of issues within a given topic"(Collins & Fauser 2005) and aims to "describe and synthesize the available literature on a topic" leading to a conclusion of that evidence (Green et al. 2015).

3.2.1. Search strategy

A systematic literature search was conducted using these databases: Medline (Ovid), Embase (Ovid), CINAHL Plus with Full Text (EBSCO), PsycINFO (Ovid), Web of Science- All Databases (Clarivate Analytics), and Cochrane Library (Wiley Online Library). All references were exported to RefWorks citation manager. Searches employed both controlled vocabularies, such as MeSH and EMTREE, and keywords representing concepts such as: ("taste disorder" or dysgeusia) AND (neoplasm or cancer) AND (survey or screen or tool). No limiters or facets were used, and search strategies were adapted for each database (see Appendix B). Literature published from inception until 2018 was searched.

3.2.2. Selection of studies

Publications were considered for evaluation if they were published in peer-reviewed English language journals and were retrievable through the University of Alberta Library Services. Studies were included in the final extraction and analyses if they used a self-reported

questionnaire designed specifically to assess TC resulting from cancer or cancer treatment irrespective of patient age, tumor type or tumor stage.

Duplicate papers retrieved within the searches were identified and removed. Two authors reviewed the abstracts. The first author evaluated resulting articles for inclusion, obtaining full text of those identified as meeting review criteria. The second author confirmed the chosen publications met the inclusion criteria. Any disagreement about a publication was discussed and resolved by consensus.

Publication formats such as books, reviews, patents, conference poster or abstracts, short communications, editorials, case studies, letters, or expert opinions were not included. Studies were also excluded if the primary focus was: 1) objective evaluations of TC; 2) interviews as the sole method for data collection; 3) TC identified as a toxicity event or common adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE) during cancer treatment drug trials; 4) assessment of oral function (xerostomia, mucositis or swallowing function); 5) changes in food intake patterns (development of aversions or preferences); 6) evaluation of smell function only. As the focus of this review is the description and comparison among questionnaires designed specifically to assess TC and the domains evaluated, we excluded quality of life, nutritional assessment questionnaires and symptom or side effect questionnaires which typically use a single question to identify the presence of a TC.

3.2.3. Data extraction

Information extracted from each eligible publication included identification and description of the questionnaire (i.e., number of questionnaire items, TC domains encompassed by the items and scale dimensions), measuring scales and scoring system used to assess TC and the timeframe of the TC assessment (Table 3.1).

3.3. Results

3.3.1. Literature search results

The literature search yielded 1,959 articles that met the search criteria; 38 articles met inclusion criteria (Fig. 3.1). The number of published articles citing the use of a TC questionnaire has

increased in recent years, with 20 of the 38 articles published between 2013 and 2018 (Fig. 3.2). The increased frequency of studies to document TC in the oncology setting suggests increased interest and recognized importance of this nutrition impact symptom.

3.3.2. Taste change assessment questionnaires

Seventeen questionnaires for the specific purpose of TC assessment were found among 38 articles. Table 1 presents the extracted data for each questionnaire. Questionnaire items were grouped according to the TC domains assessed. These domains include factors impacting or causing TC; description of TC (e.g. severity, intensity, onset and specific changes); effect of TC on food perception and eating; smell changes; presence of other nutrition impact symptoms; other areas impacted by TC such as quality of life, food enjoyment or development of food aversions; and the use of strategies for the management of TC (Figure 3.3).

Five or more TC domains were assessed in nine of the TC questionnaires while four or fewer domains were assessed in eight questionnaires (Table 3.1). Items used for the evaluation of the TC domains and the questionnaires in which they are evaluated are categorized in Table 3.2. The number of items, scoring system, timeframe, wording or phrasing and specific domains assessed varied greatly among the TC assessment questionnaires. Four TC questionnaires were cited in multiple publications while other questionnaires were cited once or twice. An overview of each questionnaire is summarized below, presented in descending order of citation frequency.

3.3.2.1.Taste and Smell Survey (TSS)

The Taste and Smell Survey is a questionnaire originally developed to evaluate the nature and severity of taste and smell complaints among HIV-infected patients (Heald et al. 1998). Hutton and others (2007) adapted its use to the oncology setting to assess the relationship between self-perceived taste and smell alterations and food intake, nutritional status and QoL among patients with advanced cancer receiving palliative care. The TSS has been used to examine the impact of cancer therapy on taste and smell changes and salivary function in brain cancer (Mirlohi et al. 2015); to assess the prevalence and characteristics of the changes in patients with solid tumors (Spotten et al. 2016); and among patients with head and neck cancer, lung cancer and advanced stages (i.e. post-treatment), to assess their relationship to quality of life (Hutton et al. 2007;

Brisbois, De Kock, et al. 2011; Alvarez-Camacho et al. 2016), dietary intake (Hutton et al. 2007; Brisbois, De Kock, et al. 2011; Belqaid et al. 2014; McGreevy, Orrevall, Belqaid, Wismer, et al. 2014), weight loss, demographic and clinical characteristics (Belqaid et al. 2014) and other symptoms (Belqaid et al. 2014). The survey has also been used in two clinical trials; one to assess delta-9-tetrahydrocannabinol as an intervention to improve food taste among patients with advanced cancer (Brisbois, Kock, et al. 2011) and another to correlate taste and smell changes with radiation doses among patients with gliomas in the central nervous system (Leyrer et al. 2014). The Swedish version of the TSS has been validated with patients receiving treatment for lung or colorectal cancer (McGreevy, Orrevall, Belqaid, & Bernhardson 2014) (Cronbach´s alpha of 0.71; 0.79 for the subset of questions about taste and 0.64 for the smell subset) and is cited in 3 additional studies among patients with lung cancer (Belqaid et al. 2014; McGreevy, Orrevall, Belqaid, Wismer, et al. 2014; Belqaid et al. 2016).

3.3.2.2.Appetite, Hunger and Sensory Perception (AHSP) questionnaire

The AHSP was developed to assess sensory perception and feelings of appetite and hunger among the elderly (De Jong et al. 1999). This questionnaire has been used to assess taste and smell and its relationship with dietary intake, food preference and body composition among patients with testicular cancer before, during and after one year of chemotherapy (IJpma, Renken, et al. 2017), and among testicular cancer survivors up to 7 years after receiving chemotherapy (IJpma, Remco J. Renken, et al. 2016). Later, the taste and smell items of the questionnaire and two questions from the TSS were utilized to compare taste and smell perception pre-treatment, immediately after treatment and 6 months post-treatment among patients with breast cancer (de Vries et al. 2018). The original AHSP questionnaire was modified (van Dam et al. 1999) to create the “Questionnaire on Olfaction, Taste and Appetite” (QOTA) which rewords the original 29 items to compare pre- and post-laryngectomy timepoints. The QOTA was cited in one subsequent publication (Risberg-Berlin et al. 2006).

3.3.2.3.Chemotherapy Induced Taste Alteration Scale (CiTAS)

The 18-item “Chemotherapy Induced Taste Alteration Scale” (CiTAS) was developed based on semi-structured interviews with 8 patients with cancer undergoing chemotherapy (Kano &

Kanda 2013). The questionnaire was translated to Turkish and Italian languages and validated (Campagna et al. 2016; Sozeri & Kutluturkan 2018). The CiTAS has shown good reliability in all versions with Cronbach α of 0.9, 0.869 and 0.82, respectively for the English, Turkish and Italian language versions.

To assess the prevalence, severity and characteristics of self-reported TC, the Italian version of CiTAS questionnaire was completed by patients receiving chemotherapy previously screened for TC and/or changes in taste of foods (Campagna et al. 2018). Patients reported the impact of TC on their QoL on a rating scale from 0 to 100 (no impact to maximum impact) (Campagna et al. 2018). Ijpma and others (IJpma, Timmermans, et al. 2017) developed a tool based on the CiTAS to investigate prevalence and possible predictors of metallic taste among patients with cancer using the 4-point scale of the EORTC-QLQ-C30. Questions were adapted and additional questions were added to assess ability to detect tastes, factors impacting taste perception, and presence of metallic taste and food aversions. The questionnaire is composed of three sections, with the second and third completed only by those patients reporting TC and a persistent taste in mouth, respectively (IJpma, Timmermans, et al. 2017).

3.3.2.4.Taste Change Survey (TCS)

The "Taste Change Survey" (Wickham et al. 1999) includes 20 demographic and disease related items, factors influencing taste and 21 items related to taste and smell changes, including interventions for self-management of TC. Content validity was established by 12 oncology nurses. The TCS was later used in a randomized controlled trial (Halyard et al. 2007) to test the efficacy of zinc sulfate as a palliative intervention to treat TC among patients with head and neck cancer undergoing radiotherapy. In a third study, the TCS was modified to describe chemotherapy associated TC and identify useful managing strategies (Rehwaldt et al. 2009). The demographic section was reduced to 8 items, response options were changed to a 4-point Likert type scale ("Not at all" to "A lot") and additional items for self-management were included. Content validity of the modified TCS was verified by eight clinical nurses (Rehwaldt et al. 2009).

3.3.2.5.Additional Questionnaires

Bernhardson and others (Bernhardson et al. 2008) developed a "Taste and Smell Questionnaire" (33-TSQ) to assess TC (n=7), smell changes (n=8), demographics, effect of taste and smell changes on daily life and the communication between patients and health care providers about taste and smell changes. The questionnaire was reviewed by nurses, pilot-tested and assessed for content through 3 think-aloud interviews. After pilot-testing, the finalized questionnaire explored the prevalence of patient-reported taste and smell changes among patients with cancer receiving chemotherapy. The authors (Bernhardson et al. 2009) utilized the 33-TSQ to assess and compare patients' reported levels of distress related to taste and smell changes and impact on daily life, socio-demographic characteristics, clinical factors, and self-care strategies.

To determine the relationship between TC and energy and nutrient intake among patients with cancer and non-patients, a 12-item "Taste Changes Questionnaire" (TCQ) (Sanchez-Lara et al. 2010) was administered together with clinical evaluations of taste acuity. The same questionnaire and threshold testing were used to assess the effects of two drugs on taste acuity and their relationship with nutrition and QoL of patients with advanced non-small-cell lung cancer (Turcott et al. 2016).

The Taste and Smell Subjective Changes Questionnaire (TSSC) was partnered with objective taste evaluations to investigate TC in a cohort of patients with breast and gynecological cancer (Steinbach et al. 2009), with smell clinical assessments also performed among patients with breast cancer (Steinbach et al. 2010). Patients rated their gustatory function and other items related to their olfactory function, appetite, reduced saliva, aversions to meals, use of food enhancers and eating pleasure.

Eight questionnaires identified in our literature search were each cited only once. Each questionnaire was developed for a specific purpose, including the characterization of TC subsequent to treatment for head and neck cancer (Maes et al. 2002; Goldberg et al. 2005) or for a variety of patients with cancer during chemotherapy treatment (Amezaga et al. 2018); assessment of prevalence, recovery time and potential association to surgery type or other aetiological factors among patients undergoing upper gastrointestinal cancer surgery (Harris & Griffin 2003); characterization of TC and impact on QoL (Ponticelli et al. 2017); to assess the efficacy of interventions including a local liposomal application to improve taste and smell

ability (Heiser et al. 2016) and flavor enhancement and nutritional information to improve nutritional status, functional and immune status and QoL (Schiffman et al. 2007); and to investigate the relationship between the palatability of oral nutritional supplements and the taste and smell function of patients with testicular cancer undergoing chemotherapy (IJpma, Remco J Renken, et al. 2016).

3.3.3. Taste change domains and items assessed in the questionnaires

The TC domain most frequently assessed is the "description of the nature of TC", evaluated by several items (e.g. changes in the sense of taste, changes in the perception of primary taste qualities, unpleasant taste perception) (Table 2). Only the AHSP questionnaire does not address this domain. Other domains commonly assessed (11 questionnaires) were "Impact on other aspects" and "Smell changes". In contrast, the domain addressing "Factors impacting/causing TC" was assessed in only 4 questionnaires. The distress caused by TC and the use of self-management strategies were each assessed in 5 different questionnaires.

The most common TC item was "unpleasant or bad taste in the mouth", assessed as "a constant", "persistent", or "experienced" bad/unpleasant taste in the mouth (n=10). The TSS and the TSQ-S identify the specific unpleasant taste perceived and only the TCQ (Sanchez-Lara et al. 2010) explored the time of day it was most noticeable. As some patients experience an unpleasant taste only during particular days and/or times throughout the day (Speck et al. 2013), the unpleasant taste description and its onset and duration are relevant in the assessment of TC.

Other frequently assessed items included changes in the sense of taste (n=8), and changes in the way food tastes (n=9). Twelve questionnaires included the assessment of nutrition impact symptom items that may influence taste or intake, especially those related to mastication and saliva including the presence of dry mouth or oral problems (n=8), reduced appetite (n=6) and perceived nausea (n=5). Assessment of oral problems is more relevant in populations such as head and neck cancer.

A less frequent item among the questionnaires addressed "changes in the perception of the taste qualities" (sweet, sour, salty, bitter) (n=6). Patients can indicate a perceptible difference in sensitivity of each of the taste qualities (Bernhardson et al. 2008; Brisbois, De Kock, et al. 2011; Kano & Kanda 2013). However, these assessments must be interpreted cautiously as patients and

healthy individuals confuse sour and bitter, particularly at low concentration (Mclaughlin 2013; Doty et al. 2017), and have difficulty recognizing bitter tastants (Mclaughlin 2013). It may be valuable to assist patient recognition of taste qualities by citing food examples (e.g. sour like lemon juice or bitter like coffee beans) as included in the TSS. The basic taste umami was only assessed in the CITAS (a Japanese questionnaire) and is not frequently included in other questionnaires as umami is not a familiar taste in western countries (Cecchini et al. 2019). Umami is present in a variety of foods associated with food palatability, selection and enjoyment (Yamaguchi & Ninomiya 2000) and strongly correlated with appetite, suggesting an important role in nutrient intake and QoL. Assessment of umami perception could permit a broader understanding of the patient TC experience.

Question item phrasing varies greatly among questionnaires and the approach to domain and item evaluation is inconsistent. Questionnaire items used to address "changes in the sense of taste" included "Have you noticed any change in your sense of taste?" (TSS, QASCC) and "have you experienced change in your sense of taste in connection with the chemotherapy treatment?" on the 33-TSQ, with the response options being yes/no in both cases. An open space to describe these TC was provided in the TSS and space to identify affected basic tastes or other TC is available in the 33-TSQ. To assess "changes in the way food tastes" the items used include all foods tasting the same (33-TSQ), improved or declined food taste (AHSP and CQ) and the taste of food is 'different' or 'changed' on the TCQ, TSS, CiTAS, QASCC and the TCQ, which additionally asks patients to describe the TC and the foods in which it occurs.

The domain "Other impacts of TC" was assessed through items including sense of distress, food aversions, food hedonics and the enjoyment of food. The effect of food temperature was assessed only in the QASCC. The DQ queried patients about their change in eating habits, food habits and the amount of food consumed.

3.4. Discussion

Our categorization of patient-reported TC questionnaires by TC domain and items within domains provides a consolidated overview to aid researchers in selection of a tool that aligns with their TC assessment purpose. Our findings reveal increased interest in the assessment of

patient-reported TC among patients with cancer and a diversity of TC items and domains for the evaluation of this complex phenomenon. Domains of TC assessment have emphasized TC description, causes or factors contributing to TC, the impact of TC on food, eating and quality of life, and patient strategies to manage TC. These domains align with the themes identified in a qualitative study designed to provide insight into the impact of chemosensory changes on food-related life among patients with esophagogastric cancer (de Vries et al. 2016).

TC terminology use differs between patients and clinicians and among clinicians (Boltong et al. 2011). Consistent use of TC terminology, such as that identified by Boltong and Keast (2015) would facilitate interpretation and understanding of patients' TC experience to support individual patient needs.

As the perception of changes in food taste is affected by the combination of taste, smell and trigeminal sensations, and influenced by temperature, touch, vision and hearing (Comeau et al. 2001; Epstein & Barasch 2010), full characterization of TC will include assessment of these sensations as well. Most TC assessment questionnaires include smell change assessment items to reflect the contribution of olfaction to flavor perception and smell changes that occur independent of TC (Gamper et al. 2012). A study among patients experiencing taste and smell alterations during chemotherapy revealed that food texture and temperature have increased importance when patients experience TC (Bernhardson et al. 2012). Hot and cold temperature hypersensitivity was reported by 20% and 36%, respectively, of patients with cancer receiving chemotherapy (Amezaga et al. 2018). The assessment of possible texture and food temperature sensitivities among other cancer settings and treatments could be studied further.

The TC experience varies with time along the disease and treatment trajectory (Belqaid et al. 2016). Timeframe for the assessment of TC among the reviewed questionnaires differed or was unspecified. The patients in McLaughlin's study reported that they did not miss how food used to taste because they no longer remembered how it tasted (Mclaughlin 2013). Thus, the use of a short reference period for the assessment of TC may be beneficial when the purpose of the evaluation is to develop patient-focused care and support. TC assessment at frequent intervals could aid identification of TC over time and their association with cancer treatment or cancer etiology itself. A scoring system to generate quantitative measurements would facilitate TC comparisons over time and permit stratification or clustering of patients according to the degree

or severity of their TC, and TC association with outcomes such as dietary intake, food preferences and quality of life. Only four questionnaires reviewed have a specified scoring system.

Comparisons among TC assessment studies is limited due to heterogeneity in domain assessment, response scales, scoring systems, phrasing, and timeframe reference among the patient-reported TC questionnaires. The need for the development and use of a validated and reliable tool for the clinical evaluation of TC has been expressed in previous literature reviews (Hovan et al. 2010; Spotten et al. 2017). Validity is a term related to the accuracy of an instrument to measure what it intends to measure (Kimberlin & Winterstein 2008); a tool is validated when it is quantitatively evaluated versus a 'gold standard' or instrument regarded as a good way to measure the same concept (Litwin 1995). As the perception of TC is a subjective and individual sensation, the "validity" of TC assessment questionnaires is not easily measured. Content validity provides a good foundation on which to build a methodologically rigorous assessment of a questionnaire's validity. Questionnaire reliability can be validated by reviewers with experience and knowledge in the field, e.g. patients and health providers; questionnaires where content validity has been evaluated against patient experience offer more validity. The "Taste change survey", the "Chemosensory questionnaire", the "Taste and smell questionnaire" and the "CiTAS" were reviewed by experienced oncology nurses and the "Taste and smell survey" was assessed for content validity index by 13 experts. Only the "chemosensory questionnaire", the Swedish language translation of the "Taste and smell survey" and the "Taste and smell questionnaire" were reviewed by a group of patients to ensure content validity.

This review did not include TC items within QoL, symptom presence and nutritional status questionnaires. TC items in those questionnaires could identify patients experiencing TC, followed by completion of a TC specific questionnaire. This two-stage approach to TC assessment, used in two studies (IJpma, Timmermans, et al. 2017; Campagna et al. 2018), could provide diagnostic information for clinical support and also reduce patient burden in both research and clinical settings by completion of comprehensive questionnaires only by those experiencing TC.

The number of TC items used in questionnaires ranges between 3 and 47. Assessment of TC presence or severity may require only one or two questions, while a broader number of assessed

items are needed to develop management therapies, monitor changes in perception over time, or assess TC relative to treatment. Additionally, TC assessment with assessment of other nutrition impact symptoms, may be relevant for patients with head and neck cancer who experience an increased number of oral problems and changes in salivary output that influence taste perception (Sroussi et al. 2017).

As assessment of all TC domains may not be necessary in all settings, we suggest the use of a question bank or validated modules similar to EORTC questionnaires. Validated modules could be used to assess changes in taste hedonics, taste qualities, food perception or sense of smell. Use of validated TC items or domains would facilitate comparisons among cancer populations and yield rich information to customize dietary support for the patient TC experience and improve upon the current support of generalized suggestions. Additionally, validated TC assessment items may be applicable for TC assessment among other populations in which TC occur, such as Parkinson's Disease (Cecchini et al. 2015), Alzheimer's Disease (Sakai et al. 2016) and schizophrenia (Ansoleaga et al. 2015).

While our search may have failed to reveal all relevant published papers, we believe that our search strategy allowed us to review the majority of tools employed to date to document patient-reported TC among patients with cancer.

3.5. Conclusions

This review reveals increased interest in the assessment of taste and smell changes among patients with cancer. Patient-reported TC questionnaires vary greatly in the number of items, timeframe assessment and TC domains assessed. Some questionnaires were cited in multiple studies while the majority of questionnaires were cited only in the study in which they were developed. Validation of TC questionnaires by patients could ensure that terms associated with TC are understood and used reliably by patients, clinicians and researchers. The more commonly assessed TC include the presence of an unpleasant taste in mouth and the perception of a TC or changes in the way food tastes.

With the certainty that what cannot be measured cannot be managed; how can we provide recommendations and/or develop treatments to manage TC if assessment is inadequate? Development of a standardized tool or validated modules to detect and characterize TC among cancer populations is required.

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Table 3.1. Taste Change Assessment tools.

Questionnaire, number of items, n= # of studies (author, year)	Target Population, Time frame	Instrument scoring, answer format
Tools assessing five or more domains of taste change		
Taste and smell questionnaire (33-TSQ), 33 items, n=2 (Bernhardson et al. 2008; Bernhardson et al. 2009)	• Patients reporting taste and smell changes during chemotherapy • Since start of cancer therapy	• Not scored. Response options can be dichotomized for analysis • Variety of scales (i.e. yes/no, multiple choice, Likert scales and open-ended)
Taste change survey (TCS) a) TCS-W, 41 items, n=2 (Wickham et al. 1999; Halyard et al. 2007) b) TCS-R, 39 items n=1 (Rehwaldt et al. 2009)	• Patients receiving chemotherapy in ambulatory settings • Not reported • Patients receiving chemotherapy and experiencing taste changes • Not reported	• Not scored, descriptive information. • Variety of scales (i.e. yes/no, multiple choice, Likert scales and open-ended) • Descriptive information. • Variety of scales (i.e. yes/no, multiple choice, Likert scales and open-ended)
Taste and Smell Survey (TSS), 16 items, n=11 (Hutton et al. 2007; Brisbois, De Kock, et al. 2011; Brisbois, Kock, et al. 2011; Belqaid et al. 2014; Leyrer et al. 2014; McGreevy, Orrevall, Belqaid, & Bernhardson 2014; McGreevy, Orrevall, Belqaid, Wismer, et al. 2014; Mirlohi et al. 2015; Belqaid et al. 2016; Spotten et al. 2016; Alvarez-Camacho et al. 2016)	• All patients with cancer • Since cancer diagnosis and over the past three months for 2 questions.	• Total chemosensory complaint score (0-16) calculated by adding the taste and smell complaint scores. To score each section, a point is given for each complaint; for two of the items, two points are given if the complaint is "severe" or "incapacitating". Two questions are not scored. • Variety of scales (i.e. yes/no, multiple choice, Likert scales and open-ended)
Chemotherapy-Induced Taste Alteration Scale (CiTAS) a) Original, 18 items, n=3 (Kano & Kanda 2013; Campagna et al. 2018; Sozeri & Kutluturkan 2018) b) CiTAS Ijpma, 47 items, n=1 (IJpma, Timmermans, et al. 2017)	• Patients undergoing chemotherapy and experiencing taste changes. • 7 days after CT. • Patients receiving chemotherapy up to 1 year of treatment completion • During your disease, over past week, compared to before treatment	• Four subscales: decline in basic taste (5 items), discomfort (6 items), phantogeusia/parageusia (3 items) and general taste alterations (4 items). Subscale scores calculated by dividing sum of all scores by number of items. • Variety of scales (i.e. yes/no, multiple choice, Likert scales) • Not scored. • Variety of scales (i.e. yes/no, multiple choice, and Likert scales)

Taste and Smell Questionnaire (TSQ-S), 9 items, n=1 (Schiffman et al. 2007)	• Elderly patients receiving chemotherapy • At the time of testing	• Not scored globally. • Yes/No and multiple choice
Taste and smell subjective changes (TSSC), 16 items, n=2 (Steinbach et al. 2009; Steinbach et al. 2010)	• Patients with breast or gynecologic cancer undergoing chemotherapy • Before and 3 months after chemotherapy	• Not scored globally • VAS 0-100; 0= no complaints; 100= severe complaints
Questionnaire for the assessment of subjective chemosensory complaints (QASSC), 34 items, n=1 (Amezaga et al. 2018)	• Patients scheduled to receive chemotherapy • From the beginning of current chemotherapy regimen, independently of cycle number	• Descriptive information, not scored Yes/No and multiple choice
Tools assessing five or more domains of TC		
Appetite, Hunger and Sensory Perception Questionnaire (AHSP),29 items, n=3 (63, 62, 61). Also called Questionnaire on Olfaction, Taste and Appetite (QOTA) in n=2 (van Dam et al. 1999; Risberg-Berlin et al. 2006)	• Originally for the elderly. Used for different patients with cancer • In "former days" and "nowadays" for AHSP. Pre-laryngectomy period and present situation for QOTA	• Four scores: taste (8 items, range 8-40), smell (6 items, range 6-30), appetite (6 items, range 6-30), and hunger (9 items, range 9-45). Low scores indicate higher deterioration. • 5-point Likert scale
Taste Questionnaire (TQ), 9 items, n=1 (Maes et al. 2002)	• Patients with head and neck cancer undergoing radiotherapy • Current	• Descriptive information • 0= Absent symptom; 4= Serious complaint
Dysgeusia questionnaire (DQ), 12 items, n=1 (Ponticelli et al. 2017)	• Patients receiving chemotherapy with or without radiation • After or during chemotherapy	• Descriptive information, not scored • Yes/no, Likert scales and multiple choice
Taste Changes Questionnaire (TCQ), 12 items, n=2 (Sanchez-Lara et al. 2010; Turcott et al. 2016)	• Patients receiving chemotherapy • Past two weeks	• Descriptive information • Yes/No, if yes option to provide more information
Chemosensory Questionnaire (CQ), 8 items, n=1 (Goldberg et al. 2005)	• Patients with head and neck cancer • Past 4 weeks	• Two scores: taste and smell (range 4-20 each). Some item responses are reversed for scoring • 1= Never; 5= Always
Standardized questionnaire (SQ), n=1, 12 items (Heiser et al. 2016)	• Patients with head and neck cancer • Now, compared to earlier times	• Not scored globally. Results of VAS for each question were compared at two time points • Open-ended questions and 10-point VAS
Taste and Smell Deficit Questionnaire (TSDQ), 3 items, n=1 (Harris & Griffin 2003)	• Patients after upper gastrointestinal cancer surgery • After surgery	• Descriptive information, not scored • Variety of scales (i.e. yes/no, fully/partially, open ended)

Subjective taste perception questions (STPQ), 4 items, n=1 (IJpma, Remco J Renken, et al. 2016)	• Patients scheduled to receive chemotherapy • Since the start of treatment	• Descriptive information, not scored • Multiple choice and open-ended

Table 3.2. Questionnaire items within each taste change domain assessed on taste change questionnaires.

Taste Change Domain	Questionnaire														
	33-TSQ	TCS	TSS	CiTAS	TSQ-S	TSSC	QASCC	AHSP	TQ	DQ	TCQ	CQ	SQ	TSDQ	STPQ
Factors causing taste changes															
Effect of medication on sense of taste			X		X										
Demographics, tobacco and alcohol use	X	X													
Description of nature of taste changes															
Presence of unpleasant/bad taste in the mouth (e.g. metallic taste)	X	X	X	X	X		X			X	X	X			X
Changes in the sense of taste	X	X	X			X	X			X			X	X	X
Changes in the perception of taste qualities	X		X	X	X				X	X					
Degree of abnormal sense of taste/ taste loss			X		X		X		X						
Onset or duration of taste changes	X	X											X	X	
Self-assessment of smell and taste ability					X										
Overall severity of taste changes		X	X							X			X		
Frequency of taste changes	X														
Description of unpleasant taste in mouth			X		X										
Time when TC are noticed the most		X													
Sensitivity to each of the taste qualities							X								
Effect of taste changes on food and eating															
Changes in the way food tastes	X	X	X	X			X	X			X	X			X
Changes in eating habits, food habits and/or amount of food consumed	X									X					
Effect of taste changes on diet										X					
Difficulty eating certain types of food				X											
Sensitivity to food temperature (hot or cold)							X								
Bothered by the smell of food				X											
Other impacts of TC															
Distressed or bothered by taste changes	X	X					X		X			X			
Effect of taste changes on quality of life	X	X	X		X										

Unpleasant food taste			X	X				X			X				
Food hedonics	X					X		X							
Food enjoyment	X							X							
Food aversions	X					X									
Food enjoyment compared to former days								X							
Difficulty cooking	X														
Management strategies															
Self-management strategies	X	X				X			X	X					
Smell changes															
Changes in the sense of smell	X	X	X	X	X	X	X	X				X	X	X	
Effect of smell alterations on quality of life	X		X		X							X			
Changes in the way food smells			X				X	X							
Severity of smell changes			X												
Ability to identify odors								X							
Sensitivity to certain odors	X	X													
Other nutrition impact symptoms experienced															
Dry mouth/ oral problems	X	X			X	X	X			X	X		X		
Loss/reduced appetite	X	X		X		X		X	X						
Nausea	X	X		X			X				X				
Weight changes	X	X				X									
Difficulty swallowing							X						X		
Vomiting	X	X													
Early Satiety	X										X				
Depression	X	X													
Hunger sensation								X							
Pain											X				
Total number of domains assessed in each questionnaire	**7**	**7**	**5**	**5**	**5**	**5**	**5**	**4**	**4**	**4**	**3**	**3**	**3**	**2**	**2**

Abbreviations: 33-TSQ: Taste and Smell Questionnaire; TCS: Taste change survey; TSS: Taste and Smell Survey; CiTAS: Chemotherapy induced taste alteration scale; TSQ-S: Taste and smell questionnaire; TSSC: Taste and smell subjective changes; QASCC: Questionnaire for assessment of subjective chemosensory questionnaire; AHSP: Appetite, Hunger and sensory Perception; TQ: Taste questionnaire; DQ: Dysgeusia Questionnaire; TCQ: Taste changes questionnaire; CQ: Chemosensory questionnaire; SQ: Standardized questionnaire; TSDQ: Taste and smell deficit questionnaire; STPQ: Subjective taste perception questions.

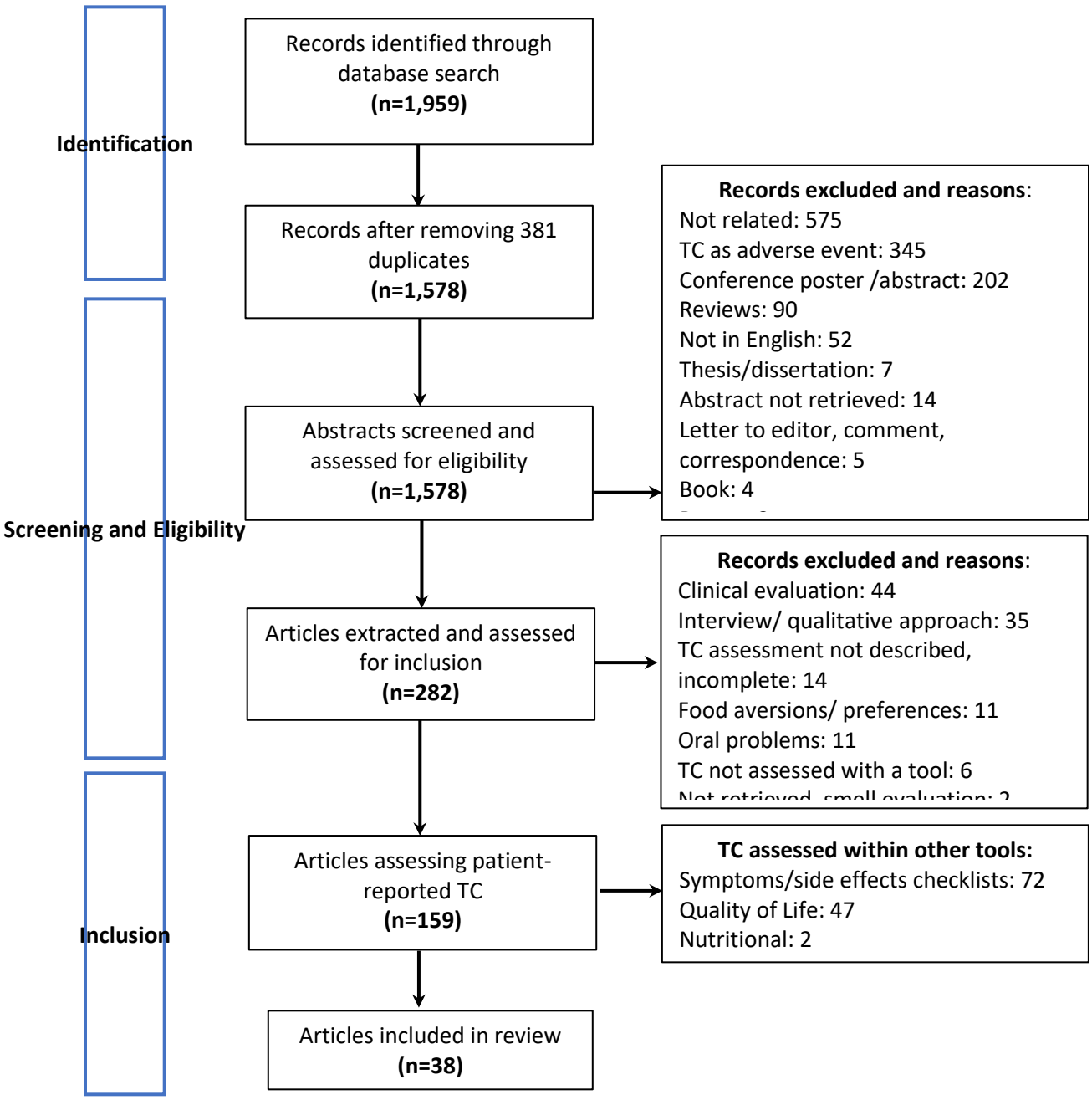

Figure 3.1. PRISMA flow diagram

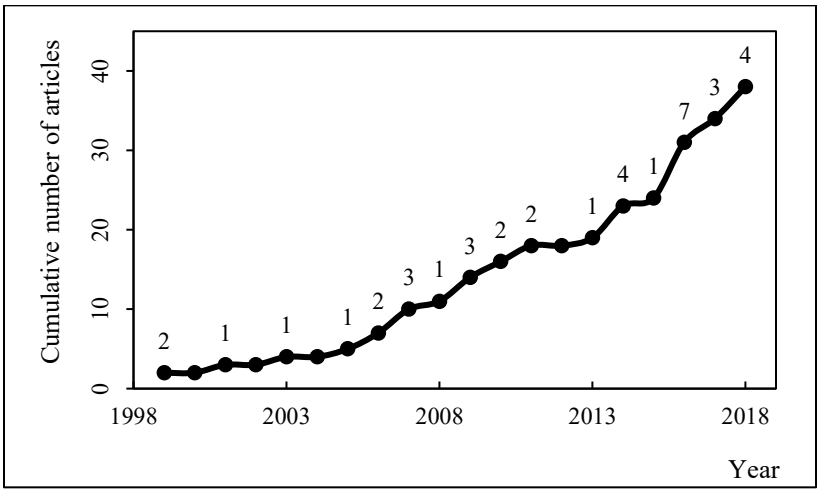

Figure 3.2. Number of articles using a taste change assessment questionnaire by year.

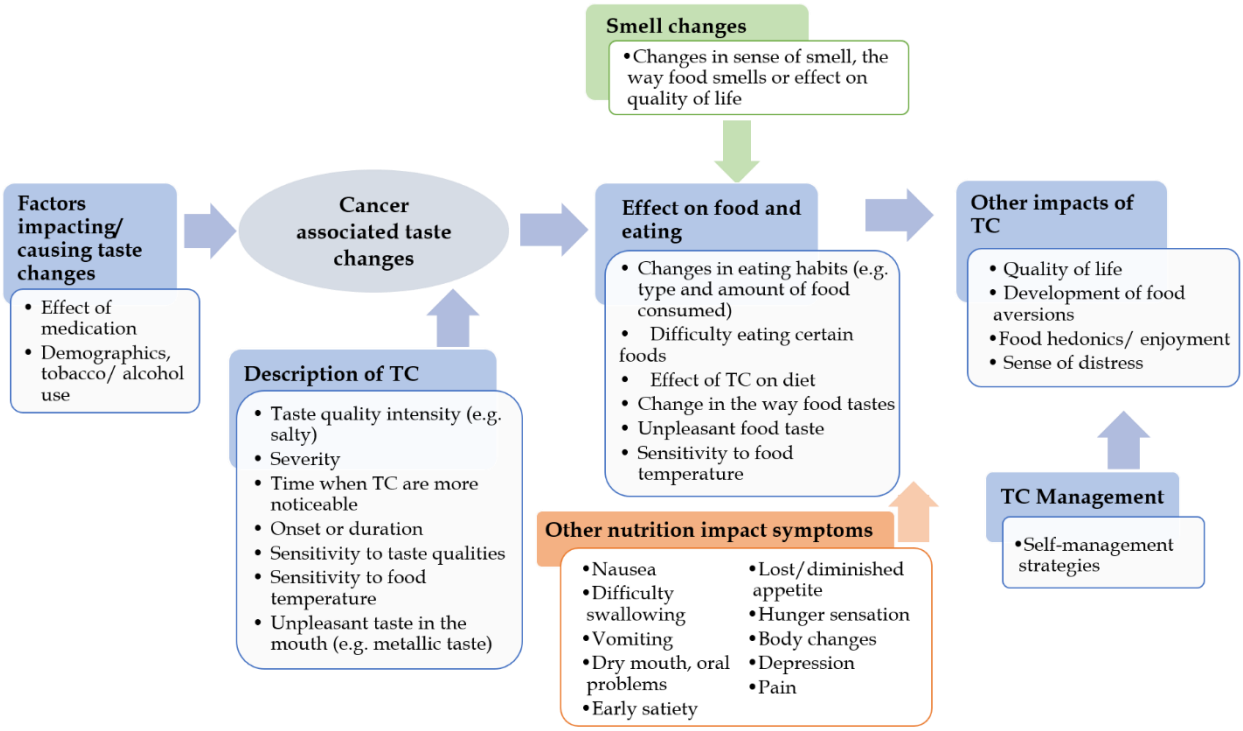

Figure 3.3 Domains of patient-reported taste changes.

CHAPTER 4: Acceptance of an oat-based beverage among patients with cancer

4.1. Introduction

The development of successful food products incorporates consumer desires and demands of the sensory properties of the product (van Kleef et al. 2005). Sensory science is an efficient tool in the development and validation of successful food products that incorporates consumer preferences and perceptions of product sensory properties (O'Sullivan 2016). Sensory science has been employed in the development and assessment of functional foods targeted to consumers with specific nutrient and sensory quality needs such as older adults (Donahue et al. 2015; Methven et al. 2016), and patients with cancer (Brown et al. 2013; IJpma et al. 2016).

Inadequate nutrient intake among patients with cancer is common and has been associated with worsened prognosis and treatment outcomes (Gellrich et al. 2015; Mantzorou et al. 2017). Adequate nutrition is essential to prevent muscle loss (Purcell et al. 2019), a frequent occurrence (Prado et al. 2020) with high impact on prognosis and survival (Prado et al. 2008). Energy intake at optimal levels and anabolic nutrients such as protein, specific amino acids, fish oil, particularly eicosapentaenoic acid (EPA), and vitamins and minerals such as vitamin D have been investigated as potential nutrition interventions for low muscle mass with different evidence levels of benefits (Prado et al. 2020). Although the specific required levels have are still unknown due to lack of strong evidence, those nutrients are recommended for this population by the European Society for Clinical Nutrition and Metabolism (ESPEN) (Arends et al. 2016). Normal food is indicated as the best way to maintain and increase energy and protein intake (Arends et al. 2016). Fortification of food products could increase the intake of recommended nutrients. However, access to palatable and varied food products with high energy density and/or containing recommended nutrients for patients with cancer is limited (Wismer 2018; Tueros & Uriarte 2018; Galaniha et al. 2020). The available options fail to consider the pleasure of eating, changes in sensory perception and food preferences, thus lowering quality of life (Tueros & Uriarte 2018). In the literature, only a few food products have been developed for people with cancer, including protein fortified and unfortified ice creams and a jelly-like product high in

protein and micronutrients, all well accepted among patients (Trinidade et al. 2012; Trachootham et al. 2015; Vieira et al. 2018; Valmorbida et al. 2019).

Our recent review revealed that product acceptance evaluations in this population commonly fail to follow best sensory science practices, complicating interpretation of study results and comparisons among studies (Enriquez-Fernández et al. 2019). Sensory evaluation of food products among patients with cancer may be challenging due to the presence of nutrition impact symptoms that interfere with the usual eating process (Ravasco 2005) and because a large proportion of patients with cancer are older adults (Roser & Ritchi 2019) who may struggle with visual and hearing impairments, use of dentures, cognitive impairments, and fatigue with large numbers of samples to be tasted (Methven et al. 2016). Rapid sensory evaluation methods with minimal participant burden have been suggested to assess liking and drivers of liking among patients with cancer (Wismer 2018).

Just-about-right (JAR) scales are used to study the appropriateness of a product's sensory attribute intensity (Ares et al. 2009; Lawless & Heymann 2010) and are one of the most popular tests for product development (Moskowitz 2008). These scales have a center or midpoint labelled as "Just-about-right" and two opposite end-anchors for "Too little" or "Too much" (e.g. "too sweet" and "Not sweet enough"). When analyzed together with hedonic assessments using penalty analysis, JAR tests provide direction to optimize specific attributes through product reformulation (Lawless & Heymann 2010). JAR scales have been previously used among older patients (Schiffman 1998; Kennedy et al. 2010; Özçagli et al. 2013) and in the optimization of a kefir product for cancer survivors (O'Brien et al. 2017). No previous publication of its use among patients with cancer or comparing the results of patients with cancer and healthy participants has been reported.

Non-sensory factors also influence food choice (Jaeger 2006; Danner et al. 2017). Knowledge of consumers' perception of food products can aid in the development of strategies to improve its consumption (de Andrade et al. 2016). Free word association has been used increasingly over the past decade to understand consumers' perceptions, behaviors, and attitudes towards food products (Ares et al. 2008; Guerrero et al. 2010; de Andrade et al. 2016; Rojas-Rivas et al. 2018). In this rapid simple method (Ares et al. 2008), participants receive a verbal or visual stimulus and provide the first words or phrases coming to their minds (Guerrero et al. 2010). The

spontaneous ideas generated through word association have fewer constraints than interviews or closed questionnaires (Wagner et al. 1996).

Oats stand out among other cereals for their high content of highly digestible quality protein with good amino acid balance, and lipids, particularly unsaturated fatty acids (Klensporf & Jeleń 2008; Rasane et al. 2013; Mäkinen et al. 2016), minerals, vitamins like Vitamin E, avenanthramides (antioxidants) and phenolic compounds. Health benefits associated with oats include glucose lowering effects (Rasane et al. 2013) and reduction of cholesterol and the risk of heart disease attributed to its soluble dietary fiber content of beta-glucan (Government of Canada 2010; European Food Safety Authority 2011; Food and Drug Administration 2018). Most patients with celiac disease can safely consume oats uncontaminated by gluten containing cereals (La Vieille et al. 2016). Oats are a convenient and low cost food product and are highly available in Canada (Bouphasiri & Verchomin 2005). Oat versatility and nutritional content offer opportunities for functional food development (Rasane et al. 2013). Beverages containing oat flour (oat-based beverages) are nutritious alternatives (Vasquez-Orejarena et al. 2018) that could be used as a vehicle for fortification to add nutrients of interest for oncology patients. The aim of this paper is to assess the acceptance of an oat-based beverage for that purpose evaluating its sensory acceptance and perceptions of oats among patients with cancer.

4.2. Materials and Methods

The oat beverage product was a commercially available powdered mix of skim milk powder, oat flour, sugar, xanthan gum and flavoring of natural vanilla, cinnamon or cocoa powder. The product can be mixed with hot or cold milk and when mixed with milk provided protein (9.77 g/serving of 200mL) and vitamin D (272 IU/serving), both nutrients with potential to prevent and reverse low muscle mass in cancer (Prado et al. 2020). Nutrition facts of the product are presented in Table 4.1. The product was fortified to increase protein content and add fish oil. The product brand is confidential and thus, not disclosed.

The overall study design consisted of three studies to achieve the study aim; the first two studies used sensory acceptance testing and a survey was used in the third study. Each study required unique ethics board approval. The sub-objectives of the study were to 1) confirm

acceptance of the product in the clinical setting by patients with cancer and healthy participants; 2) determine acceptance of a fortified formulation; 3) assess consumption and perceptions of oats among patients with cancer.

4.2.1. Evaluation of the oat-based beverage in the clinical setting

The powdered product was mixed with milk at the appropriate temperature using a blender. The blended mix was kept in a thermal carafe and served to each participant right before he/she was going to taste it. The blended product was kept in the carafe up to two hours after preparation. The beverages were evaluated at the Cross Cancer Institute (Edmonton, AB, Canada), the largest comprehensive cancer center for northern Alberta. Participants were recruited in highly transited areas and during patient wait times. Study details were provided and participants consenting to participate evaluated the product. Evaluations were conducted between September 2017 and June 2018. Ethics approval for this study was granted by the Health Research Ethics Board of Alberta (HREBA) Cancer Committee (Ehics ID HREBA.CC-17-0026).

Evaluations were conducted by patients with cancer (n=92) and their accompanying caregivers as well as staff and volunteers (n=136). Participants tasted 80mL of the cold (4°C) or hot (60°C) beverage presented in a 100 mL Styrofoam cup and assessed liking of the product on a 9-point hedonic scale with JAR evaluation of the sweetness, thickness and flavor intensity of the products using 5-point scales (Lawless & Heymann 2010). A combination of flavor/ temperature was randomly selected and prepared each day until each combination was evaluated by at least 30 participants, considering the recommended sample size of 25-50 subjects per product (Stone & J.L. Sidel 2004). Only one product was evaluated by each participant; participants were informed of the beverage flavor before tasting it. Participants provided demographic (sex, age, role (i.e. patient with cancer, caregiver/accompanying a patient, healthcare professional, other), brief clinical information (tumor type, treatment(s) received in the last 3 months), and self-assessed nutrition impact symptoms and food intake on questions drawn from the abridged Patient Generated - Subjective Global Assessment (abPG-SGA), a tool designed and validated to assess nutritional status in cancer (Gabrielson et al. 2013). Information was collected on REDCapTM (Research Electronic Data Capture) software presented on a tablet.

4.2.2. Acceptance of fortified oat-based beverages by healthy participants

The cold chocolate product was fortified to increase the protein content and incorporate fish oil as a source of EPA, both nutrients with anabolic potential and recommended for the oncology population (Arends et al. 2016; Thompson et al. 2017). Different sources and contents of animal and plant protein and fish oil were evaluated and tested at laboratory level until two formulations with a similar sensory profile to the regular (unfortified) product were obtained. The ingredients, energy and nutrient content of the two fortified formulations one with higher protein and fish oil (HPFO), and one with lower protein and fish oil (LPFO), and the regular product are presented in Table 4.1).

The three formulations were blended with cold milk and evaluated by a convenience panel of 60 healthy participants at the University of Alberta. As beverage samples were fortified post-manufacture, evaluations among patients with cancer were not permitted by Health Canada. Each participant evaluated 80mL of each product at 4°C in 90 mL clear plastic containers blinded with three-digit random codes. Samples were presented following a balanced randomized design. Participants completed demographic questions (age, sex, oats products consumed regularly and frequency of consumption of oat products and milk products) and evaluated overall liking on a 9-point hedonic scale and JAR evaluation of sweetness, thickness and flavor intensity of each product using the previously described questionnaire. The sensory science questionnaire was presented on cloud-based sensory evaluation software (Compusense Academic Consortium, Compusense Inc., Guelph, Ontario, Canada). The study protocol was approved by a Research Ethics Board at the University of Alberta (Project No. Pro00075398). All participants completed written informed consent.

4.2.3. Consumption and perceptions of oats among patients with cancer

A survey was used (Appendix C) to assess frequency of consumption, identification of currently consumed oat food products and perception of oats as part of a larger study with a focus on development of fortified snack foods (Chapter 5). No product tasting was performed by study participants. Oat perception was generated through a free-word association task asking patients to indicate the first associations, ideas thoughts or feelings coming to their minds when thinking about oat food products (Guerrero et al. 2010). A convenience sample of 150 adult patients

diagnosed with any cancer, stage and treatment regimen, and able to freely communicate in English, was recruited in the chemotherapy and radiotherapy clinic waiting areas of the Cross Cancer Institute. The study was granted ethics approval by the HREBA Cancer Committee (Ethics ID HREBA.CC-19-0210).

4.2.4. Data analysis

Kruskal-Wallis test was used to assess differences in liking among the products for the temperature, flavor and participant (patients with cancer vs. healthy participants) combinations. Chi-squared tests were used to compare age and sex between patients and healthy participants. Penalty Analysis was conducted on JAR and hedonic scale evaluations (Lawless & Heymann 2010). The two responses for the lower than JAR responses were combined as "Not enough", "Too thin" or "Too weak" and the higher intensity responses were combined as "Too sweet", "Too thick" or "Too strong" for the attributes of sweetness, thickness and flavor intensity, respectively. Frequencies of participants selecting those options were used to create Penalty Analysis graphs representing the drops in mean overall acceptance by a proportion of participants by two groups, patients with cancer and healthy participants (caregivers, staff, volunteers).

Analysis of Variance (ANOVA) was conducted to assess differences in overall liking among the regular and fortified products and to compare liking of the regular beverage among the three participating groups of the first two studies (patients with cancer and healthy participants in study 1 and healthy university participants in study 2). Tukey's multiple comparison tests were conducted when appropriate. Penalty analyses were conducted on JAR results as described previously. All statistical analyses were conducted using XLSTAT software (Addinsoft 2020) at a significance value of $p \leq 0.05$.

Analysis of free-word association responses was conducted as described by Guerrero and others (2010). Frequencies of mentions for all elicited words or phrases were determined and words were grouped into categories which were merged into dimensions. Categorization was conducted independently by three authors (PK, BEF, WW), one experienced in oncology nutrition and two in food science and chemosensory changes in oncology patients. Agreement was reached by consensus. Frequencies of mention of categories and dimensions identified by at

least 5% of the patients are reported as percentages (Guerrero et al. 2010; de Andrade et al. 2016).

4.3. Results

4.3.1. Evaluations of oat-based beverages in the clinical setting.

Participant characteristics are shown in Table 4.2. Most patients were not experiencing a high symptom burden affecting their food intake; a majority (54%) indicated no symptom interference when eating. Among patients experiencing symptoms, the most frequent were fatigue (24%), dry mouth (16%), taste changes (13%) and pain (12%). Food intake in the past month compared to usual was 'unchanged' for 57.6% of patients, 'less than usual' for 28%, and 'more than usual' for 11%. There was no significant difference in the proportion of males/females between patients with cancer and healthy participants, but there was a significantly higher proportion of healthy participants under 65 years ($p<0.0001$).

All products had a mean liking close to 7 ("Like moderately") on the 9-point hedonic scale, indicating products were highly acceptable (Everitt 2009). No significant difference was observed in liking among flavors, temperatures or participant groups, Table 4.3. There was no difference in liking between the hot and cold products.

Despite the lack of significant differences in overall liking, penalty analysis (Fig. 4.1) revealed that perception of non-JAR sweetness ("Too sweet") significantly decreased liking of the cold cinnamon and cold vanilla products among healthy participants and of hot cinnamon among patients with cancer. Flavor intensity was rated as "Just-about-right" by more than 82% of the participants for all products and thus it was not included in the figure. The proportion of participants perceiving attributes as non-JAR and the penalty given differed between patients with cancer or healthy participants. Patients with cancer consistently rated beverage sweetness intensity as JAR or "Too sweet", except for a single evaluation and over 20% of healthy participants perceived the cold vanilla and cinnamon (Fig. 4.1, d and e) products as "Too thin" while this was not observed among patients with cancer. The cold chocolate product was chosen to be fortified as most participants who evaluated the product in the clinical setting considered its sweetness and texture as JAR.

The perception of thickness and sweetness was also influenced by product serving temperature. At hot temperature, 23% of patients with cancer perceived the chocolate flavored beverage as “Too sweet”, but the subsequent penalty on acceptance was low. The product was considered “Too thin” at cold temperatures by over 20% of healthy participants.

4.3.2. Evaluations of oat-based beverages in the clinical setting.

A majority of the participants were female (73%) and between 18 and 29 years (71%). Usual consumption of oats and of milk products was at least once a week for 70% and 73.3% of the participants, respectively. Overall liking of HPFO was not significantly different from the regular formulation; both with values close to “Like slightly” on the hedonic scale and greater than the LPFO formulation (Fig. 4.2).

Just-about-right results provided insight about product perception and the drivers of liking/disliking (Fig. 4.3). Sweetness and thickness of the regular formulation was perceived as JAR by 60% of the participants. Product fortification increased the number of participants considering the products as “too sweet” and “too thick” (Fig. 4.3a and b). Thus, attributes that could be modified to improve acceptance of the fortified products are the high sweetness of all products and the thickness of the low protein fortified product.

The higher protein level through the inclusion of a higher level of whey protein in the HPFO product resulted in increased frequency of participants considering the product as “too thick”, and a lower number of participants perceiving it as “too sweet”, compared to LPFO. Changes in perceived flavor intensity were not straightforward; some participants considered flavor intensity as “too weak’ and others as “too strong”. Flavor identity was not indicated and could have been either the chocolate flavor or the perception of off-flavors. Penalty analysis for the three formulations is presented in Fig. 4.4.

Analysis of variance results comparing liking evaluation for the cold chocolate beverage by the three participant groups revealed that university participants evaluated the product significantly lower in liking ($p<0.001$) (Table 4.4). The proportion of university participants in the age group 18 to 29 years was significantly higher compared to the participants in the clinical setting.

4.3.3. Consumption and perceptions of oats among patients with cancer

Oat food products were consumed by 115 (77%) of the patients and 58% of them consumed oat products at least once per week. The word association task was completed by 89% of recruited patients. The most frequently eaten oat products were oatmeal, oat cereal, cookies and bars. A total of 401 words or ideas related to oats were generated by patients and sorted into 19 categories merged across 6 dimensions (Table 4.5). The positive perception of oats was reflected in a majority of patients who consumed oats regularly. Common words associated with oats were oatmeal or porridge, cookies, filling, fiber, healthy, nutritious, bars and good. Over 92% of patients mentioned Health dimension terms, including nutrients in oats, satiety, and health benefits and detriments. The second most common dimension was food products that described foods made with or commonly eaten with oats. Sensory characteristics and hedonics were mainly associated with taste, liking and texture.

Oat products were also perceived within the context of agricultural and farming and for some participants (6.9%) memories related to childhood or specific moments and persons. Negative associations of oats were related to the presence of chemicals such as pesticides, allergies, genetical modifications (health detriments, 5.6%) and eating challenges (9.0%) such as high content of carbohydrates or swallowing issues.

4.4. Discussion

This is the first study to assess the acceptance of oat-based beverages among patients with cancer. Overall, the three flavors of the oat-based beverage were liked by patients at both cold and hot temperatures, but some indicated that the products were perceived as “Too sweet”. Patients were aware of positive health benefits of oats and consumed them in some form frequently. We assessed the potential of oat-based beverages for fortification with protein and EPA, both nutrients recommended by ESPEN oncology nutrition guidelines (Arends et al. 2016) and studied as potential interventions to prevent muscle loss in this population (Prado et al. 2020). The addition of those nutrients into the chocolate flavored product did not change liking compared to the unfortified product. Our results contribute to the scarce literature available regarding products developed and evaluated in oncology aiming to increase their nutritional intake considering product nutritional and sensory features. These positive results suggest that

oat-based products may be appropriate for nutrient fortification among patients with cancer and could guide future product development in this area.

Liking of the oat-based beverage was not significantly different between patients with cancer and healthy participants. Changes in food preferences, development of food aversions and the presence of symptoms such as taste and smell alterations or oral symptoms are common in this population and can contribute to differences in perception of patients compared to healthy participants (Kubrak et al. 2010; Boltong & Keast 2012; Drareni et al. 2019; Nolden & Reed 2019; Galaniha et al. 2020). As the reported symptom burden by most participants was low, the observed similar comparison of acceptance between these two groups of participants could be due to the age as healthy participants were younger. When comparing liking evaluations of healthy participants and patients with cancer, differences are more likely to be found if the panels are sex- and age or age-matched (Enriquez-Fernández et al. 2019).

The penalty analyses of JAR evaluations of the oat-based beverage in the clinical setting showed an effect of the product's serving temperature. An increased sweetness perception with higher serving temperatures has been previously described for diluted sugar solutions (Bartoshuk et al. 1982) and could be attributed to the high temperature sensitivity of TRPM5, a cation channel with a key role in the perception of sweet, bitter and umami tastes (Talavera et al. 2005). The increased thickness perception in the hot products could be attributed to starch gelatinization induced by heating the products. Although temperature affects the volatility of flavor compounds (Ross et al. 2012), no differences were observed in the perceived flavor intensities.

In this study, patients with cancer were ambulatory and free-living and most reported regular food intake and low symptom presence. Although capturing the perception of patients experiencing a greater number of nutrition impact symptoms would be beneficial, recruitment of those patients is more challenging as they may be less willing to participate in sensory evaluations. Additionally, as with any consumer field test, only the people interested in the product are willing to try them, resulting in an initial positive bias (Lawless & Heymann 2010).

This is the first study in the literature reporting the use of JAR scales among patients with cancer. No issues were reported by the participants with the use of these scales, in agreement with the findings in cohorts of older adults (Methven et al. 2016). Product modification directed by JAR scale results and subsequent product evaluation would confirm JAR scale benefits.

Sweetness levels could be a challenging attribute for JAR evaluation and product reformulation as some patients with cancer avoid sugar-containing products (Depeint et al. 2018). However, only for the hot cinnamon product the high perception of sweetness decreased liking while the same effect was observed among healthy participants for two products (i.e. cold cinnamon and cold vanilla).

The evaluation of fortified products was conducted only in a healthy population. Evaluation of the HPFO by the target population is necessary to confirm fortified product acceptance observed in the healthy population. Moreover, a multi-sip test would reveal if perception of product drivers of liking and disliking change with the consumed volume (Methven et al. 2010).

The number of selected attributes in both sensory evaluations were limited to key product attributes. Additional attributes evaluated in JAR tests could provide more specific product information for reformulation. Assessment of the attribute 'aftertaste' may be relevant as shown by a study evaluating the sensory properties of high protein dairy beverages containing oat beta-glucan, in which the main attributes influencing acceptability were thickness (mouthfeel), sweetness and aftertaste (Vasquez-Orejarena et al. 2018). Sensory evaluations completed by patients with cancer should provide as much information as possible without being too long and burdensome (Wismer 2018).

The free word association results identified non-sensory factors that could influence product consumption. Studies to assess factors that affect consumption of food products among patients with cancer are limited and have used interviews (Ottosson et al. 2013; Hogan et al. 2019) and a repertory grid method (Álvarez-Camacho et al. 2016). Free word association provides less conscious responses and is less laborious compared to other qualitative methods such as interviews (Roininen et al. 2006), hence, it can provide insightful responses without adding extra burden to patients. A majority (89%) of patients completed the task and results identified the main concepts associated with food products for this population.

Overall, the majority of patients consumed oats regularly and oats were considered nutritious and healthy products, high in fiber and related to satiety. The most frequently mentioned terms, considered most relevant for consumer conceptualization of the product and with higher influence in their decisions (Roininen et al. 2006), were specific oat-based food products and health dimensions of filling, fiber, healthy, nutritious and good. Two of the eating challenges

associated with oats (i.e. hard to swallow and hard to eat) were likely associated with oatmeal, a hot cereal, and could be solved by the beverage presentation format. As early satiety experienced by some patients with cancer reduces food intake (Fearon et al. 2003; van der Meij et al. 2012), successful new oat-based food products for cancer patients should consider perceived satiety and serving size.

In this study, patients with cancer were the targeted consumers of nutrient fortified food product formulations. They assessed liking of the original unfortified product as recommended in the early stage of product development to increase product success (Costa and Jongen 2006; MacFie 2007). A limitation of the initial beverage assessment in the clinical setting was the small number of participants for each combination of flavor/temperature among patients with cancer and healthy participants; 25 to 50 consumers per product are recommended for laboratory-based sensory liking tests (Stone and Sidel 2004). Acceptance tests among frail older people typically include less than 50 subjects (Methven et al. 2016), thus sensory assessment studies of food products among older people and those with chronic diseases may routinely have smaller participant numbers than similar assessments in the healthy population. To decrease patient burden and provide the context of the usual eating environment on consumption and perception of food products, home use tests could be used in the oncology setting to generate ecologically valid results (Meiselman 2013; Stelick and Dando 2018). Another study limitation is that recruitment was not targeted to a specific tumor group or stage which may result in variable representation of tumor groups.

Together, the positive sensory acceptance of flavored oat beverages and their perceived and established health benefits, reveal the potential for oats to be included in fortified and unfortified products targeted to patients with cancer. Future developed products must be evaluated by consumer panels of patients with cancer to confirm product and sensory attribute acceptance, which may differ from the healthy population. Furthermore, the evaluated oat-based beverages may be accepted by older adults and other populations with similar nutrient needs and eating challenges.

4.5. Conclusions

Overall, three flavors of an oat-based beverage served at two temperatures showed good sensory acceptance by both healthy participants and patients with cancer. The chocolate flavored beverage was acceptable when fortified with protein and fish oil and could be considered for further product development for oncology patients. Penalty analyses of JAR and hedonic scales revealed that high perception of sweetness significantly influenced liking of the cold cinnamon and cold vanilla products among healthy participants and of the hot cinnamon product among patients with cancer.

Oats and their products were commonly consumed by a majority of participants. Perception of oat food products was associated with specific *food products*, *health benefits* and oat product *sensory characteristics*. Oat food products were considered high in fiber and satiety, nutritious and healthy, while some barriers for their consumption were identified by few patients.

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Table 4.1. Ingredients, protein and fish oil content of the fortified oat-based beverages.

	Regular formulation (R)	High protein, fish oil product (HPFO)	Low protein, fish oil product (LPFO)
Ingredients	Milk, whole oat flour, sugar, xanthan gum, cocoa powder.	R + skim milk (No Name®, Canada), whey protein (Boost®, Nestle Canada), faba bean powder (VITESSENCE™ Pulse CT 3602 Protein, Ingredion, USA), microencapsulated fish oil (Marinol® Omega-3 HS Powder, Stepan Lipid Nutrition, USA)	RF + skim milk (No Name®, Canada), faba bean powder (VITESSENCE™ Pulse CT 3602 Protein, Ingredion, USA), microencapsulated fish oil (Marinol® Omega-3 HS Powder, Stepan Lipid Nutrition, USA)
Fish oil content (g/serving*)	-	0.54	0.54
Protein content (g/serving)	9.77	17.68	13.74
Carbohydrates (g/serving)	26.53	31.69	32.22
Total fat (g/serving)	4.01	6.12	6.26
Dietary fiber (g/serving)	0.89	1.24	1.26
Energy content (kcal/serving)	177.75	247.62	235.18

*Serving size of 200mL of the beverage containing milk and the powdered product; size recommended by the product manufacturer.

Table 4.2. Characteristics of participants evaluating an oat-based beverage in the clinical setting (n=228).

	Number of participants (%)
Sex	
Male	76 (33.3)
Female	152 (66.7)
Age range	
18 - 29 years	17 (7.5)
30 - 49 years	41 (18.0)
50 - 65 years	90 (39.5)
Greater than 65 years	80 (35.1)
Role	
Patient with cancer	92 (40.4)
Caregiver/ accompanying a patient	73 (32.0)
Other (healthcare professional, volunteers)	63 (27.6)
For patients with cancer:	
Tumour site	
Breast	25 (27.2)
Lymphoma / Leukemia	11 (12.0)
Prostate	9 (9.8)
Lung	9 (9.8)
Gastrointestinal	7 (7.6)
Myeloma	7 (7.6)
Head and Neck	6 (6.5)
Other	18 (19.6)
Treatment modality over past 3 months*	
Chemotherapy	46 (50.0)
Radiation therapy	24 (26.1)
No treatment	23 (25.0)
Surgery	10 (10.9)
Other	10 (10.9)

*Total percentage over 100 because some participants were undergoing more than one treatment.

Table 4.3. Mean liking scores[a] of an oat-based beverage in the clinical setting.

Flavor	Temperature*	Mean liking ± Standard Deviation (n=number of participants)	
		Patients with cancer	**Healthy participants**
Chocolate	Cold	7.0 ± 1.3 (n=24)	7.5 ± 0.8 (n=22)
	Hot	7.7 ± 0.6 (n=13)	7.3 ± 1.1 (n=28)
Vanilla	Cold	7.7 ± 0.5 (n=11)	7.5 ± 1.2 (n=24)
	Hot	7.1 ± 1.9 (n=16)	7.2 ± 1.5 (n=17)
Cinnamon	Cold	7.5 ± 0.9 (n=15)	7.5 ± 1.2 (n=22)
	Hot	7.1 ± 1.7 (n=13)	7.5 ± 1.3 (n=23)

[a]9-point hedonic scale where 1=Dislike extremely, 9=Like extremely; *Cold temperature =4°C; hot temperature =60°C.

Table 4.4. Mean liking and standard deviation results for the evaluation of the cold chocolate beverage by patients with cancer (n=92), healthy participants (n=136) (clinical setting) and healthy participants in a non-clinical setting convenience sample (n=60).

Testing location	**Clinical setting**		**Non-Clinical setting**
Participants	Patients with cancer	Healthy participants	Healthy participants
Mean liking ± Standard deviation	6.96[a]	7.50[a]	6.18[b]

*Means with different letters within the same row are significantly different ($p \leq 0.05$).

Table 4.5. Perceptions of oat products among patients with cancer obtained by Free Word Association (n=144).

Dimensions	Categories	Most common words/ terms in descending order of mention	Frequency of mention by patients*
Health			**92.4%**
	Nutrients	Fiber, nutritious, vitamins, protein, energy	25.7%
	Satiety	Filling, fullness, satisfying	19.4%
	General health	Healthy, unhealthy	16.7%
	Health benefits	Easy to digest or aids digestion, gluten-free, lowers cholesterol, heart health, regularity	16.0%
	Eating challenges	Carbohydrate content, hard to swallow, allergies, hard to eat	9.0%
	Health detriments	Pesticides or chemicals, genetically modified	5.6%
Food products			**74.3%**
	Foods from oats	Oatmeal or porridge, cookies, bars, cereal, baking, crisps, muffins	66.0%
	Complementary foods	Milk, maple syrup or flavor, fruits, brown sugar, yogurt	8.3%
Sensory characteristics and hedonics			**67.4%**
	Taste	Tasty, taste, bland, taste good, flavor, little or no taste, plain	20.8%
	Liking	Good, like, love, yummy	18.1%
	Texture	Dry, texture, chewy, crunchy, mushy	13.2%
	Temperature	Warm, hot	8.3%
	Dislike	Not good, yucky, unattractive	6.9%
Consumption details			**23.6%**
	Time of consumption	Breakfast, morning, snack	9.0%
	Ease of use	Easy to eat, easy, easy to cook/ prepare	8.3%
	Other benefits / reasons for consumption	Comfort food, easy to swallow, long lasting, no side effects, sugar-free	6.3%
Agriculture and farming			**11.8%**
	Agriculture	Field, harvest, sunshine fields, farm	6.3%
	Feed	Horses, cows, piglets	5.6%
Memories			**6.9%**
	Memories	Family member, childhood memories	6.9%

* Some percentages higher than 100% as patients could provide up to four responses.

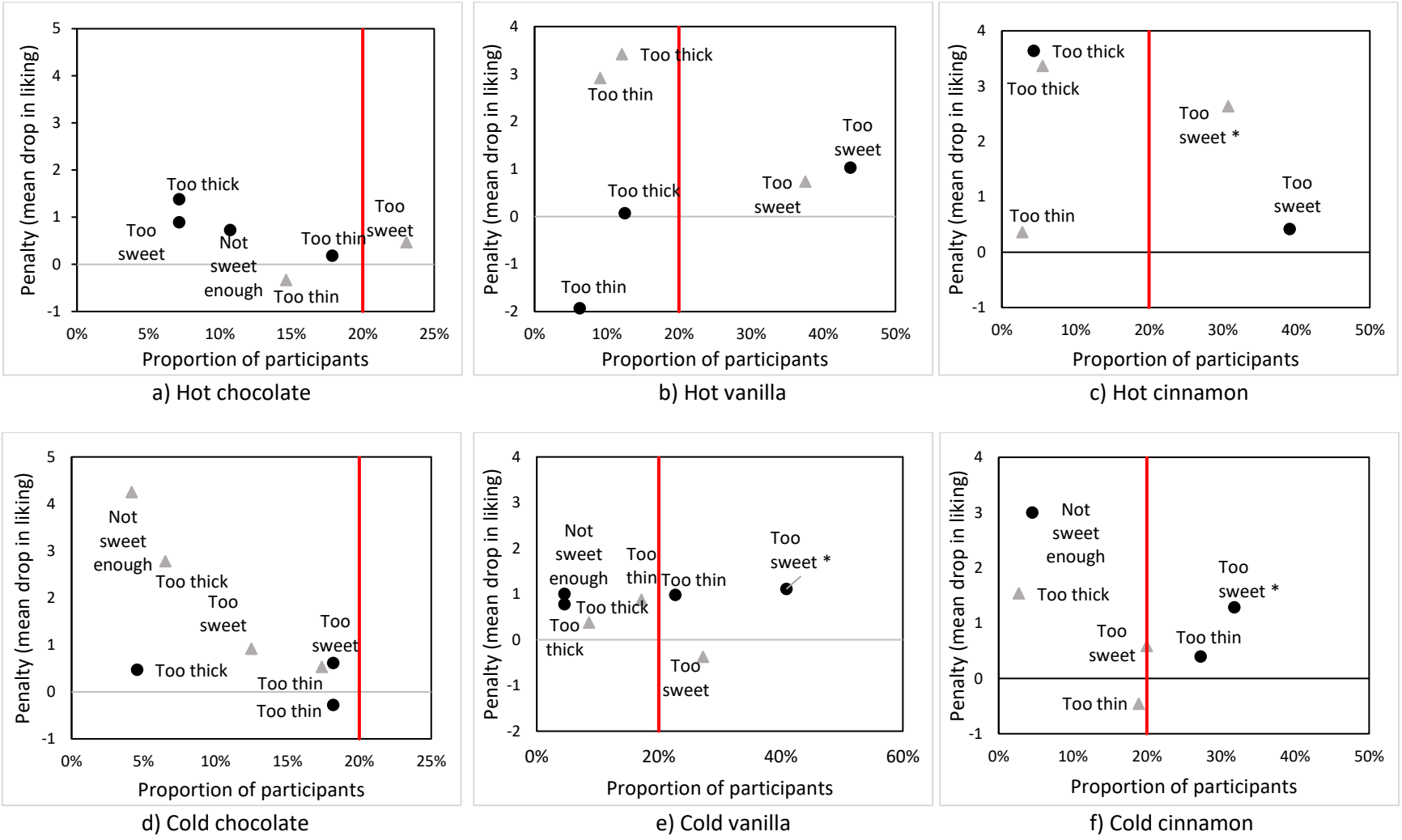


Figure 4.1. Penalty analysis plots for three flavors of oat beverages at hot (60°C) and cold (4°C) temperature evaluated in the clinical setting.

Grey triangles (▲) = evaluations by patients with cancer; Black circles (•) = evaluations by healthy participants. *=Significant non-JAR categories

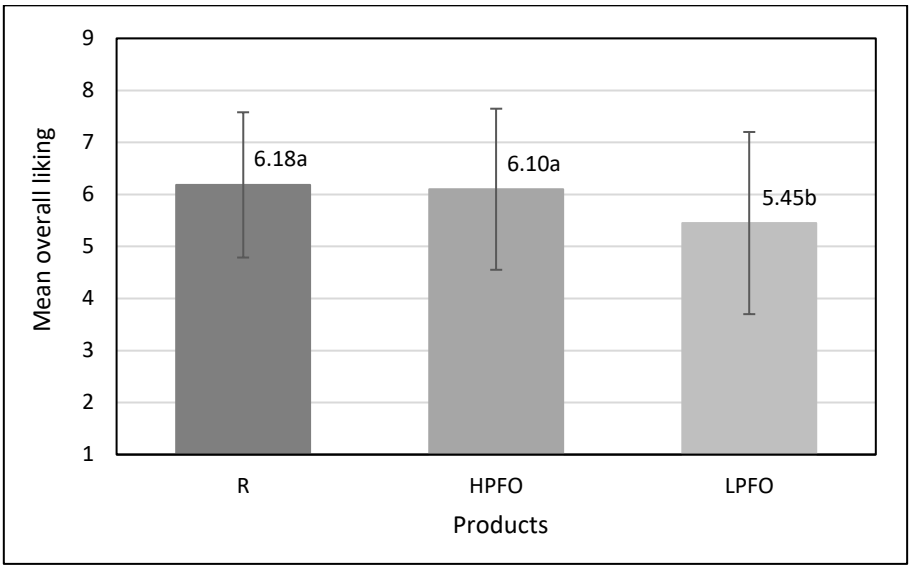
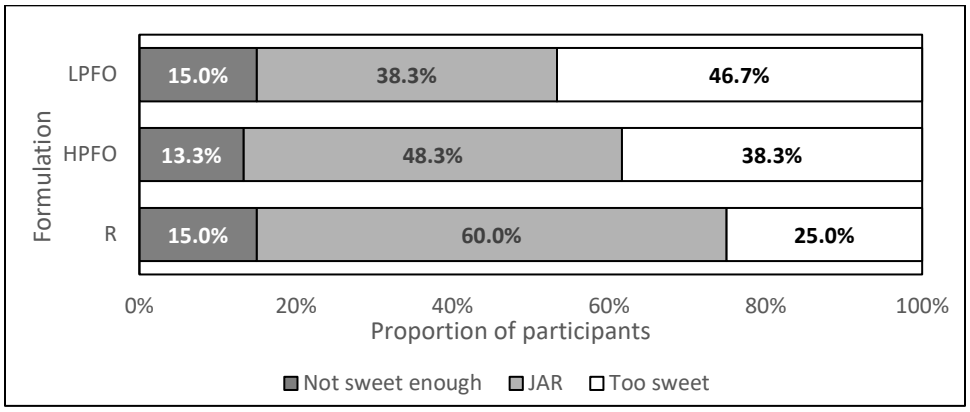
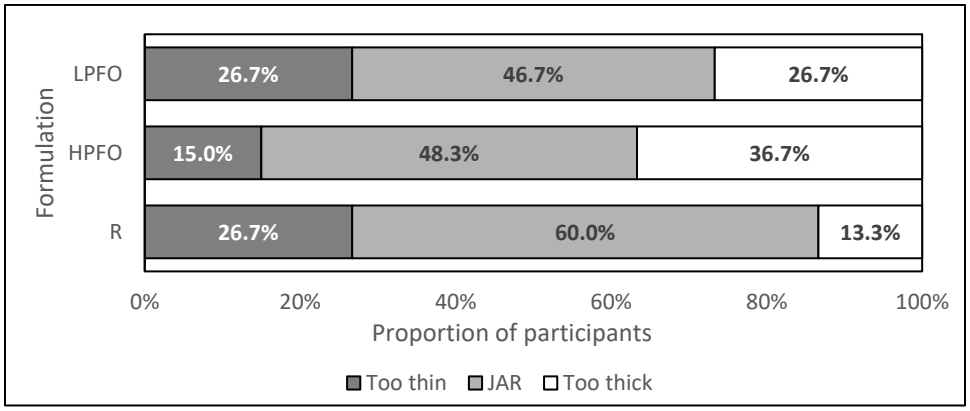


Figure 4.2. Overall liking on the 9-point hedonic scale for the fortified chocolate oat-beverage evaluated by healthy participants (n=60).

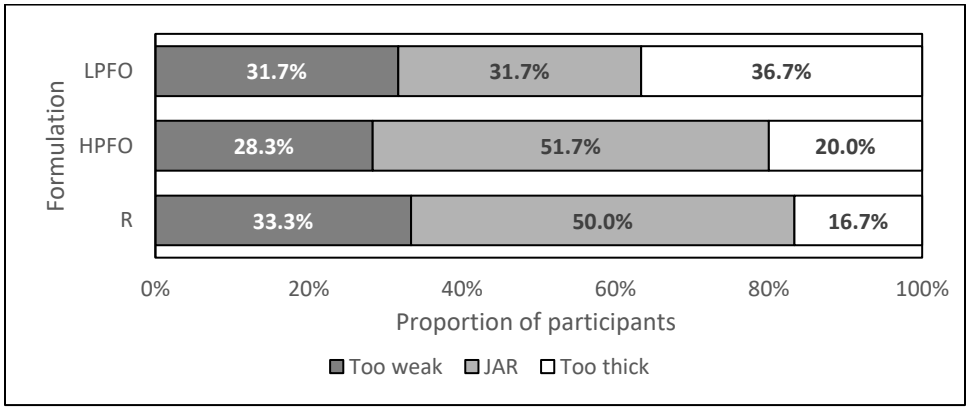
Means with different letters are significantly different ($p \leq 0.05$). R= Regular Formulation; HPFO= High-Protein + fish oil; LPFO= Lower-protein + fish oil.



a)



b)



c)

Figure 4.3. Just-about-right (JAR) results for a) sweetness, b) thickness and c) flavor intensity for the fortified (HPFO, LPFO) and regular (R) products as evaluated by healthy participants (n=60).

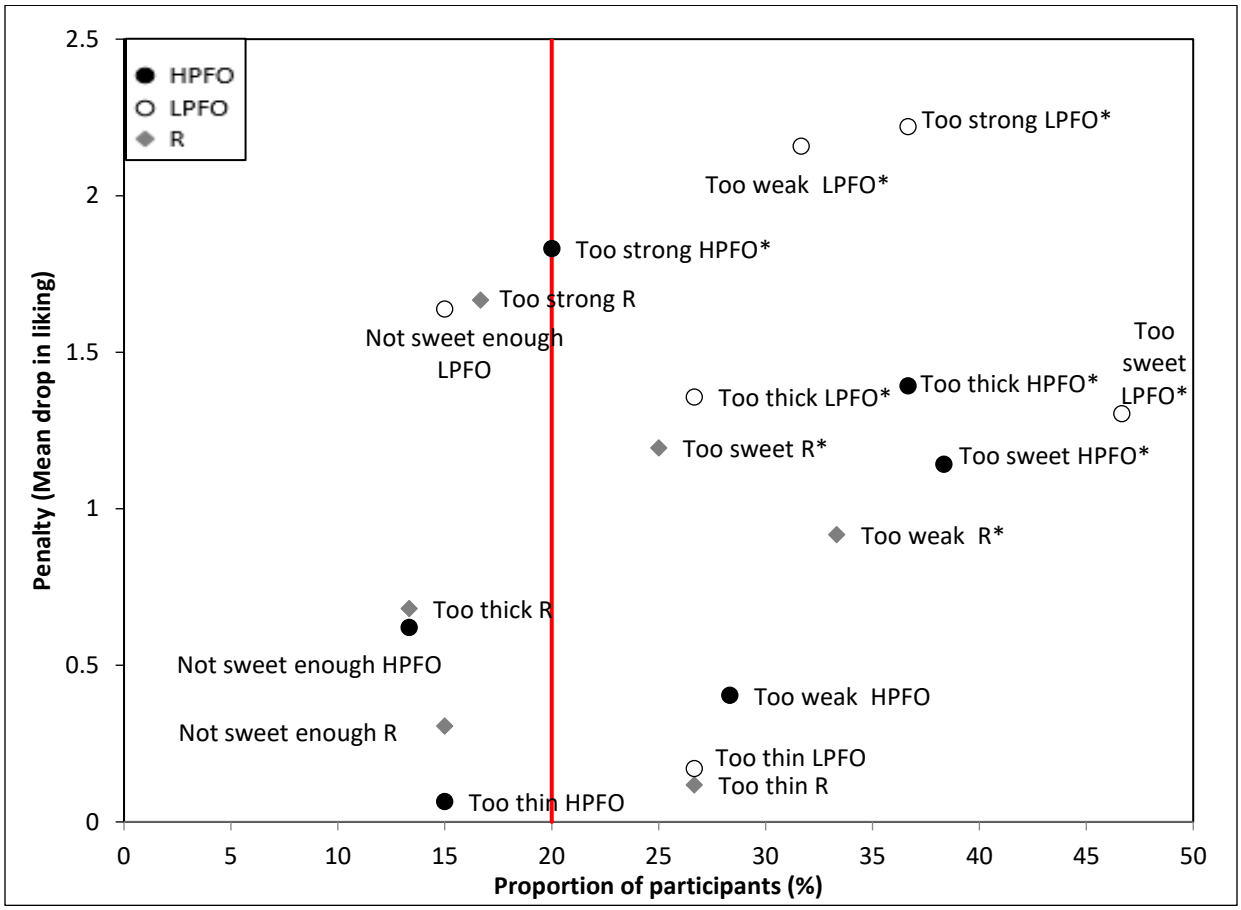


Figure 4.4. Penalty analysis graph for the fortified and regular chocolate oat beverage as evaluated by healthy participants (n=60).

(R= Regular, HPFO= High-protein and fish oil added product, LPFO= Lower-protein and fish oil added product; *= Significant non-JAR categories ($p<0.05$).

CHAPTER 5: Fortified snack preferences among patients with cancer

5.1. Introduction

Reduced food intake and malnutrition are frequent among patients with cancer (Mantzorou et al. 2017) as a consequence of the tumor and its treatment. Diminished appetite and the presence of nutrition impact symptoms contribute to reduced food intake (Arends et al. 2016). Inadequate nutrient intake among patients with cancer has been associated with malnutrition and decreased quality of life, lower performance status, increased toxicities, reduced response to treatment and decreased survival (Aaldriks et al. 2013; Gellrich et al. 2015; Maasberg et al. 2017; Mantzorou et al. 2017). Despite the high incidence of cancer worldwide and the known contribution of appropriate and adequate nutrition to patient outcomes (Gellrich et al. 2015; Mantzorou et al. 2017), specialized nutrition support is not currently accessible to all patients (Ravasco 2019) and few commercially available products have been developed to promote and increase nutrient intake among people with cancer (Tueros & Uriarte 2018).

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines for oncology patients state that "the best way to maintain or increase energy and protein intake is with normal food" (Arends et al. 2016). Snacks, defined as food and beverages consumed in-between main meals have been associated with increased energy and nutrient intake among older adults (Zizza et al. 2007), hospitalized patients (Gall et al. 1998; Mills et al. 2018) and patients with cancer (Hutton et al. 2006; Lindman et al. 2013). Protein intake above 1g/kg body weight/day, vitamins and minerals consumed in amounts equal to the recommended dietary allowance and long-chain omega-3 fatty acids supplementation have been recommended for oncology patients (Arends et al. 2016). Fortification of regular foods with recommended nutrients is a simple alternative to increase intake in this population (Guerdoux-Ninot et al. 2016), especially among patients experiencing symptoms like poor appetite and/or early satiety (Okkels et al. 2016). Fortified foods, such as a ready-to-eat nutritious jelly and fortified ice creams (Casas et al. 2012; Trinidade et al. 2012; Vieira et al. 2018; Valmorbida et al. 2019) have good acceptability ratings among patients suggesting this is a feasible approach.

Current commercially available food products to increase nutrient intake among people with cancer are mainly liquids (soups and milk-, yogurt- or juice-based shakes) and puréed foods

(Woodward 2010; Tueros & Uriarte 2018). While these products target some of patient's nutrient requirements, they fail to consistently address patient preferences, hedonics, the enjoyment and sociocultural aspects of food and eating, and the presence of taste and smell alterations and other nutrition impact symptoms that impact food perception (Casas et al. 2012; Leedo et al. 2017; Tueros & Uriarte 2018). Early identification of consumer needs in food product development increases product success (van Kleef et al. 2005) as success of new food products depends on their ability to meet needs (Van Kleef & Van Trijp 2002) and preferences of the targeted consumer population (van Kleef et al. 2005; van der Zanden & van Trijp 2017). Consumer research methods such as surveys, focus groups, interviews and projective techniques (e.g. word association) have been used to identify potential snack foods for fortification among older adults (Van der Zanden et al. 2014; van der Zanden et al. 2015; Song et al. 2019). In the oncology setting, preferences for snacks were identified through a survey of 222 patients with diverse tumor sites (Danhauer et al. 2009) and by completion of a picture-aided questionnaire among 112 hospitalized hematological patients (Okkels et al. 2016). A survey among 255 patients with different tumor types assessed among other aspects, the preferred characteristics in foods, preferred snacks to eat, consumption of fortified foods and motivations or preference for new fortified products (i.e. frozen, canned, fresh or other) (Guerdoux-Ninot et al. 2016). Research to identify preferred snack food products to be fortified among patients with cancer has not been reported.

The aim of this study was to identify snack foods preferred for fortification among patients with cancer and to determine the influence of experienced symptoms on snack food selection. Specific nutrients of interest to patients, current snack consumption, preferences for snack food products and perception of oral nutritional supplements (ONS) were also evaluated. Perception of ONS was queried as our previous work identified them as a frequently consumed product facilitating micronutrient intake (Nejatinamini et al. 2018). These results could be used to guide new food product development of fortified snacks that appeal to patients with cancer.

5.2. Materials and Methods

5.2.1. Study design and survey contents

This observational study used a self-administered survey specifically designed to assess current preferences for snacks and preferred fortified snacks, as well as nutrition impact symptoms that influence dietary intake and food preferences (Supplementary Material S1). The survey contained five sections:

- Demographics (age range, sex), cancer-related information (primary tumor type and treatment), and presence and interference with eating of 17 symptoms using the Head and Neck Patient Symptom Checklist (HNSC©) (Kubrak et al. 2013).
- Current food intake compared to usual using Question 2 from the Patient Generated - Subjective Global Assessment (PG-SGA Short Form©); number of meals in a day, preferred food characteristics and food aversions as assessed by Guerdoux-Ninot et al. (2016).
- Consumption and perception of ONS among patients consuming them using a free word-association task (Guerrero et al. 2010), an increasingly popular qualitative method to investigate consumer perception of food products (Pontual et al. 2017). Consumers are asked to provide the first words or phrases associated with a visual or verbal stimulus (Guerrero et al. 2010).
- Satisfaction with Food-Related Life (SWFL) using a five-item questionnaire validated among older people (Grunert et al. 2007). Each item is scored from 1 ("Disagree completely") to 7 ("Completely agree"). Total scores range from 5 to 35, where higher scores reflect a greater SWFL.
- Agreement with a list of 33 suggested snack products as suitable vehicles for fortification, assessed on a 5-point Likert scale (1 = "Strongly disagree" to 5 = "Strongly agree". Patients were asked to imagine the products were available with added nutrients and at the same price as the unfortified product. Open space was available to suggest other snacks. The list of snacks included at least one item from each of the categories of commonly consumed snacks in the United States, excluding alcohol and soft drinks (Hess & Slavin 2017). Additionally, patients indicated product characteristics and nutrients or ingredients desired in a fortified snack using Check-All-That-Apply type questions (Ares & Jaeger 2015).

5.2.2. Recruitment procedure

Eligible participants were older than 18 years, diagnosed with any cancer at any stage under any treatment regimen, and able to freely communicate in English. A convenience sample of 150 patients was recruited in the chemotherapy and radiotherapy clinic waiting areas of the Cross Cancer Institute (Edmonton, Canada), the oncology treatment center for northern Alberta. A volunteer or research assistant approached patients and briefly described the study. Interested patients received the survey in which the first two pages described the study details. Patients completed surveys in paper-based form (n=145) or on a tablet device (n=5). A research assistant was available for question clarification and supported patients with writing difficulties. The study was granted ethics approval by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-19-0210).

5.2.3. Data analysis

A total of 11 survey responses were considered invalid and excluded from further analyses because the patients used a single Likert scale response option for all proposed snacks. Agglomerative hierarchical clustering (AHC) was conducted to cluster patients based on similarity of reported symptom presence. Ward's method and squared Euclidean distance measures were used to create the clusters. The basic principle of hierarchical clustering helps in identifying the variables or cases with similar characteristics to form a group or cluster. A symptom was considered "present" if patients reported scores of 2 to 5 ("A little bit" to "A lot") in the symptom presence section of the HNSC© (Kubrak et al. 2013). Symptom interference and total symptom scores were calculated as previously reported (Jin et al. 2019).

Categorical variables were reported as frequencies and percentages. Chi-squared tests were performed to evaluate relationships between two categorical variables. Cochran's Q tests were used for all Check-All-That-Apply questions to assess differences in the frequency of selection for the options. When appropriate, McNemar's multiple comparisons with Bonferroni correction were used. Total scores for SWFL were calculated by summing the scores for all questions and compared among the clusters using one-way analysis of variance (ANOVA).

Free-word association responses were analyzed as described by Guerrero and others (2010). Frequencies of mentions for all valid elicited words or phrases were determined. Words were

grouped into categories which were merged into dimensions. Categorization of the words was conducted independently by three authors (PK, BEF, WW), one experienced in oncology nutrition and two in food science and chemosensory changes in oncology patients; subsequent agreement was reached by consensus. Frequencies of mention of categories and dimensions identified by at least 5% of the patients are reported as percentages. As patients could provide more than one response, frequency percentages are higher than 100% (Guerrero et al. 2010; de Andrade et al. 2016).

Results of the 5-point Likert scales used to assess agreement with the suggested snacks for fortification were considered ordinal and thus, non-parametric, and Kruskal-Wallis test was used to assess differences among the snacks. Dunn multiple pairwise comparisons using Bonferroni correction was used to assess specific differences. Likert scale responses were collapsed into three groups: "Disagree" if options 1 and 2 were selected, "Undecided" for responses of 3 and "Agree" if 4 or 5 were selected. To assess the effect of symptom presence on the agreement with each snack mean value scores for patients with and without specific symptoms were compared . Only symptoms experienced by over 10% of patients were considered significant. All statistical analyses were conducted using XLSTAT software (Addinsoft 2020) and SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A p-value <0.05 was used for statistical significance.

5.3. Results

Results are presented for all 139 patients and by cluster. Most patients were female (58.3%), over 50 years of age (82.7%) and represented a variety of tumor types (Table 5.1). Patients were undergoing treatment, with 92 (66%) undergoing more than one treatment modality. Over 56% of the patients reported consuming the same food intake or higher compared to their normal intake. Among patients with reduced food intake, most (48 out of 60) were consuming "normal" food.

"Low", "High" and "Moderate" patient clusters were identified according to their reported number of symptom present (Table 5.2). Lack of energy and feeling full were the only symptom reported by over 50% of patients in the Low symptom presence cluster. In contrast, patients in

the High symptom cluster had 12 of 17 symptoms reported by over 60% of the patients, and they were more likely to experience difficulty chewing and swallowing, vomiting, and sore mouth. Patients in the Moderate symptom cluster experienced mainly presence of appetite loss, feeling full, diarrhea, lack of energy, nausea and taste changes. Patients in the High symptom cluster had the highest scores ($p<0.05$) for symptom interference with eating (mean=27.3), followed by the Moderate and Low symptom clusters (means=13.5 and 7.8, respectively).

5.3.1. Food intake, snack consumption and satisfaction with food-related life

Patients in High and Moderate symptom presence clusters were more likely to have reduced food intake compared to usual, while patients in the Low symptom presence cluster more commonly reported food intake as unchanged (Table 5.1). No other differences were found when comparing the demographics of the three clusters.

The number of meals consumed throughout the day among all patients varied from 1 to 6; most patients consumed 4 meals. Breakfast, lunch, dinner and afternoon snacks were consumed by 82, 78, 76 and 96% of patients, respectively. Morning snacks were consumed by 57% of patients and were commonly fruits (n=37), bread, pastries and baked goods (n=20), cheese (n=9), yogurt or Greek yogurt (n=8), cookies, including sugar-free (n=6) and crackers (n=6). The most commonly mentioned afternoon snacks were similar to the morning with increased consumption of salty snacks: fruits (n=36), cheese (n=19), bread, pastries and baked goods (n=18), crackers (n=14), nuts and seeds (n=13), chips, popcorn and cheese snacks (n=13), yogurt and Greek yogurt (n=11) and cookies (n=11).

The frequencies of selected characteristics of preferred food products are presented in Figure 5.1. Over 50% of patients indicated preference for salty, sweet or hot food products. Patients in Low and Moderate symptom presence clusters were more likely to select “salty”. Patients in the High symptom presence cluster were more likely to select “creamy” compared to the other patients, and none of the patients in this cluster selected “spicy”.

Forty-four patients (31.7%) reported nausea or aversion to specific foods. The most reported food aversions were spicy foods and peppers (n=10), meat including beef and pork (n=6), coffee (n=3), and tomatoes or tomato-based foods (n=3).

The overall mean for SWFL of all patients was 27.4 (SD=5.6). Patients in the Low symptom presence cluster had significantly higher SWFL mean scores (28.5) compared to the High symptom presence cluster (24.5) ($p<=0.05$). Mean SWFL scores for the Moderate symptom cluster (26.4) were not different compared to the other clusters.

5.3.2. Preferred snacks for fortification

The agreement with each suggested fortified snack differed among the patients (Fig. 5.2). Products with agreement by 60% or more of the patients were soup, yogurt, cheese, fruit juice, egg product and protein bar. Over 30% of patients disagreed that burritos, flavored milk, candies, pretzels, nacho and potato chips, cake, pastries and cookies were suitable. Burritos, non-dairy beverages and puréed fruit or vegetables each had a high frequency of patients neither agreeing nor disagreeing with their suitability for fortification.

Patients in the High symptom presence cluster were more likely to agree with fortification of ice cream bar (data not shown); no other associations were observed between cluster and fortified snack choice agreement. Nutritious, flavorful, convenient, ready to eat, easy to chew or easy to swallow were selected significantly more frequently as desired fortified snack attributes than other characteristics like plain aroma or flavor and coarse, liquid and soft texture (Fig. 5.3). Patients in the High symptom presence cluster more frequently selected the attributes easy to swallow, liquid, soft texture and warm compared to the other clusters.

Over 54% of patients ($n\geq76$) indicated interest in vitamins (all), minerals, protein, antioxidants, fiber, omega-3 fatty acids and a low or null sugar content in a fortified product (Fig. 5.4). The more commonly selected desirable protein sources were plant, egg, meat and dairy ($p<0.05$), while only 13 patients indicated interest in insects as protein source. Calcium, iron, potassium or “All minerals” were more frequently selected compared to the other minerals.

Table 5.3 identifies symptoms associated with significantly decreased or increased agreement of the suitability of a food product as a snack across all patients. As Likert scales are most reliable when treated as non-continuous data, these associations should be considered as trends. The presence of appetite loss, feeling full, or thick saliva influenced a greater number of products compared to other symptoms. Patients experiencing thick saliva were more likely to agree that

viscous products are suitable as fortified snacks. The presence of appetite loss associated with increased agreement of yogurt drink and milk, and the presence of feeling full decreased the agreement of five products as snack formats.

5.3.3. Consumption and perception of ONS

Consumption of ONS was reported by 49% of patients. Patients in the High and Moderate symptom clusters were more likely to have consumed ONS, while a majority (58.7%) of patients in Low symptom cluster had not consumed ONS since their diagnosis. A total of 182 words or ideas mentioned by 69 patients consuming ONS were categorized and grouped into 3 dimensions (Table 5.4). The most frequently mentioned words were protein, taste, thick, filling and the name of product brands.

The dimension Sensory characteristics was most frequently mentioned. Most words in this dimension are related to positive characteristics (taste, flavor, specific preferences); negative perceptions included too sweet, bland taste and dislike. Specific nutrients such as protein, health benefits and reasons for consumption and satiety related words were frequent in the Nutrition and health dimension, as well as perceived health detriments and consumption challenges.

Overall, the perception was divided with some patients finding ONS appealing, satisfying, healthy and to provide benefits, while others indicated barriers for the consumption of these products including disliking, high sweetness and induction of nausea or vomiting. The patient description "… drink because good for me not because I like them" reflects the perception of the benefits of these products despite their low acceptance for some patients. Statements like "Useful when I can't eat", or "When extreme fatigue or lack of appetite" suggest that ONS can be particularly useful for patients experiencing nutrition impact symptoms interfering with their food intake, which may explain the higher consumption observed among patients in the High symptom cluster in this study.

5.4. Discussion

This is the first study to identify snack foods that patients with cancer consider suitable for fortification and to evaluate the presence of nutrition impact symptom on snack product choice.

Given the few commercially available food products to promote and increase nutrient intake among people with cancer (Tueros & Uriarte 2018) and the impact of the vehicle or carrier on acceptance and perceived healthiness of fortified products (Ares & Gámbaro 2007; Bimbo et al. 2017; Song et al. 2019), the selection of the appropriate carrier is of utmost importance. Soup, yogurt and cheese, fruit juice, egg products, and protein bars were selected by 60% or more of the patients as suitable fortified snacks. Associations between symptoms presence and the desired snacks, their attributes, preferred characteristics in foods, ONS consumption and SWFL were found, highlighting the influence of symptom presence.

Soup was considered a suitable fortified snack by the majority of patients. In a survey among 1199 patients with cancer, soup was among the five preferred foods (Coa et al. 2015). Soup has many of the most frequently selected preferred food characteristics (salty, hot) and desired snack characteristics (easy to chew and swallow and can be flavorful and nutritious) identified by patients. Additionally, it is a comfort food (Spence 2017) and was mentioned as a quick and easy food choice among patients with chemosensory alterations (Bernhardson et al. 2012). In our survey, yogurt and cheese also had high agreement as fortified snacks. In a study of patients with head and neck cancer, consumption of yogurt, milk, milk-based beverages, soups and oral nutritional supplements increased after treatment compared to intake before treatment (Nejatinamini et al. 2018), suggesting their suitability with increased symptom presence.

While food products may be accepted as snacks for regular consumption, preferences for fortification vehicles are affected by their perceived healthiness, with healthier products preferred among older adults (Siegrist et al. 2008; Van der Zanden et al. 2014; Song et al. 2019). Our results identify fruits, cheese and yogurt as currently preferred snacks suitable for fortification. However, bread, pastries and baked goods, cookies, crackers and some salty snacks were identified as current snack choices but showed lower agreement as suitable nutrient fortification vehicles. Three previous studies evaluated preferences for unfortified snack foods in general (Guerdoux-Ninot et al. 2016) or to be offered in the clinic or hospital (Danhauer et al. 2009; Okkels et al. 2016). Some of the preferred reported products were selected by patients in our survey.

The high frequency of selection of nutritious, flavorful, convenient and ready to eat as desired attributes in fortified snacks reported by the survey respondents have also been identified as

motivators for snack consumption among healthy US adults (Bloom 2019). The frequency of selection of easy to chew and easy to swallow highlights the importance of texture on food preferences and could have been influenced by the age group of the participants in which dysphagia and xerostomia can be common (Hall & Wendin 2008). Similar to our results, a survey among 255 French patients with cancer patients revealed that taste, nutritional value and prescription were the main motivators for purchasing a new dietary product (Guerdoux-Ninot et al. 2016). Food attribute preference for hot and small pieces was also observed among French patients. The preference for salty products over sweet ones reported in their study may reflect cultural differences between French and Canadian taste preferences.

Protein or specific amino acids, omega-3 polyunsaturated fatty acids and micronutrients (e.g. vitamin D) provide recognized benefits among patients with cancer (Arends et al. 2016; Ravasco 2019). Our research identifies vitamins, minerals and protein as nutrients of interested to patients. It is unknown if patients selected those nutrients due to their familiarity or their perceived nutritional benefits. Expressed interest in reduced sugar content of foods has been previously documented (Bernhardson et al. 2012; Depeint et al. 2018). Cannabinoids, recently approved for addition to foods in Canada, were of little interest. Higher acceptance has been reported for fortified foods in which added nutrients are perceived as a "natural" match with the fortification vehicle (Ares & Gámbaro 2007; Bimbo et al. 2017). Therefore, potential snack products for future studies could include egg products with increased omega-3 fatty acids and/or protein, or dairy products (yogurt and cheese) with increased protein content or added, calcium and vitamins D and A.

Our convenience sample represented a broad group of patients with a diversity of symptoms experiences, not only those struggling with food intake and a high symptom presence. Patients with all types and stages of cancer undergoing any type of treatment were included to reflect the heterogeneity of this population (Guerdoux-Ninot et al. 2016) and the practicality of developing fortified food products preferred and consumed by a general cancer population. However, we recognize that patients undergoing specific treatments or with tumors such as head and neck cancer might have particular preferences and needs for fortified food products as they frequently experience a high burden of nutrition impact symptoms (Kubrak et al. 2013) that influence their characterization of food (Álvarez-Camacho et al. 2016). Given that highly symptomatic patients

might be less interested and willing to respond to surveys, our results may not reflect the preferences of those patients.

Clustering by symptom presence effectively stratified patients and permitted association between symptom presence and proposed snacks, their desired attributes, current food consumption and attributes of preferred foods, consumption of ONS and SWFL. Patients in the High symptom cluster had lower food intake, interest in creamy, easy to swallow, liquid, soft and warm foods, and had low preference for salty and spicy foods which may have contributed to their higher consumption of ONS. Similarly, consumption of ONS has been reported to be more common among patients with advanced cancer and head and neck cancer with high consumption of other liquid foods (Hutton et al. 2006; Nejatinamini et al. 2018). The presence of lack of energy, taste changes, appetite loss, difficulty chewing and dry mouth has been associated with reduced food intake (Kubrak et al. 2013; de Vries et al. 2017), and lower intake of specific foods among patients with breast cancer compared to healthy controls (de Vries et al. 2017). The presence of multiple prevalent symptoms could complicate the identification of desired fortified products. Future studies could assess in detail the effect of symptoms presence, frequency and severity on preferences of patients with cancer for fortified foods as it is so clearly linked to food choice.

Surveys were an effective method to capture patient preferences. Their completion during wait times favored patient participation. Although use of software is desirable for its security features and item randomization, preference for paper-based surveys over the use of electronic devices was observed.

Perception of ONS focused on product sensory characteristics, confirming the importance of sensory attributes as for any food product. The use of ONS is recommended to accompany nutritional counselling for patients at risk of malnutrition (Arends et al. 2016). However, these products have been criticized for failing to consider patient preferences and food enjoyment (Trinidade et al. 2012; Tueros & Uriarte 2018). Patient comments indicated use of and acknowledged nutrition support provided by ONS, particularly when the symptom experience was high.

In this survey, preferences were assessed on potential food products and products ideas rather than actual fortified snacks. Considering the importance of symptom presence and sensory

attributes on product acceptance and perception, future studies among patients with cancer are needed to assess the taste and other sensory attributes of newly developed fortified snack foods in the context of their usual consumption.

5.5. Conclusions

The suitability of foods as fortified snacks among patients with cancer was evaluated through a survey. Higher frequencies of participant agreement were observed for soup, yogurt, cheese, fruit juice, egg products and protein bars. Some differences between snacks currently consumed by patients and those perceived as potential or fortified snacks were observed, suggesting an influence of the perceived healthiness of products on their suitability for fortification. Nutritious, flavorful, convenient, ready to eat, easy to chew or easy to swallow were characteristics desired in a fortified snack.

Low, Moderate and High symptom presence clusters of patients were identified. Some associations were observed between symptom presence and the preferred characteristics in foods, desired attributes for fortified snacks, ONS consumption and SWFL. Patient perceptions of ONS focused on both positive and negative sensory qualities of the product. Nutrition support provided by ONS consumption was acknowledged, particularly when the symptom experience was high.

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Table 5.1. Demographic characteristics of all patients and 3 patient clusters of symptom presence*.

	All patients (n=139)	Low symptom presence (n=92)	High symptom presence (n=28)	Moderate symptom presence (n=19)
Sex				
Female	81 (58.3)	54 (58.7)	15 (53.6)	12 (63.2)
Male	58 (41.7)	38 (41.3)	13 (46.4)	7 (36.8)
Age				
30-49	24 (17.3)	13 (14.1)	5 (17.9)	6 (31.6)
50-65	56 (40.3)	37 (40.2)	12 (42.9)	7 (36.8)
Over 65	59 (42.4)	42 (45.7)	11 (39.3)	6 (31.6)
Cancer types				
Breast	32 (23)	24 (26.1)	5 (17.9)	3 (15.8)
Gastrointestinal	19 (13.7)	10 (10.9)	6 (21.4)	3 (15.8)
Colorectal	12 (8.6)	7 (7.6)	1 (3.6)	4 (21.1)
Lung	12 (8.6)	9 (9.8)	3 (10.7)	-
Non-Hodgkin lymphoma	11 (7.9)	7 (7.6)	3 (10.7)	1 (5.3)
Head and neck	7 (5%)	2 (2.2)	5 (17.9)	-
Other type[a]	53 (38.1)	33 (35.9)	5 (17.9)	8 (42.1)
Treatment(s) received in last three months				
No medical treatment	26 (18.7)	18 (19.6)	5 (17.9)	3 (15.8)
CT	48 (34.5)	34 (37	8 (28.6)	6 (31.6)
CRT	13 (9.4)	6 (6.5)	5 (17.9)	2 (10.5)
Immunotherapy	13 (9.4)	9 (9.8)	3 (10.7)	1 (5.3)
Surgery	2 (1.4)	1 (1.1)	-	1 (5.3)
Surgery + CT	12 (8.6)	8 (8.7)	2 (7.1)	2 (10.5)
Surgery + CRT	4 (2.9)	2 (2.2)	-	1 (5.3)
Surgery + RT	2 (1.4)	1 (1.1)	-	1 (5.3)
RT	6 (4.3)	3 (3.3)	3 (10.7)	-
Immunotherapy + other treatment modality	9 (3.6)	6 (4.3)	1 (3.6)	2 (10.5)
Other (experimental drug, drug trial, hormonal therapy)	4 (2.9)	2 (2.2)	1 (3.6)	1 (5.3)

[a] Tumor types with less than 10 patients: Bone, brain, gynecological, head and neck, Hodgkin lymphoma, leukaemia, liver, melanoma, multiple myeloma, prostate, thyroid, metastasized to more than one site.

* Clusters determined by agglomerative hierarchical clustering.

Table 5.2. Number and frequency (%) of patients indicating the presence[a] of each symptom for the whole population and categorized by clusters[b].

	All patients	Low symptom presence (n=92)	High symptom presence (n=28)	Moderate symptom presence (n=19)	Association between cluster and variable
Symptom					
Pain	**70 (50.4)**[C]	43 (46.7)	**23 (82.1)**	4 (21.1)	*
Anxiety	63 (45.3)	33 (35.9)	**21 (75.0)**	9 (47.4)	*
Dry mouth	61 (43.9)	37 (40.2)	**20 (71.4)**	4 (21.1)	*
Loss of appetite	**71 (51.8)**	31 (33.7)	**25 (89.3)**	**16 (84.2)**	*
Constipation	53 (38.1)	27 (29.3)	**21 (75.0)**	5 (26.3)	*
Feeling full	**86 (61.9)**	**46 (50.0)**	**26 (92.9)**	**14 (73.4)**	*
Depression	43 (30.9)	19 (20.7)	**17 (60.7)**	7 (36.8)	*
Thick saliva	35 (25.2)	15 (16.3)	**18 (64.3)**	2 (10.5)	*
Diarrhea	51 (36.7)	26 (28.3)	13 (46.4)	**12 (63.2)**	*
Sore mouth	30 (21.6)	14 (15.2)	13 (46.4)	3 (15.8)	*
Lack of energy	**94 (67.6)**	**48 (52.2)**	**27 (96.4)**	**19 (100)**	*
Nausea	44 (31.7)	13 (14.1)	**16 (57.1)**	**15 (78.9)**	*
Difficulty chewing	17 (12.2)	10 (10.9)	6 (21.4)	1 (5.3)	NS
Smells bother you	49 (35.3)	22 (23.9)	**19 (67.9)**	8 (42.1)	*
Vomiting	11 (7.9)	4 (4.3)	5 (17.9)	2 (10.5)	NS
Difficulty swallowing	23 (16.5)	11 (12.0)	10 (35.7)	2 (10.5)	*
Taste changes	69 (49.6)	33 (35.9)	**26 (92.9)**	**10 (52.6)**	*
Food intake compared to normal[d]					
More than usual	13 (9.4)	6 (6.5)	6 (21.4)	1 (5.3)	*
Unchanged	66 (47.5)	54 (58.7)	5 (17.9)	7 (36.8)	*
Less than usual	60 (43.2)	32 (34.8)	17 (60.7)	11 (57.9)	*

[a] Score of 2 to 5 ("A little bit" to "A lot") selected in the symptom presence section of the Head and Neck Symptom Checklist©.

[b] Clusters determined by agglomerative hierarchical clustering according to reported symptom presence.

[c] Symptoms present for 50% or more patients within each cluster are bolded.

*$p<0.05$.

NS: Not significant difference between groups

Table 5.3. Associations* between symptom presence and agreement scores of snack products (n=139).

Symptom	Products with increased agreement	Products with decreased agreement
Anxiety	Chocolate	
Appetite loss	Yogurt drink, milk	Soy, almond or rice beverage
Depression	Yogurt drink	
Difficulty chewing	Flavoured milk	
Difficulty swallowing	Flavoured milk	
Dry mouth		Meat product
Feeling full		Fruit juice, vegetable juice, cookies, pretzel, burritos
Lack of energy	Pudding or custard, yogurt drink	
Nausea	Flavoured milk	
Pain	Iced coffee or tea	Protein bar, fish product
Taste changes	Oral nutritional supplements	
Thick saliva	Oral nutritional supplements, porridge, mashed potatoes, yogurt drink	

* Associations obtained through penalty analysis of symptom presence scores and Likert scale responses.

Table 5.4. Perceptions of oral nutritional supplements obtained from free-word association (n=69).

Dimensions	Categories	Most common words/ terms in descending order of mention	Frequency of mention by patients*
Sensory characteristics			**Over 100.0%**
	Taste and flavour	Taste, sweet or too much sugar, bland, not flavourful, flavour	38.4%
	Like / preference	Good, tasty, OK, preferred flavour, preferred brand	32.9%
	Dislike	Don't like, gross, unappealing, yucky, awful, not good in long run	17.8%
	Texture	Thick, chalky, creamy, gritty	17.8%
	Temperature	Cold, temperature	6.8%
Nutrition and health			**97.2%**
	Nutrients	Protein, vitamins and minerals	20.5%
	Health benefits or consumption reasons	Useful/safe when can't eat, healthy, supplement, settles stomach, soothing, when extreme fatigue or lack of appetite, maintain health	20.5%
	Satiety	Filling, satisfying, satisfies hunger, full	19.2%
	Health detriments and consumption challenges	Too much sugar, nauseating, stomach-ache, diarrhea, feel like vomiting, oil-based, hard to swallow, healthy meals would have same effect	15.1%
	Nutrition	Nutrition, nutritious, nutrients, oral nutrition	12.3%
	Energy and weight	Energy, weight gain, calories, weight maintenance	9.6%
Other characteristics			**31.5%**
	Brands	Ensure, Boost	15.1%
	Convenience	Quantity, convenient, easy, quick, simple	8.2%
	Time/ way of consumption	Breakfast, morning, in between meals	8.2%

* Frequency percentages can be higher than 100% as patients could provide more than one response.

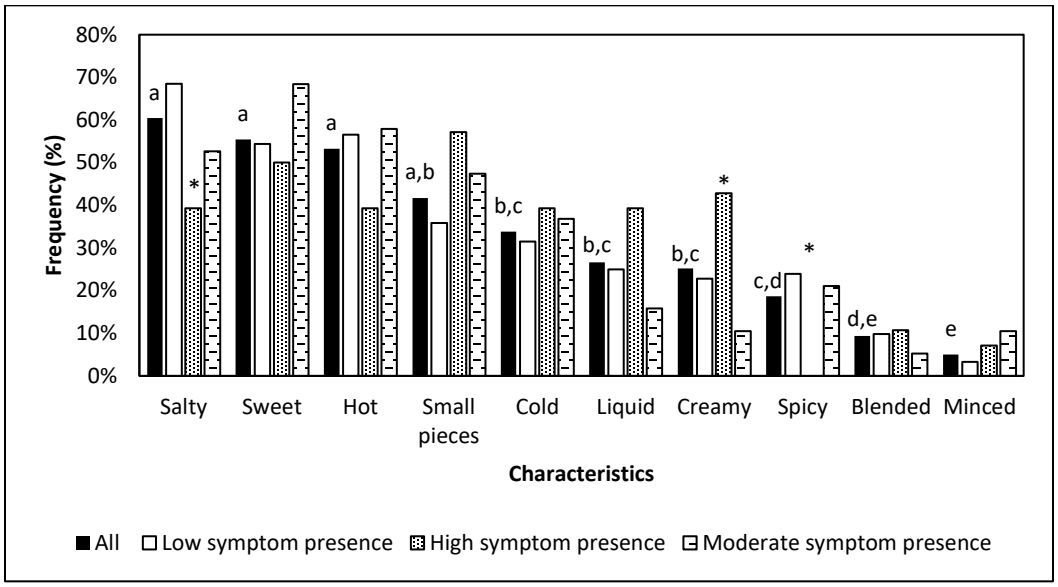

Figure 5.1. Characteristics of food products preferred by patients with cancer (n=139).
Different letter superscripts indicate significant differences in the frequency of selection among all participants ($p<0.05$). * indicates differences in frequency of selection among the clusters.

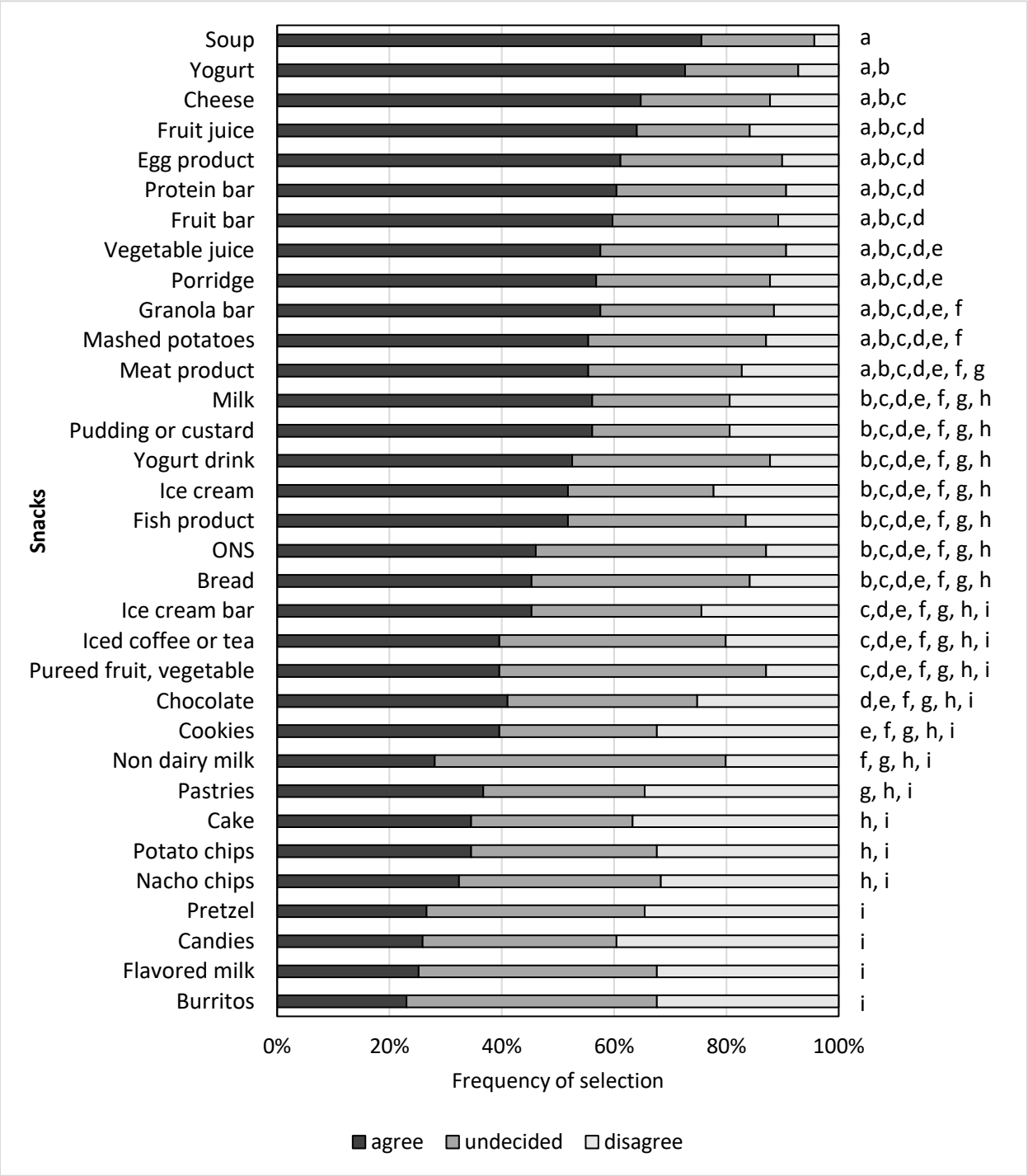

Figure 5.2. Frequencies and agreement levels for snacks proposed for fortification.

Different letter superscripts indicate significant difference ($p<0.001$).

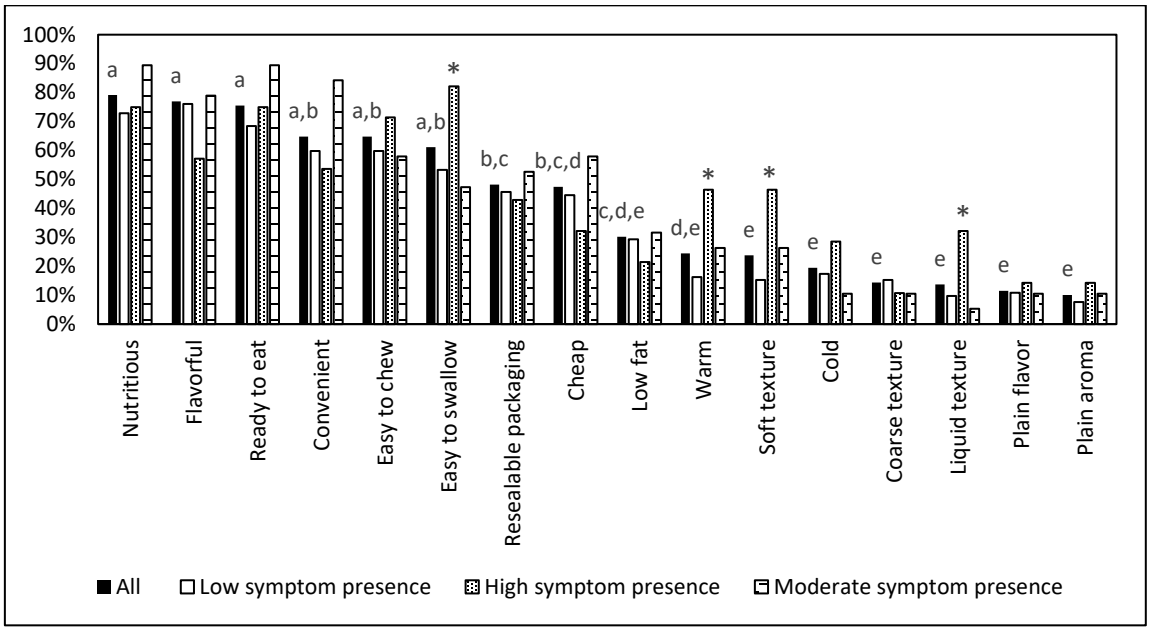

Figure 5.3. Frequencies of selection for characteristics patients would like to have in a nutrient-enhanced snack (n=139).

Different letter superscripts indicate significant differences in the frequency of selection for all participants ($p<0.001$). * indicates differences in frequency of selection among the clusters.

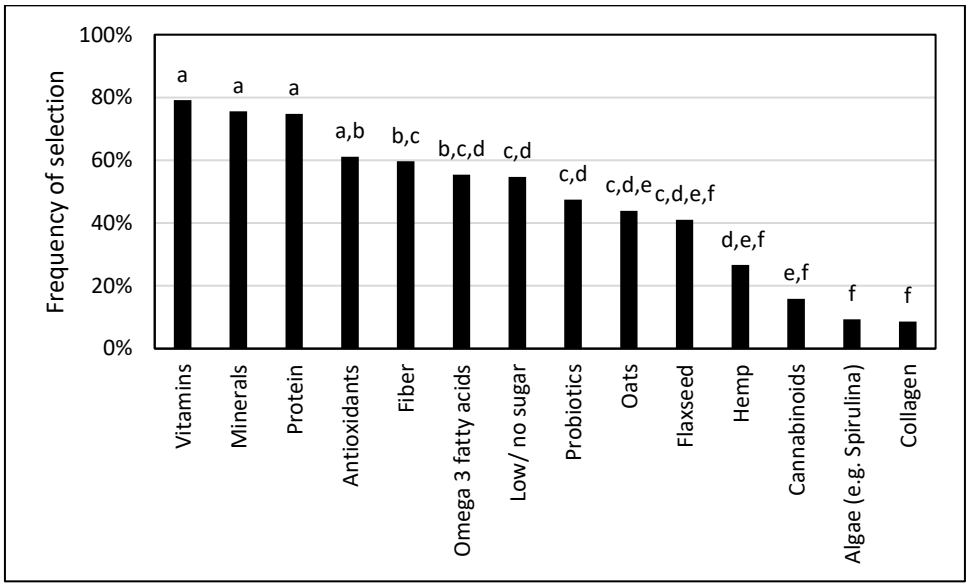

Figure 5.4. Frequencies of selection of nutrients patients would like to have in a nutrient-enhanced snack (n=139).

Different letter superscripts indicate significant differences in the frequency of selection for all participants ($p<0.001$).

CHAPTER 6: Proposed protocol for a 14-day feasibility trial of daily consumption of a supplemented beverage by patients with head and neck cancer

6.1. Introduction

Maintaining appropriate nutritional intake is important in cancer management because it directly impacts patient QOL, improves nutritional status, reduce complications and improves prognosis (Ravasco et al. 2004). Inadequate nutrition intake has been associated with poorer outcomes such as increased morbidity, prolonged length of hospitalization, increased treatment toxicities , decreased performance status, reduced response or tolerance to cancer treatment and diminished QOL (Senesse et al. 2008; Laky et al. 2010; Tan et al. 2015).

Cancers of the head and neck include a heterogeneous group of tumours in these regions, including the larynx, pharynx, oral and nasal cavities, salivary glands and paranasal sinuses (Argiris et al. 2008). The presence of symptoms caused by the disease and its treatment presents a barrier to oral nutritional intake and contributes to cancer related malnutrition (Omlin et al. 2013). Nutrition impact symptoms (NIS) include pain, fatigue/weakness, vomiting, nausea, appetite loss, constipation, dry mouth, early satiety, anxiousness and taste and/or smell changes (Barbera et al. 2010; Aklan et al. 2014). Patients with HNC are a particularly vulnerable group due to the additional NIS caused by the cancer site, including mouth sores, xerostomia, difficulty chewing and swallowing, all compounding to reduced food intake (Kubrak et al. 2010).

People with cancer undergoing treatment modify their dietary intake after cancer diagnosis (Gavazzi et al. 2018). Dietary changes can be motivated by aiming to adopt a healthier diet, manage specific eating related symptoms or tumour related complaints (Gavazzi et al. 2018). Changes in food habits can include more healthy eating, increase in fruit and vegetable consumption, eating more nutrient dense foods or avoidance of specific foods or nutrients (e.g. eating less red and processed meat, sugary foods or less fat), considered unhealthy or due to food aversions (Patterson et al. 2003; Danhauer et al. 2009; Gavazzi et al. 2018). Patients with HNC commonly eat foods characterized as easy to eat or having a low potential to worsen symptoms, and avoid foods characterized as having a dry texture, even at 4-10 months following the end of treatment (Álvarez-Camacho et al. 2016). Therefore, nutritional counselling or any food product

focused on increasing the dietary intake of this cancer population must consider the symptoms experienced by the patients and promote the consumption of products that will not worsen symptoms and will create an enjoyable eating experience.

Dietary counselling with or without oral nutritional supplements (ONS) has been effective to increase body weight and nutritional intake among malnourished patients (Ravasco et al. 2005; Baldwin & Weekes 2011). However, use of ONS has to be considered carefully because it may substitute for voluntary dietary intake, causing caloric or nutrient intake to remain the same or be reduced (Fearon et al. 2003; Woodward 2010). Moreover, use of ONS can be limited by low acceptance of its sensory characteristics (taste, colour, flavour, aftertaste, texture and palatability) (Bolton et al. 1992; Rahemtulla et al. 2005; Brown et al. 2013), development of taste fatigue (Ravasco 2005) or patient preference for food products (Danhauer et al. 2009; Prado et al. 2012) unless food choices are limited to the consumption of other liquid foods (soups, juices) (Hutton et al. 2006; van der Meij et al. 2012).

Additionally, anorexia (appetite loss) and early satiety are NIS that impact ONS consumption. Early satiety, the desire to eat associated with a subsequent inability to eat except for small amounts, due to a sense of fullness (Davis et al. 2006) is a commonly reported symptom and has an impact on suboptimal adherence with ONS consumption (van der Meij et al. 2012). Moreover, greater weight loss with ONS consumption compared to food consumption at similar energy intakes in the absence of nutritional counselling has been reported (Giles et al. 2016). Considering all those factors, alternatives to nutritionally complete ONS may achieve higher nutrient intakes among patients. As stated in the ESPEN Guidelines on Nutrition for Patients with Cancer, “the best way to maintain or increase energy and protein intake is with normal food” (Arends et al. 2016).

6.1.1. Use of highly nutrient dense snacks to increase nutrient intake

In a study where 24-hour dietary recalls were evaluated for over 2000 older adults, it was observed that people consuming snacks (food in between meals) had significantly higher energy, protein, carbohydrate and fat intakes, with snacks contributing 22.5% of their daily energy intake (Zizza et al. 2007). In the same way, hospitalized elderly and orthopedic patients consuming fortified meals and between meal snacks improved energy and protein intakes (Gall et al. 1998).

This strategy of offering between meal snacks may also improve the caloric and nutrient intake among people with cancer for whom low appetite and early satiation can be present. In fact, the American Cancer Society recommends the consumption of snacks throughout the day to meet the caloric needs among patients losing weight. Recommended snacks are those rich in protein and easy to prepare (The American Cancer Society editorial content medical team 2019).

Dietary changes experienced by patients undergoing treatment have been explored in some cancer populations. Among patients with advanced lung and colorectal cancer, the largest proportion of calories was acquired from meats (16% of the caloric intake) followed by other foods (11%; includes condiments, alcoholic beverages, drink crystals, soft drinks and hard candies), desserts (9%), fruits (9%), white bread (7%) and milk (7%). Interestingly, only 5% of patients consumed meal replacement supplements (Prado et al. 2012). When the food intake patterns of patients with advanced cancer were characterized, similar food categories (meat, desserts, fruit, milk and white bread in descending order) were the greatest contributors to caloric intake (Hutton et al. 2006). A significant relationship was found between the number of eating occasions (eating frequency) and total caloric intake, in which snacks or small meals consumed frequently throughout the day resulted in higher caloric intakes (Hutton et al. 2006).

The described dietary patterns suggest an opportunity to provide nutritious products in the form of desserts, snacks, and beverages to patients with cancer. This study proposes the use and evaluation of an oat-based supplemented food product consumed in between-meals to increase micro and macronutrient intake of patients with HNC.

6.1.2. Supplemented food products (SFP) as snacks for people with cancer

As a nutritious alternative that can be easily prepared at home, this study proposes to evaluate the feasibility of daily consumption of an oat-based supplemented food product by patients with HNC. The commercially available product is a dry blend of dry skim milk, wheat-free whole oat flour, sugar, xanthan gum and either natural vanilla flavour, cinnamon or cocoa powder, respectively, for each flavour (vanilla, cinnamon and chocolate) designed to be mixed with milk, water, yogurt or fruits to create smoothies and other beverages. This novel presentation represents an alternative to consume oats throughout the day. The potential of the products to be incorporated into the diet is increased by the option to consume it either hot or cold.

Oats contain high amounts of valuable nutrients such as dietary fibre, ß-glucan (soluble fibre), proteins, unsaturated fatty acids, vitamins, minerals and antioxidants. Canada is the leading producer of oats and one of the countries with the highest per capita consumption of oats (Bouphasiri & Verchomin 2005), usually as breakfast oatmeal.

Before conducting this trial, a product acceptance study was performed at the local treatment center where patients with any type of cancer rated the acceptance (liking) of the product. The beverages were well liked among patients with cancer, with an average liking of 7.3 on the 9-point hedonic scale, corresponding to a value between “Like moderately” and “Like very much”. Importantly, 62% of participants “Agreed” or “Strongly agreed” they would consume this product regularly, while 26% were undecided without knowledge of product price and purchase location. The intent to consume the product was also reflected by participant interest in the product and its purchase location. Finally, when asked about the time of day they would prefer to consume the product, 53% of the participants selected breakfast, 21% indicated morning snack, 17% said that it could be consumed anytime and the remaining 11% of the participants would prefer to consume it at lunch, as an afternoon snack or at dinner.

A supplemented food product show a benefit by demonstrating that it increases total caloric or nutrient intake or QOL, symptom management or nutritional status improvement, only if it is consumed over a time period specific to the period of time required to determine the benefit. It is necessary to assess the feasibility of adherence (Shader 2018) with recommended consumption over time. In this regard, a study of surgical patients exploring the reasons for patient adherence with nutritional supplements, found that flavour and volume were the major themes associated with it, followed by texture or consistency, impact on dietary intake and motivation for supplement consumption (Hogan et al. 2019). Some studies have examined how long-term consumption of an ONS affects liking of the product. Bolton and others (Bolton et al. 1990) allowed patients to consume their preferred ONS at home for three weeks, observing that most patients consumed the product for 21 days without decreasing acceptance. However, 16.7% of participants stopped consuming the product due to a decrease in product liking. When patients were randomly assigned an ONS flavour, 54% of the participants stopped consuming the supplement due to initial taste disliking and/or flavour fatigue (Bolton et al. 1992). As shown, adherence with the consumption of any supplemented food product is highly influenced by product liking.

Given that liking over time might change and impact consumption, the goal of this study is to assess the feasibility of 14 day adherence to the recommended intake of an oat-based beverage mix, determine influences of intake over time on product acceptance and assess the product's contribution to energy and protein intake. Moreover, the present study considers a wider approach where not only the liking of the product and amount consumed are assessed, but also symptom presence, QOL and effect of the product consumption on overall intake.

6.2. Objectives

The primary objective is the evaluation of the feasibility of 14-day adherence with the consumption of oat-based beverages by patients with HNC.

To accomplish the primary goal, the following secondary objectives will also be pursued:

1) Assess the effect of product consumption on caloric and protein intake; evaluate the influence of intake over time on the product´s acceptance
2) Assess factors known to influence sensory perception and dietary intake (age, NIS, presence of taste and/or smell alterations, and type of cancer treatment) on the product´s liking and consumption over time
3) Determine the effect of product consumption on patient SWFL and health-related QOL.

The results of the current study will identify if consumption of the product for a sustained period of time is feasible and if the product remains liked among patients and therefore could be used as a daily snack to increase nutrient intake. The oat mix beverage product could then be fortified in a future study to achieve improved nutritional intake. Additionally, the results may identify a specific point of treatment/disease where patients are most willing to consume the product. Finally, the proportion of eligible people willing to participate, the accrual rate, the number of participants who comply with the product consumption and if any, the number of participants who drop out of the trial will be obtained to guide future trials.

We hypothesize that the consumption of this palatable beverage will be successfully incorporated into patient's habitual dietary patterns and maintained over the 14-day trial period, will increase their caloric and protein intakes, as well as their SWFL.

6.3. Methods and Design

6.3.1. Study design

A within subject design will be used, where each participant will act as their own control. After a baseline period of at least 3 days (maximum 7 days) to complete the three-day diet record, a 14-day supplementation period will commence. Patients will be able to choose the flavor(s) of the desired product every week to avoid flavor fatigue.

During the supplementation period, patients will be asked to consume at least one daily serving (30g) of the SFP, with the option to consume a maximum of two servings per day. The timeline of study enrolment, interventions and the assessments to be completed at each time point are shown in Table 6.1 according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines (Chan et al. 2013). The specific assessment tools are described in the study assessments section of this protocol. The SPIRIT checklist for this study protocol is included in Appendix D.

6.3.2. Study population

Adult patients with HNC at any stage of the disease or treatment are eligible.

6.3.3. Inclusion Criteria

- ≥18 years of age.
- Able to communicate freely in English.
- Able to provide written informed consent.
- Capable of oral intake.
- Diagnosed with HNC including the oral cavity, salivary glands, paranasal sinuses, oropharynx, nasopharynx, hypopharynx and larynx.
- All tumour stages according to American Joint Committee for Cancer.
- All forms of therapy.

6.3.4. Exclusion criteria

Allergy or sensitivity to any of the product´s ingredients.

6.3.5. Sample size

Sample size was calculated considering that a sample size of 20 would be adequate for a feasibility/pilot study. Considering that a previous study by our research group (Barlow 2006) showed that 50% of the participants can be "compensators" who substitute the calories of the supplement from those of their usual food intake, the initial number was doubled. Moreover, we know from this previous study that about 10% of the participants who tried the product dislike it. Finally, also from previous experiences (Barlow 2006), it has been observed that the drop-out rate in interventional studies with people with cancer can be around 25%. Considering that, 55 participants will be recruited for this study.

6.3.6. Patient Recruitment

Patients will be recruited at the Cross Cancer Institute, Edmonton, AB. A research team member will screen charts of patients with HNC to determine patient eligibility. In accordance with the Alberta Health Services (AHS) Health Information Act, a potential study participant will not be approached for recruitment until an AHS employee has informed the patient of the study and obtained patient consent to be approached. Once consent has been granted, a study team member who does not have a pre-existing relationship with the potential participant will then approach the patient for study recruitment. A brochure containing the study information (Appendix E) will be given to the patient outlining the purpose of the study, benefits of participation, minimum eligibility criteria, product ingredients and the patient's role in the study. If the patient is interested, a consent form will be provided, details of the protocol will be discussed, and any questions answered.

If the patient expresses continued interest in the study, the "Informed Consent Form" (Appendix F) can be taken home to read in detail. Potential participants receiving the Informed Consent Form will be asked for permission to be contacted (using the contact method of their choice) by the research assistant at a later point to answer any questions, confirm interest in the study and set up an appointment to sign the Informed Consent Form and start study participation.

After consenting, participants will receive a 3-day diet record to be completed over two weekdays and one weekend day. Diet records will be collected to identify if the consumption of

the beverage was in addition to patient's regular food intake or it replaced other meals. Once the completed diet record is received, the remaining baseline assessments will be completed, and the supplementation period will begin. To facilitate product consumption, participants will receive a booklet of suggestions for mixing the product.

On days 0 and 7, participants will receive the product to be consumed for the following week and one grocery store gift card for 25 $CAD, which can be used to purchase milk, fruit etc. to mix with the oat beverage blend.

6.3.7. Study assessments and tools

The assessments to be completed at each time point are shown in Table 6.2. The following tools will be used for each assessment.

- Product liking and consumption tracking

Product liking and consumption over the past three days will be recorded by patients on a five-item questionnaire to assess any change in liking of the product over time, the amount of product consumed and the ingredients it was mixed with. Individual items assessed are time of day when the product was consumed, food product added to (i.e. milk, water, yogurt, fruit smoothie, ice cream, pudding, etc.), favorite food item to mix the product with, and amount of product consumed (none, a little, half, a lot or all) and the product liking using a 9-point hedonic scale (1= "dislike extremely", 9= Like extremely").

- Dietary intake

Three-day food records will be collected before day 0 and during the last 3 days of the supplementation period. This method has shown to be appropriate to for dietary intake assessment of people with cancer (Bruera et al. 1986).

A 24-hour dietary recall will be collected on day 7 in person using a paper-and-pencil approach and the validated United States Department of Agriculture USDA 5-Step Multiple-Pass Method (Moshfegh et al. 2008). Initially, patients will be asked if the previous day food intake was "normal" and the response will be recorded. Then, the five steps will be completed: quick list, forgotten foods, time and occasion, details and final probe. Food intake will be analyzed

using Food Processor Software (ESHA Research Inc., Salem, OR), ideally on the same day as the 24-hour recall or three-day diet record collection (in case any questions arise).

- Sociodemographic information

A questionnaire will be completed to identify patient age, sex, personal contact information, marital status, education level, income, occupation, alcohol and smoking status and dietary restrictions. Patients will be asked to permit access to their medical record to confirm their age, co-morbidities, cancer tumour and treatment variables as described above.

- Food aversions/preferences

A modified shorter version of the "Food aversions/preferences questionnaire" used by Guerdoux-Ninot and others (Guerdoux-Ninot et al. 2016) will be conducted to obtain information about the patient dietary preferences, aversions and eating patterns.

- Symptom burden and interference with eating

Patients will indicate the presence and frequency of 17 nutrition-impact symptoms and symptom interference with eating using the Head and Neck Symptom Checklist (HNSC®) (Kubrak et al. 2013).

Additionally, the Appetite, Hunger and Sensory Perception (AHSP) questionnaire (de Vries et al. 2017) will be completed. It consists of 28 items (7 for taste, 6 for smell, 6 for appetite and 9 regarding hunger), assessed on 5-point Likert scales. Higher scores represent a more positive judgement about current taste and smell perception as well as appetite and hunger. This questionnaire has been used in the elderly and cancer populations (Mathey 2001; de Vries et al. 2017).

- Nutritional status

Relevant sections (1, 2 and 4) of the abridged version of the Patient Generated Subjective Global Assessment (abPG-SGA) will be completed to assess patient nutritional status. The abPG-SGA is a validated tool for detecting malnutrition in the outpatient oncology setting (Gabrielson et al. 2013). Given that the nutrition impact symptoms in Section 3 are already included in the HNSC, this section will not be completed to reduce patient burden.

- Quality of life

Two different tools will be used, the SWFL questionnaire and the University of Washington Quality of Life (UW-QOL) version 4 questionnaire. Satisfaction with food-related life questionnaire is composed by 5 items to assess food-related satisfaction by the evaluation of objective indicators of food enjoyment and satisfaction (Grunert et al. 2007). This result will be compared to other components evaluated in the protocol to determine the impact of symptoms including taste or smell alterations on food satisfaction and enjoyment.

The UW-QOL v.4 is a commonly used tool to assess quality of life among patients with HNC (Rogers & Lowe 2010). The tool includes 12 domains (i.e. pain, appearance, activity, swallowing, recreation, speech, chewing, shoulder function, taste, saliva, anxiety and mood), with each question scaled from worst (0) to best (100) and three global QOL questions on Likert scales. A higher score represents better QOL. The questionnaire has been translated to different languages and has shown construct validity (Rogers & Lowe 2010).

6.3.8. Data collection

Study data (except the 3-day food record, 24-hour dietary recall and the product liking and consumption tracking questionnaires) will be collected and managed using REDCap™ (Research electronic data capture) (Harris et al. 2009) hosted by the Women & Children's Health Research Institute. Software access is provided by the University of Alberta. When completing the questionnaires at the hospital location, the patients will be handed a laptop or tablet to respond to the questionnaires on the REDCap™ platform. Assistance with the use of the electronic devices and survey completion will be provided to the participants if required. The remaining questionnaires can be completed online at home using any device with internet access. REDCap was designed to protect patient privacy and confidentiality in clinical research.

6.3.9. Data Analyses

Statistical analyses will be performed using statistical software R (R Core Team 2015). A repeated measures statistical analysis will be conducted. Specific statistical analyses will be confirmed based on the quality and nuances of the data. In general, information about demographics, SWFL and symptoms will be analysed using descriptive statistics. Mean and standard deviation will be reported for continuous variables and frequency (percentages) will be reported for categorical variables. Median and range will be reported for non-normal data. Product consumption will be assessed as categoric scale (full, 25, 50 or 75% of product's serving).

One-way Analysis of Variance (ANOVA) will be used to determine any significant differences in product liking over the supplementation period among the samples overall initially and over time. If appropriate, Tukey´s test will be used to determine statistically significant differences among the sample means. A p-value of 0.05 will be considered for statistical significance.

The abPG-SGA will be scored following the scoring guidelines. Each symptom/option has an associated score. For the Head and Neck Symptom Checklist, study participants will be stratified by severity of NIS (mild, moderate or severe) to determine if the severity of NIS influences product liking and adherence.

6.4. Discussion

As with any food product, acceptance of SFP and functional foods has been recognized as key to product success. Although acceptance is influenced by several factors such as price, quality and convenience or health claims, taste and sensory perception are critical factors to product acceptance (Kosseva 2013). Importantly, health or functional benefits of a functional food product may add value to consumer perception and acceptance, but those benefits do not outweigh the product's sensory properties including taste, appearance and aroma (Siró et al. 2008).

In the case of the SFP proposed in this trial, one-sip acceptance was previously confirmed. Additionally, patients trying the product indicated interest in consuming this product as a part of their daily diet. We encourage anyone designing a nutrition adherence trial to confirm initial

sensory acceptance of the trial product by target participants before commencing the trial. This initial tasting step will help to confirm one-sip acceptance and interest. Another step to facilitate product incorporation into their daily lives is to provide participants with the booklet with suggestions of foods and amounts to mix with the SFP.

The guidelines, timeline and assessments suggested in this trial could be applied in the future to evaluate the feasibility of incorporating a similar product into the diet of patients with cancer. Moreover, the results of this trial could determine the guidelines for a larger trial with a greater number of participants. If adherence is feasible, the possibility of including additional nutrients to the product (fortification) will be evaluated in the future. Weight gain is not assessed as an outcome in this study as it is unexpected. Importantly, this trial considers also the presence of nutrition impact symptoms that patients may present and two different QOL assessments, one only related to the satisfaction with food.

6.5. Trial status

Ethics approval of the version 1 of the protocol was obtained on August 11th, 2018 under the identification number HREBA.CC-18-0061. The version 2 which is described in this protocol was approved on February 11th, 2019. This protocol, informed consent form and all recruitment materials were submitted to review to the Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC) which provides ethical review and oversight for all cancer and cancer-related research involving humans (adult and pediatric), their information and/or samples. The study will not be performed as the funder withdrew financial support.

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Table 6.1. SPIRIT table with study enrolment, interventions and assessments.

	STUDY PERIOD						
	Enrolment	Baseline	Supplementation period*				Close-out
TIMEPOINT			Day 0	Day 3	Day 7	Day 11	Day 14
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Completion of three-day diet record		X					
INTERVENTION:							
Daily consumption of one serving of the SFP			→	→	→	→	
ASSESSMENTS:							
Sociodemographic information			X				
Product liking and consumption			X	X	X	X	X
Food aversions/ preferences			X				X
Quality of life			X		X		X
Appetite, hunger and sensory perception			X		X		X
Dietary intake		X			X		X

*Day 7 and 14 will be approximate, coinciding with a patient's regularly scheduled clinic visit.

Table 6.2. Study assessments.

Study assessments	Purpose	Day 0	Day 3	Day 7	Day 10	Day 14
Sociodemographic information	Patient assessment	X				
3-day food record	Assess nutrient intake and food choice	X				X
24-hour diet recall				X		
Food aversions/ preferences questionnaire	Assess impact of cancer diagnosis/ treatment on food choices	X				X
Head and Neck symptom checklist (HNSC®)	Characterize symptom burden and interference with eating	X				X
Appetite, Hunger and Sensory Perception questionnaire						
Abridged version of Patient-Generated Subjective Global Assessment (PG-SGA) sections 1, 2, 4	Characterize patient nutritional status	X				X
University of Washington quality of life	Characterization of patient quality of life and SWFL and evaluate effect of the supplement on patient quality of life (if any)	X		X		X
Satisfaction with food-related life						
Product liking and consumption tracking	Assess product acceptance, amount and form of consumption of the product and willingness to continue in the study	X	X	X	X	X

CHAPTER 7: Summary, final discussion and future directions

7.1. Summary

The main objective of this research was to study nutrient-rich snacks as an option to promote nutrient intake among patients with cancer. Factors that impact the acceptance of those snacks in the oncology population were considered through the completion of two literature reviews, three research studies and the design of an intervention trial, all described in this thesis.

Chapters 2 and 3 synthetized previous knowledge of the preferences for SFP among patients with cancer, the sensory evaluation methods typically used for their assessment, and the different approaches for the assessment of self-reported taste changes. In **Chapter 2**, a systematic review identified SFP that have been evaluated through sensory evaluation methods, finding mostly oral nutritional supplements (ONS) and a few fortified foods. The inconsistent use of reliable and validated methods and the heterogeneity of patients complicated a conclusion regarding specific preferences for SFP and the effect of taste changes on those preferences. However, preference for fresh-milk-based supplements when compared to other supplement types was observed and study results suggested that sensory preferences for SFP of patients with cancer differs from that of healthy participants.

Given the prevalence of taste alterations in patients with cancer and the relevance of those changes on food perception and choice, questionnaires used to assess patient-reported taste changes in the oncology setting were reviewed in **Chapter 3**. It was found that the seventeen different published questionnaires assessed up to seven different domains related to taste changes. An inconsistent approach to item and domain evaluation and differences in item phrasing, timeframe and scoring of the questionnaires was observed. As no standard tool or approach is used, reports of self-reported taste changes, it was suggested to develop a bank of standardized validated questions or modules for the assessment of this symptom.

The initial approach to this work was the evaluation of the acceptance of a commercially available oat-based beverage that could be consumed as a snack among patients with cancer. Those evaluations are presented in **Chapter 4**. The hypothesis that products would be accepted (mean overall liking on hedonic scale higher than 7) was confirmed. Differences in sweetness perception were observed between patients with cancer and healthy participants in three of the

products, confirming another hypothesis. However, there was no significant difference in liking among the products, complicating the selection of a product to be fortified. The fortification and sensory evaluations of the cold-chocolate product confirmed that the formulation containing 1.8 times the protein content of the unfortified product and 0.54g/serving of fish oil was not significantly different in liking compared to the regular product, confirming the stated hypothesis. Given that oats were the main ingredient of an oat-based beverage evaluated as part of this work and their potential to be used in products destined to patients with cancer, the perception of oats was assessed using free-word association. Health, food products and sensory characteristics were the dimensions with a higher frequency of mention. Oats were considered nutritious and healthy, high in fiber and related to satiety, but some health detriments and barriers for product consumption were also mentioned by participants including presence of chemicals, allergies, genetical modifications, high content of carbohydrates or swallowing issues. Together, sensory acceptance of an oat-based beverage and the perceived health benefits of oats confirmed their potential incorporated in fortified and unfortified products for patients with cancer.

As was hypothesized for **Chapter 5**, patients with cancer showed preference for some snack products to be fortified. Significant differences were found in the agreement towards the different products and several products were identified with potential to be fortified (i.e. soup, yogurt, cheese, fruit juice, egg products and protein bars). Nutritious, flavorful, convenient, ready to eat, easy to chew and easy to swallow were desired characteristics. It was also confirmed that the symptoms experienced by patients with cancer can impact their preferences. Three clusters of patients were identified according to symptoms presence, differing in their food intake, satisfaction with food-related life, consumption of ONS, desired characteristics of fortified snacks and preferred snacks for fortification.

7.2. Potential of oats and an oat-based beverage as carriers or ingredients of fortified snacks.

The oat-based beverages were selected based on their nutritional content and with the assumption that their sensory characteristics (mild flavor and texture) could reduce the possibility of aversions. Moreover, the three different flavors and the possibility of consuming

the product with water, milk, yogurt or smoothies, increased variety, which has been suggested to promote adherence with consumption of ONS (Ravasco 2019). Another potential advantage of the products was that contained powdered milk. Preference for fresh milk products was observed in the systematic review presented in Chapter 2, which also aligns with increased consumption of milk products after treatment among patients with head and neck cancer (HNC) (Nejatinamini et al. 2018).

The findings confirmed the potential of the evaluated oat-based beverage to be consumed among patients with cancer and its potential as a carrier for nutrient fortification. The positive perception of oats could explain why most participants responding to the survey presented in Chapters 4 and 5 consumed oats regularly, and over 56% of them agreed with porridge as an appropriate snack carrier for fortification. Moreover, more participants were consuming oat products than consuming ONS. However, only 43% selected oats as a desired ingredient in a fortified snack. Therefore, sensory evaluation and perception of non-sensory factors of future snacks for patients with cancer containing oats would be necessary.

A palatable product with increased nutrient content targeted to patients with cancer was developed. However, evaluations were conducted with a convenience panel and not by the targeted consumers as recommended in product development (O'Sullivan 2016). Therefore, the fortified product with high protein could be manufactured by the company and evaluated among patients with cancer to confirm acceptance and attributes perception.

7.3. Preferences of snacks to be used as carriers for fortification

The oat-based beverages selected and evaluated in this thesis are a nutritious commercial food product but are another form of beverage, the most common type of SFP available. As shown in previous research on dietary patterns of patients with cancer, some patients can show preference for liquid foods, but others continue consuming their regular foods (Hutton et al. 2006; Prado et al. 2012; Nejatinamini et al. 2018). The incorporation of the "voice of the consumer" at initial stages of product development can identify potential opportunities by understanding unmet consumer needs, which can be a critical success factor for product development (Van Kleef & Van Trijp 2002; van Kleef et al. 2005). Nutrients can be incorporated into a variety of food

products (i.e. carriers), however not all combinations of carriers and nutrients appeal to consumers (van der Zanden et al. 2015). This was shown in our results as cookies, bread, and pastries were commonly reported as consumed snacks, but were not considered adequate for nutrient fortification by a high number of participants. Perception of their healthiness could have influenced their potential as healthy products have been considered more appropriate carriers for fortification in other consumer studies with older adults (Van der Zanden et al. 2014; Song et al. 2019).

Vitamins, minerals and protein, which are typically found in commercial ONS were more frequently selected among patients responding to our survey. It is unknown if those nutrients were selected due to familiarity with them or interest in their nutritional benefits among this population. It is also unknown why only 20% of the patients were interested in the addition of cannabinoids, recently approved in Canada for addition to foods. Future qualitative research studies could answer that.

7.4. Perception of oral nutritional supplements

In this thesis, a free-word association task was included as part of the survey described in Chapter 5 to assess the perception of patients with cancer who have consumed these products since their diagnosis. ONS are recommended when food intake is not adequate in the oncology population (Arends et al. 2016) and a "food first" approach is not enough. However, adherence with consumption of ONS is generally low (Ravasco 2005; Hubbard et al. 2012) and studies on factors influencing ONS consumption have more commonly been related to their sensory attributes. Our free-word association task adds to the limited research available regarding the perception, motivations and personal factors that influence ONS consumption. Prolonging independence and small improvements in quality of life were reported as reasons for ONS consumption by older adults interviewed with a soft laddering technique (den Uijl et al. 2015). The most frequent dimensions we found through the free-word association method (Sensory characteristics of ONS and Nutrition and health) align with the results of semi-structured interviews among 20 patients undergoing pelvic surgery for cancer (Hogan et al. 2019) in which sensory characteristics (flavour, texture), volume and its effect on dietary intake, and motivators

(improve condition and assist with research) were the major themes associated with adherence to ONS consumption.

7.5. Effect of symptoms on snacks preference and product's acceptance

Overall, our results showed opposing views regarding ONS with some patients perceiving them as appealing, satisfying, acceptable, healthy and beneficial and others reporting dislike or disgust, high sweetness, and induction of symptoms as barriers for their consumption. Mentions of ONS being useful among patients experiencing difficulty eating, high fatigue or lack of appetite evidenced that these products can be useful especially for patients undergoing nutrition impact symptoms. This aligns with our findings of patients with higher symptom presence being more likely to consume those products, and previous research showing higher consumption among patients with advanced cancer consuming mostly other liquid foods (Hutton et al. 2006) and patients with HNC with high ONS consumption showing greater total nutrition impact symptom scores (Nejatinamini et al. 2018).

7.6. Effect of symptoms on snacks preference and product's acceptance

Findings from the analysis of the fortified snacks survey showed that the experienced symptoms can impact food consumption and preferences. The presence and severity of nutrition impact symptoms has been associated with nutritional status (Barbosa-Silva & Barros 2006), QOL (Tong et al. 2009), weight loss and dietary intake (Kubrak et al. 2010; Kubrak et al. 2013; Farhangfar et al. 2014), food choices (Bressan et al. 2017) and adherence with SFP consumption (Fearon et al. 2003; van der Meij et al. 2012). The development and sensory evaluation of any food product focused on increasing dietary intake of oncology patients must consider the symptoms experienced and promote the consumption of products that will not worsen symptoms and create an enjoyable eating experience.

The systematic review presented in Chapter 2 highlighted that the only symptom assessed when studying preferences for SFP among patients with cancer were taste and smell alterations (TSA), assessed in 5 out of 19 studies. As TSA and other symptoms can influence food perception, in our sensory evaluation of an oat-based beverage, presence of symptoms was

assessed. Self-reported food intake compared to usual was also assessed. The low presence of symptoms among patients evaluating the oat-based beverage might explain why no differences in liking for the beverage were found. Future studies evaluating sensory properties and preferences among patients with cancer could focus in assessing in detail the effect of symptom presence, frequency and severity on preferences of patients with cancer for fortified foods.

Taste and/or smell alterations are one of the more frequent patient-reported NIS among people with cancer (Omlin et al. 2013), as was also found in our studies. Given the importance of TSA on food perception and food behaviour, appropriate standardized assessment of this symptom is necessary. However, as identified in Chapter 3, assessment and reporting of TC comprises the assessment of different aspects of this nutrition impact symptom.

7.7. Strengths, limitations and future research

This research contributes to our overall knowledge of food behaviour among patients with cancer, particularly related to snacks and fortified products. Sensory evaluation and consumer research methods commonly used in the food industry were applied to identify acceptance of fortified and regular oat-based beverage and desired carriers and attributes for fortified snacks. A fortified oat-based beverage was developed incorporating recommended nutrients for patients with cancer and maintaining the product's sensory acceptance. Findings from this research can be used to develop fortified products tailored to the nutritional and sensory needs of people with cancer. By including symptoms assessment throughout these research studies, it was possible to not only characterize our population, but identify the importance of symptoms experienced on product acceptance, particularly in the preferences for fortified snacks. Additionally, the fortification of a food product with nutrients of benefit for oncology patients maintaining the product's sensory characteristics was achieved. The developed formulation could be marketed especially for patients with cancer.

Future research in this field would benefit from the application of sensory evaluation standards and facilitate analysis and comparisons among different studies. As evidenced by the literature review presented in Chapter 2, research conducted regarding fortified food products and ONS (both denominated supplemented food products (SFP) in this work) is not extensive and previous studies follow typical product development in which a product is developed

entirely and one or a few of those products are evaluated through sensory evaluation methods. This is the first study reporting the use of Just-about-right (JAR) scales among patients with cancer. Another novel aspect of this research is the involvement of patient participation from early stages of product development by initially confirm product acceptance, then fortification of the most liked product ensuring that sensory characteristics were maintained, and finally, planning to conduct a 14-day trial to confirm that liking was maintained over a short term consumption period (Chapter 6). As the trial could not be conducted, it is important to highlight that to confirm current acceptance and perception results of the oat-based beverage with or without fortification, future research is needed.

A limitation of both studies evaluating oat-based beverage is that small sample volumes (80 and 90mL) were used as opposed to the consumption of a full serving. Research has shown that increased consumption volumes of ONS permits perception of attributes not perceived in a one-sip tasting that can accumulate and influence liking (Methven et al. 2010; Thomas et al. 2016; Thomas et al. 2018). This could be particularly important for the fortified products in which off-flavours from the fish oil or the added protein could build-up and impact attribute perception and acceptance. Therefore, studies assessing full volume consumption are necessary. Moreover, to identify the impact of context, eating environment and consumption over time, home-use tests or studies assessing consumption over time would generate more ecologically valid results (Bolton et al. 1992; Stelick & Dando 2018).

To my knowledge, our survey is the first to assess preferred carriers for snack fortification among patients with cancer. Satisfaction with food-related life, a five-item questionnaire validated among older adults (Grunert et al. 2007) was used for the first time among patients with cancer. Patients with lower symptom presence had higher mean satisfaction scores compared to the cluster of participants with higher symptom presence. This research provides new information about snack consumption, preferred characteristics and desired fortified food products. By including symptom assessment, it was possible to stratify patients and assess the impact of symptom presence on preferences for snacks and their attributes. The survey study included participants with any type and stage of cancer and undergoing any type of treatment to reflect the heterogeneity found in this population. It would be difficult to develop specific products for specific particular tumor types and food companies will likely continue developing

products targeted to a general cancer population that might be preferred and consumed by a high number of patients. Currently available liquid SFP and similar products can be useful for patients with preference for liquids or those undergoing a high burden of nutrition impact symptoms that influence their characterization of food, such as patients with HNC (Kubrak et al. 2013; Álvarez-Camacho et al. 2016). The main limitation of the survey study is that product identities were assessed as opposed to actual product,s which might limit the ecological validity of the results (Song et al. 2019).

To the best of my knowledge, this thesis applied for the first time a free-word association method among patients with cancer to elucidate patient perception of food products. The use of this qualitative method contributed to the knowledge and understanding of how ONS are perceived and some benefits and barriers to their consumption beyond their sensory characteristics. By applying this method to study perception of oat foods, it was confirmed that oats are perceived as appealing and mostly beneficial and could be used in other food products designed for patients with cancer.

Although in the past years, interest in studying how food intake, preferences and attitudes among patients with cancer is affected by TSA or other symptoms experienced has increased (Guerdoux-Ninot et al. 2016; de Vries et al. 2017; Drareni et al. 2019), further research is required to provide a better understanding of patient food behaviour over the course of their disease and treatment. Over the studies conducted in this research work, it was observed that most patients participating in product tastings and survey completion experienced a low symptom burden and had an unchanged food intake. Considering the importance of the symptom experience on food behaviour, strategies to capture the perception of patients undergoing a higher symptom burden are needed. Different recruitment techniques or recruitment of patients undergoing nutritional counselling could aid in this matter.

7.8. Conclusions

Over the duration of this research, new information regarding the development and acceptance of snacks as alternatives to promote nutrient intake among patients with cancer was revealed. The assessment of an oat-based beverage as a potential fortified product and the fortification of one

of the products showed their potential as fortified snacks. Moreover, the qualitative research approach provided valuable information regarding preferences and desired attributes for potential carriers for fortification in future trials, and the influence of symptom presence on those preferences and desires. The research presented is an initial step for the development of fortified snacks targeted to the nutritional, sensory and consumption needs of patients with cancer.

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Appendices

Appendix A. Search strategies of the systematic review presented in Chapter 2 (search terms for each database).

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> Searched July 26, 2016
Search Strategy:
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1 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or radiation* or radiotherap* or chemotherap* or
metast*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3670728)
2 exp Neoplasms/ (2874307)
3 1 or 2 (3980067)
4 ((food* or diet* or nutrition*) adj3 (therap* or enrich* or supplement*)).ti,ab. [mp=title, abstract, original
title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (61084)
5 *functional food/ or fortifi*.ti,ab. or (oral adj3 (nutrit* or supplement* or enrich*)).ti,ab. (19254)
6 Dietary Supplements/ (40598)
7 *Food Additives/ (3990)
8 Food, Fortified/ (8254)
9 *Foods, Specialized/ (126)
10 *Vitamins/ (19001)
11 *Trace Elements/ (10322)
12 (vitamin* or trace element* or ONS).ti,ab. (189352)
13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (290193)
14 (exp *Taste/ or exp *Odors/) and (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking).mp. (1909)
15 ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or sensor perception* or diet)
adj3 (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking)).mp.
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3329)
16 14 or 15 (4792)
17 exp Food Preferences/ (11381)

18 Taste Perception/ (1035)
19 (palatab* or eating problem* or eating difficult* or swallowing problem* or swallowing difficult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (7825)
20 16 or 17 or 18 or 19 (23059)
21 3 and 13 and 20 (106)

Database: Embase <1974 to 2016 July 26>
Search Strategy:
---
1 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or radiation* or radiotherap* or chemotherap* or metast*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (4643768)
2 exp neoplasm/ (3724477)
3 1 or 2 (5181925)
4 ((food* or diet* or nutrition*) adj3 (therap* or enrich* or supplement*)).ti,ab. [mp=title, abstract, headingword, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (75281)
5 *functional food/ or fortifi*.ti,ab. or (oral adj3 (nutrit* or supplement* or enrich*)).ti,ab. (24444)
6 diet supplementation/ or supplementation/ or exp mineral supplementation/ (100653)
7 *diet therapy/ (8837)
8 food additive/ (9144)
9 nutritional support/ (15440)
10 exp *vitamin supplementation/ (5594)
11 exp *trace element/ (17740)
12 (vitamin* or trace element* or ONS).ti,ab. (241805)
13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (410926)
14 (taste/ or "smelling and taste"/ or exp odor/) and (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking).mp. (4689)
15 ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or sensor perception* or diet) adj3 (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (4391)
16 14 or 15 (8237)
17 food preference/ (11227)
18 organoleptic property/ or nutritional tolerance/ (1418)
19 (palatab* or eating problem* or eating difficult* or swallowing problem* or swallowing difficult*).mp. [mp=title,abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name,keyword] (10719)

20 16 or 17 or 18 or 19 (29732)
21 3 and 13 and 20 (292)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 27, 2016>, EBM Reviews - ACP Journal Club <1991 to June 2016>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Central Register of Controlled Trials <June 2016>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> Search Strategy:
---
1 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or radiation* or radiotherap* or chemotherap* or
metast*).ti,ab. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (103931)
2 ((food* or diet* or nutrition*) adj3 (therap* or enrich* or supplement*)).ti,ab. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (7916)
3 *functional food/ or fortifi*.ti,ab. or (oral adj3 (nutrit* or supplement* or enrich*)).ti,ab. (3870)
4 (vitamin* or trace element* or ONS).ti,ab. (14432)
5 2 or 3 or 4 (23726)
6 ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or sensor perception* or diet) adj3 (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking or dislik* or aversion)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (943)
7 (palatab* or eating problem* or eating difficult* or swallowing problem* or swallowing difficult*).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (773)
8 6 or 7 (1650)
9 1 and 5 and 8 (27)

Note: OVID EBM ALL – no longer accessible in September 2017 – search was updated in Wiley Cochrane Library.

Database: PsycINFO <1987 to July Week 3 2016>
Search Strategy:
---
1 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or radiation* or radiotherap* or chemotherap* or metast*).ti,ab. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (59619)
2 exp neoplasms/ (39844)
3 1 or 2 (62214)

4 ((food* or diet* or nutrition*) adj3 (therap* or enrich* or supplement*)).ti,ab. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (3185)
5 (fortifi* or (oral adj3 (nutrit* or supplement* or enrich*))).ti,ab. (672)
6 dietary supplements/ (1469)
7 *food additives/ (110)
8 *vitamins/ (1719)
9 (vitamin* or trace element* or ONS).ti,ab. (5280)
10 4 or 5 or 6 or 7 or 8 or 9 (9503)
11 (food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or sensor perception* or diet).mp. and exp AVERSION/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (254)
12 ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or sensor perception* or diet) adj3 (prefer*or percept* or perceiv* or blandness or comply* or accept* or complian* or likeability or liking or dislik* or aversion)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures](3278)
13 11 or 12 (3396)
14 exp Food Preferences/ or exp food intake/ (12023)
15 Taste Perception/ or exp Olfactory Perception/ or exp ODOR DISCRIMINATION/ (10139)
16 palatab*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (2139)
17 13 or 14 or 15 or 16 (24557)
18 3 and 10 and 17 (21)

Proquest Dissertations and Theses Searched August 2, 2016

ti((food OR gustat* OR taste OR tasting OR tastes OR tasted OR flavour* OR flavor* OR sensor perception* OR diet) AND (prefer* OR percept* OR perceiv* OR blandness OR comply* OR accept* OR complian* OR likeability OR liking OR dislik* OR aversion) OR palatab*) AND all(((food* OR diet* OR nutrition* or oral) AND (therap* OR enrich* OR supplement) OR vitamin* or trace element* or ONS or fortifi*)) AND all(cancer* OR neoplasm* OR tumor* OR tumour* OR oncolog* OR radiation* OR radiotherap* OR chemotherap* OR metast*) = 3

ab((food OR gustat* OR taste OR tasting OR tastes OR tasted OR flavour* OR flavor* OR sensor perception* OR diet) AND (prefer* OR percept* OR perceiv* OR blandness OR comply* OR accept* OR complian* OR likeability OR liking OR dislik* OR aversion) OR palatab*) AND all(((food* OR diet* OR nutrition* or oral) AND (therap* OR enrich* OR supplement) OR vitamin* or trace element* or ONS or fortifi*)) AND all(cancer* OR neoplasm* OR tumor* OR tumour* OR oncolog* OR radiation* OR radiotherap* OR chemotherap* OR metast*) = 40

SCOPUS - Searched August 2, 2016

(TITLE (((food* OR diet* OR nutrition*) W/3 (therap* OR enrich* OR supplement*))) OR TITLE ("functional food" OR onl OR "food additive" OR "trace element" OR vitamin*) AND TITLE-ABS-KEY (((food OR gustat* OR taste OR tasting OR tastes OR tasted OR flavour* OR flavor* OR sensory) W/3 (prefer* OR percept* OR perceiv* OR blandness OR comply* OR accept* OR complian* OR liability OR liking))) AND TITLE-ABS-KEY (cancer* OR neoplasm* OR chemotherap* OR tumor* OR tumour* OR radiotherap* OR metasti*)

CINAHL Searched August 2, 2016

Search ID#	Search Terms	Search Options	Actions
S17	S3 AND S11 AND S16	**Search modes** - Find all my search terms	View Results (70)
S16	S12 OR S13 OR S14 OR S15	**Search modes** - Find all my search terms	View Results (26,321)
S15	(taste or tasting or flavour* or flavor* or tasted or gusta* or sensory)	**Search modes** - Find all my search terms	View Results (22,979)
S14	((MH "Taste") OR (MH "Smell")) AND (prefer* or percept* or perceiv* or liking or dislik* or aversion* or likability or complian* or comply* or accept*)	**Search modes** - Find all my search terms	View Results (1,079)
S13	(MH "Food Preferences")	**Search modes** - Find all my search terms	View Results (3,481)
S12	palatab*	**Search modes** - Find all my search terms	View Results (524)
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	**Search modes** - Find all my search terms	View Results (71,385)
S10	(food* or diet* or oral or nutrition*) N3 (supplement* or enrich* or enhanc* or formulated* or fortifi* or therapy or therapies)	**Search modes** - Find all my search terms	View Results (57,662)
S9	(MM "Diet Therapy")	**Search modes** - Find all my search terms	View Results (1,321)
S8	(MM "Vitamins")	**Search modes** - Find all my search terms	View Results (2,731)
S7	(MM "Trace Elements")	**Search modes** - Find all my search terms	View Results (528)
S6	vitamin supplement*	**Search modes** - Find all my search terms	View Results (11,064)
S5	(MH "Functional Food") OR (MH "Food, Fortified") OR (MH "Food, Formulated+") OR (MH "Food Additives+")	**Search modes** - Find all my search terms	View Results (16,024)
S4	(MH "Dietary Supplements+") OR (MH "Dietary Supplementation")	**Search modes** - Find all my search terms	View Results (31,673)
S3	S1 OR S2	**Search modes** - Find all my search terms	View Results (376,554)
S2	(cancer* or neoplasms or oncolog* or tumour* or malignan*) AND (carcinoma* or metasti* or tumor*)	**Search modes** - Find all my search terms	View Results (119,625)
S1	(MH "Neoplasms+")	**Search modes** - Find all my search terms	View Results (346,415)

AGRICOLA - Searched August 2, 2016

ID#			
S17	S3 AND S11 AND S16	**Search modes** - Find all my search terms	View Results (23)
S16	S12 OR S13 OR S14 OR S15	**Search modes** - Find all my search terms	View Results (10,517)
S15	ti (taste or tasting or tasted or gusta* or sensory or flavor* or flavour* or food*) and ti (prefer* or percept* or perceiv* or liking or dislik* or aversion* or likability or complian* or comply* or accept*)	**Search modes** - Find all my search terms	View Results (3,177)
S14	(DE Taste OR DE Smell") AND (prefer* or percept* or perceiv* or liking or dislik* or aversion* or likability or complian* or comply* or accept*)	**Search modes** - Find all my search terms	View Results (1,926)
S13	DE Food Preferences or DE taste perception or DE taste perception and smell	**Search modes** - Find all my search terms	View Results (2,710)
S12	palatab*	**Search modes** - Find all my search terms	View Results (3,698)
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	**Search modes** - Find all my search terms	View Results (74,750)
S10	(food* or diet* or oral or nutrition*) N3 (supplement* or enrich* or enhanc* or formulated* or fortifi* or therapy or therapies)	**Search modes** - Find all my search terms	View Results (42,403)
S9	DE Diet Therapy or DE Nutritional Support	**Search modes** - Find all my search terms	View Results (5,359)
S8	DE Vitamins	**Search modes** - Find all my search terms	View Results (19,661)
S7	DE Trace Elements	**Search modes** - Find all my search terms	View Results (4,848)
S6	vitamin supplement*	**Search modes** - Find all my search terms	View Results (9,280)
S5	DE Functional Food OR DE Food, Fortified OR DE Food, Formulated OR DE Food Additives	**Search modes** - Find all my search terms	View Results (10,732)
S4	DE Dietary Supplements OR DE Dietary Supplementation	**Search modes** - Find all my search terms	View Results (13,593)
S3	S1 OR S2	**Search modes** - Find all my search terms	View Results (54,691)
S2	(cancer* or neoplasms or oncolog* or tumour* or malignan* or carcinoma* or metasti* or tumor*)	**Search modes** - Find all my search terms	View Results (54,691)
S1	DE Neoplasms	**Search modes** - Find all my search terms	View Results (16,653)

ABI - Searched August 2, 2016

Search History: CABI: CAB Abstracts® and Global Health®

Save History / Create Alert | Open Saved History

Set	Results	
# 19	462	#18 AND #15 AND #4 *Indexes=CAB Abstracts Timespan=All years*
# 18	357,743	#17 OR #16 *Indexes=CAB Abstracts Timespan=All years*
# 17	7,154	**TITLE:** (chemotherap*) *Indexes=CAB Abstracts Timespan=All years*
# 16	352,423	**TOPIC:** (cancer* or neoplasm* or tumor* or tumour* or oncolog* or radiation* or radiotherap* or metast*) *Indexes=CAB Abstracts Timespan=All years*
# 15	53,549	#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 *Indexes=CAB Abstracts Timespan=All years*
# 14	9,701	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 accept*) *Indexes=CAB Abstracts Timespan=All years*
# 13	889	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 aversion*) *Indexes=CAB Abstracts Timespan=All years*
# 12	1,233	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 complian*) *Indexes=CAB Abstracts Timespan=All years*
# 11	297	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 dislik*) *Indexes=CAB Abstracts Timespan=All years*
# 10	8,062	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 lik*) *Indexes=CAB Abstracts Timespan=All years*
# 9	1	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 blandness) *Indexes=CAB Abstracts Timespan=All years*
# 8	1,797	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 perceiv*) *Indexes=CAB Abstracts Timespan=All years*
# 7	18,784	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 prefer*) *Indexes=CAB Abstracts Timespan=All years*
# 6	3,355	**TOPIC:** ((food or gustat* or taste or tasting or tastes or tasted or flavour* or flavor* or diet*) NEAR/3 percept*) *Indexes=CAB Abstracts Timespan=All years*
# 5	14,787	**TOPIC:** (palatab*) *Indexes=CAB Abstracts Timespan=All years*
# 4	369,274	#3 OR #2 OR #1 *Indexes=CAB Abstracts Timespan=All years*
# 3	306,422	**TOPIC:** ((food or diet* or nutrition* or oral) NEAR/2 therap*) *Indexes=CAB Abstracts Timespan=All years*
# 2	7,967	**TOPIC:** ((food or diet* or nutrition* or oral) NEAR/3 enrich*) *Indexes=CAB Abstracts Timespan=All years*
# 1	78,085	**TOPIC:** ((food or diet* or nutrition* or oral) NEAR/3 supplement*) *Indexes=CAB Abstracts Timespan=All years*

PROSPERO Searched August 2, 2016

No hits for line : (taste perception or taste preference or gustat*) and (food supplement* or nutritional supplement* or onl or enrich* food*) and (cancer* or neoplasm* or chemotherap* or radiotherp* or metast* or tumour* or tumor

Appendix B. Search strategies of the review presented in Chapter 3 (search terms for each database)

Medline (Ovid)

607 Results

1 Taste Disorders/ (1514)

2 DYSGEUSIA/ (361)

3 Taste Perception/ (1387)

4 (ageusi* or hypogeusi* or dysgeusi* or parageusi*).mp. (1321)

5 ((Taste or TCting or Tastes or Tasted) adj3 (distort* or dysfunction* or disorder* or alter* or change* or

abnormal* or blind* or impair*)).mp. (3370)

6 (gustatory adj3 (perception* or sensitiv* or distort*)).mp. (293)

7 1 or 2 or 3 or 4 or 5 or 6 (5758)

8 Neoplasms/ (386244)

9 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or meTCt* or malignan* or premalignan* or

pre-malignan*).mp. (3702908)

10 8 or 9 (3702908)

11 (questionnaire* or measure* or survey* or scale* or tool or tools or module* or evaluat* or therap* or test or

tests or tested or testing).ti,ab. (9459404)

12 (validat* or validity or reliab*).ti,ab. (878001)

13 (strateg* or counselling or counseling or intervention*).ti,ab. (1681957)

14 (case finding or casefinding).ti,ab. (4408)

15 screen*.ti,ab. (642358)

16 "Surveys and Questionnaires"/ or EVALUATION STUDIES/ (627712)

17 Counseling/ (33186)

18 11 or 12 or 13 or 14 or 15 or 16 or 17 (10633602)

19 7 and 10 and 18 (607)

Embase (Ovid)

468 Results

1 Taste disorder/ (7706)

2 dysgeusi*.ti,ab. (1385)

3 Taste/ (22626)

4 (ageusi* or hypogeusi* or parageusi*).mp. (1303)

5 ((Taste or TCting or Tastes or Tasted) and (distort* or dysfunction* or disorder* or alter* or abnormal* or

blind* or impair*)).mp. (18885)

6 (gustatory and (perception* or sensitiv* or distort*)).mp. (1875)

7 1 or 2 or 3 or 4 or 5 or 6 (39096)

8 exp neoplasm/ (4129854)

9 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or meTCt* or malignan* or premalignan* or

pre-malignan*).ti,ab. (3730724)

10 8 or 9 (5014607)

11 (questionnaire* or measure* or survey* or scale* or tool or tools or module* or evaluat* or test or tests or

tested or testing).ti. (1589757)

12 (validat* or validity or reliab*).ti. (162448)

13 (strateg* or counselling or counseling or intervention*).ti. (336355)

14 (case finding or casefinding).ti. (1323)

15 screen*.ti,ab. (887413)

16 *counseling/ (15977)

17 *questionnaire/ (31567)

18 11 or 12 or 13 or 14 or 15 or 16 or 17 (2789065)

19 7 and 10 and 18 (468)

CINAHL Plus with Full Text (EBSCO)

261 Results exported

S16	S6 AND S9 AND S15	**Search modes** - Find all my search terms	**View Results** (263)	
S15	S10 OR S11 OR S12 OR S13 OR S14	**Search modes** - Find all my search terms	**View Results** (2,959,527)	
S14	(MM "Counseling")	**Search modes** - Find all my search terms	**View Results** (12,174)	
S13	(MM "Surveys+") OR (MM "Structured Questionnaires") OR (MM "Health Perceptions Questionnaire") OR (MM "Open-Ended Questionnaires")	**Search modes** - Find all my search terms	**View Results** (43,650)	
S12	"case finding" or casefinding	**Search modes** - Find all my search terms	**View Results** (1,067)	
S11	validat* or validity or reliab* or strateg* or counselling or counseling or intervention* or screen*	**Search modes** - Find all my search terms	**View Results** (883,990)	
S10	(questionnaire* or measure* or survey* or scale* or tool or tools or module* or evaluat* or therap* or test or tests or tested or testing)	**Search modes** - Find all my search terms	**View Results** (2,765,537)	
S9	S7 OR S8	**Search modes** - Find all my search terms	**View Results** (566,072)	

PsycINFO (Ovid) 69 Results

1 *Taste disorders/ or *Taste perception/ (6112)

2 (ageusi* or hypogeusi* or dysgeusi* or parageusi*).mp. [mp=title, abstract, heading word, table of contents, key

concepts, original title, tests & measures] (104)

3 ((Taste or TCting or Tastes or Tasted) adj3 (distort* or dysfunction* or disorder* or alter* or change* or

abnormal* or blind* or impair*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (826)

4 (gustatory adj2 (perception* or sensitiv* or distort*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (103)

5 1 or 2 or 3 or 4 (6596)

6 exp NEOPLASMS/ (47085)

7 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or meTCt* or malignan* or premalignan* or pre-malignan*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

(77092)

8 6 or 7 (78033)

9 (questionnaire* or measure* or survey* or scale* or tool or tools or module* or evaluat* or therap* or test or tests or tested or testing).ti,ab. (2116704)

10 (validat* or validity or reliab* or strateg* or counselling or counseling or intervention* or screen*).ti,ab.

(928996)

11 (case finding or casefinding).ti,ab. (683)

12 *Surveys/ or *Questionnaires/ (16441)

13 exp COUNSELING/ (74515)

14 9 or 10 or 11 or 12 or 13 (2471837)

15 5 and 8 and 14 (69)

Cochrane Library (Wiley Online Library)

505 Results

ID	Search Hits
#1	[mh "Taste Disorders"] 126
#2	[mh DYSGEUSIA] 31
#3	[mh "Taste Perception"] 60
#4	ageusi* or hypogeusi* or dysgeusi* or parageusi* 741
#5	((Taste or TCting or Tastes or Tasted) adj3 (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind* or impair*)) 226
#6	(gustatory adj3 (perception* or sensitiv* or distort*)) 3
#7	#1 or #2 or #3 or #4 or #5 or #6 1102
#8	[mh Neoplasms] 78453
#9	(cancer* or neoplasm* or tumor* or tumour* or chemotherap* or radiation* or radiotherap* or oncolog* or meTCt* or malignan* or premalignan* or pre-malignan*) 203900
#10	#8 or #9 208605
#11	(questionnaire* or measure* or survey* or scale* or tool* or module* or evaluat* or therap* or test or tests or tested or testing or screen*):ti,ab,kw 894880
#12	(validat* or validity or reliab*):ti,ab,kw 48182
#13	(strateg* or counselling or counseling or intervention*):ti,ab,kw 228480
#14	(case finding or casefinding):ti,ab,kw 1231
#15	[mh "Surveys and Questionnaires"] 53166
#16	[mh "EVALUATION STUDIES"] 25
#17	[mh Counseling] 5085
#18	#11 or #12 or #13 or #14 or #15 or #16 or #17 937940
#19	#7 and #10 and #18 505

Web of Science- All Databases (Clarivate Analytics)

49 Results

#4	49	#3 AND #2 AND #1 *Timespan=All years* *Search language=Auto*
#3	2,375	TI=((ageusi* or hypogeusi* or dysgeusi* or parageusi*) or ((Taste or TCting or Tastes or Tasted) NEAR/3 (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind* or impair*)) or (gustatory NEAR/3 (perception* or sensitiv* or distort*))) *Timespan=All years* *Search language=Auto*
#2	10,858,571	TI=(questionnaire* or measure* or survey* or scale* or tool or tools or module* or evaluat* or therap* or test or tests or tested or testing or screen* or validat* or validity or reliab* or strateg* or counselling or counseling or intervention* or “case finding” or casefinding) *Timespan=All years* *Search language=Auto*
#1	12,265,694	TOPIC: ((cancer* or neoplasm* or tumor* or tumour* or chemotherap* or radiation* or radiotherap* or oncolog* or meTCt* or malignan* or premalignan* or pre-malignan*)) *Timespan=All years* *Search language=Auto*

Appendix C. Survey About Preferences for Fortified Snacks among Patients with cancer

Section 1. Demographics and clinical information

Are you?

- ◯ Female
- ◯ Male
- ◯ Other

What is your age range?

- ◯ 18 - 29 years
- ◯ 30 - 49 years
- ◯ 50 - 65 years
- ◯ Greater than 65 years

Please indicate your primary tumour site

- ◯ Bladder
- ◯ Bone
- ◯ Brain
- ◯ Breast
- ◯ Colorectal
- ◯ Gallbladder
- ◯ GI (appendix, stomach, pancreatic, esophageal, bile duct, intestinal)
- ◯ Gynecological
- ◯ Head and neck
- ◯ Hodgkin lymphoma
- ◯ Kidney or adrenal
- ◯ Leukemia
- ◯ Liver
- ◯ Lung
- ◯ Melanoma
- ◯ Mesothelioma
- ◯ Multiple myeloma
- ◯ Non-Hodgkin lymphoma
- ◯ Prostate or testicular
- ◯ Skin
- ◯ Soft tissue sarcoma
- ◯ Spinal
- ◯ Thyroid
- ◯ Other. Please specify ____

In the last 3 months, have you received any of the following treatments for your cancer? (Check all that apply)

- ◯ I did not receive any medical treatment for cancer in the last three months
- ◯ Surgery (do not consider biopsy or insertion of medication ports to be surgery)
- ◯ Immunotherapy
- ◯ Chemotherapy
- ◯ Radiation therapy
- ◯ Bone marrow or stem cell transplant (do not consider bone marrow biopsy to be a transplant)
- ◯ I received treatment but I can't remember it
- ◯ Other. Please specify _____

Section 2. Food Intake:

As compared to my normal intake, I would rate my food intake during the past month as:

- ◯ More than usual
- ◯ Unchanged
- ◯ Less than usual

I am now mostly taking:

- ◯ Normal food but less than normal amount
- ◯ Little solid food
- ◯ Only liquids
- ◯ Only nutritional supplements
- ◯ Very little of anything
- ◯ Only tube feedings or only nutrition by vein

What meals and snacks do you currently have in one day?

- □ breakfast
- □ light morning snack
- □ lunch
- □ light mid-afternoon snack
- □ dinner
- □ other

What do you currently prefer to eat (check all that apply):

- □ salty
- □ sweet
- □ spicy
- □ hot
- □ cold
- □ small pieces
- □ minced
- □ blended
- □ creamy
- □ liquid
- □ other _____

Since your cancer diagnosis, have you developed nausea or aversion to any food?

- □ Yes
- □ No

If yes, specify to which foods_____

Select the **three most important food attributes** that stimulate your appetite.

- __ taste
- __ aspect appearance?
- __ smell
- __ consistency or texture
- __ quantity
- __ presentation
- __ other _____

What foods do you currently consume when you snack?

Morning snacks: _____

Afternoon snacks: _____

Evening snacks: _____

Since your cancer diagnosis, have you consumed Oral Nutritional Supplements (e.g. Boost, Ensure)

□ Yes

□ No

If yes, please write the first four associations, ideas thoughts or feelings that come to your mind when you think about those products.

_____

Section 3. Satisfaction with Food-Related Life questions

Please think of all the things you do and experience in relation to food and meals (e.g., planning meals, shopping, preparing meals, eating meals) and then, using the 1–7 scale below, indicate your agreement with each item by marking the corresponding circle.

Item	Disagree completely (1)	Disagree (2)	Slightly disagree (3)	Neither agree or disagree (4)	Slightly agree (5)	Agree (6)	Completely agree (7)
Food and meals are positive elements in my life	○	○	○	○	○	○	○
I am generally pleased with my food	○	○	○	○	○	○	○
My life in relation to food and meals is close to my ideal	○	○	○	○	○	○	○
With regard to food, the conditions of my life are excellent	○	○	○	○	○	○	○
Food and meals give me satisfaction in my daily life	○	○	○	○	○	○	○

Section 4. Symptoms influencing food intake

Instructions: Below is a list of 17 symptoms. Please circle the option that describes how often you experienced the symptom during the past 3 days, and if it interfered with your eating.

During the past 3 days:	**How often did you have this symptom?**					**Has this symptom interfered with eating?**				
Symptom	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**A lot**	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**A lot**
Pain	1	2	3	4	5	1	2	3	4	5
Anxious	1	2	3	4	5	1	2	3	4	5
Dry mouth	1	2	3	4	5	1	2	3	4	5
Loss of appetite	1	2	3	4	5	1	2	3	4	5
Constipation	1	2	3	4	5	1	2	3	4	5
Feeling full	1	2	3	4	5	1	2	3	4	5
Depressed	1	2	3	4	5	1	2	3	4	5
Thick saliva	1	2	3	4	5	1	2	3	4	5
Diarrhea	1	2	3	4	5	1	2	3	4	5
Sore mouth	1	2	3	4	5	1	2	3	4	5
Lack of energy	1	2	3	4	5	1	2	3	4	5
Nausea	1	2	3	4	5	1	2	3	4	5
Difficulty chewing	1	2	3	4	5	1	2	3	4	5
Smells bother me	1	2	3	4	5	1	2	3	4	5
Vomiting	1	2	3	4	5	1	2	3	4	5
Difficulty swallowing	1	2	3	4	5	1	2	3	4	5
Taste changes	1	2	3	4	5	1	2	3	4	5
Other: Specify	1	2	3	4	5	1	2	3	4	5

If you have indicated that food tastes different than usual, please select the option that best applies to you

- ○ I have a persistent bad taste in my mouth after meals
- ○ I have a persistent bad taste in my mouth all the time
- ○ Food tastes less intense than it used to taste
- ○ Food tastes more intense than it used to taste
- ○ Specific drugs interfere with my sense of taste
- ○ Other

Please specify_____

Section 5. Nutrient-enhanced snacks preference

Below is a list of commonly consumed snacks.

Imagine that you can purchase this snack product with added nutrients specifically for cancer patients. The price of this snack product is the same as the snack product without added nutrients. **To what extent do you agree that this product with added nutrients would be a good choice as a snack for cancer patients?**

Item	Disagree strongly		Neither agree nor disagree		Agree strongly
Fruit bar	○	○	○	○	○
Fruit juice					
Pureed fruit or vegetable					
Cheese					
Muesli or Granola bar					
Protein bar					
Soy/almond/oat or rice drink					
Burritos					
Egg product					
Meat product					
Fish product					
Cake					
Cookies					
Pastries					
Candies					
Vegetable juice					
Mashed potatoes					
Pudding or custard					
Flavoured milk					
Milk					
Ice cream					
Ice cream bar					
Yogurt					
Yogurt drink					
Chocolate					
Potato Chips					
Pretzels					
Whole grain bread					
Bread					
Nacho chips					
Porridge					
Iced coffee or tea					

Soup					
Other, please specify_____					
Oral Nutritional Supplements (e.g. Boost, Ensure)					

Which characteristics would you like in a nutrient-enhanced snack? (Check all that apply)

- ◯ Cheap
- ◯ Coarse texture
- ◯ Cold
- ◯ Convenient
- ◯ Easy to swallow
- ◯ Easy to chew
- ◯ Flavorful
- ◯ Liquid texture
- ◯ Low fat
- ◯ Nutritious
- ◯ Plain aroma
- ◯ Plain flavor
- ◯ Ready to eat
- ◯ Resealable packaging
- ◯ Soft texture
- ◯ Warm
- ◯ Other, please specify_____

Which of the following would you like added to a nutrient-enhanced snack? (Check all that apply)

- ◯ Antioxidants
- ◯ Cannabinoid derivates
- ◯ Collagen
- ◯ Fiber
- ◯ Low/no sugar
- ◯ Minerals
  - If yes:
    - ◯ Calcium
    - ◯ Phosphorus
    - ◯ Sodium
    - ◯ Potassium
    - ◯ Magnesium
    - ◯ Sulfur
    - ◯ Iron
    - ◯ Zinc
    - ◯ Other
    - ◯ All of the above
    - ◯ Any mineral
- ◯ Omega 3 fatty acids
- ◯ Other, please specify
- ◯ Probiotics
- ◯ Protein
  - If yes:
    - ◯ Dairy protein (casein, whey)
    - ◯ Egg protein
    - ◯ Insect protein
    - ◯ Meat protein
    - ◯ Plant protein
    - ◯ All of the above
    - ◯ Any protein

◯ Spirulina algae
◯ Oats
◯ Flaxseed
◯ Hemp seeds
◯ Vitamins

If yes:
◯ Vitamin A
◯ B Vitamins
◯ Vitamin C
◯ Vitamin D
◯ Vitamin E
◯ Vitamin K
◯ All of the above
◯ Any vitamin

Perception and opinions of oat and oat products

Please write the first four images, associations, thoughts or feelings that come to your mind when you think about oats and oat food products.

_____
_____
_____

Do you currently consume oats and/or oat products?

- ○ Yes
- ○ No

If yes, please indicate how often do you consume those products

- ○ Never
- ○ Once per month or less
- ○ 1-3 times per month
- ○ 1-2 times per week
- ○ 3 or more times per week

If yes, please indicate What type of oat products do you consume regularly? (Check all that apply)

- ○ Oat Cereal
- ○ Oatmeal
- ○ Oat bars
- ○ Oat based beverages
- ○ Oat cookies
- ○ Other _____

Please indicate your level of agreement or disagreement with the following statements about oat food products.

Statement	Strongly disagree	Disagree	Undecided	Agree	Strongly agree
Oats are highly nutritious packed with important vitamins, minerals and antioxidants					
Oats contain large amounts of beta-glucan, a type of soluble fiber with several health benefits					
It is easy to incorporate oat products into my daily diet					
Oats may help relief constipation					
Oat fibre helps reduce/lower cholesterol, (which is) a risk factor for heart disease					

Appendix D. Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____135_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____146_____
Funding	4	Sources and types of financial, material, and other support	_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____
	5b	Name and contact information for the trial sponsor	_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____N/A_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____N/A_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____135-139___
	6b	Explanation for choice of comparators	_____N/A_____
Objectives	7	Specific objectives or hypotheses	_____139_____

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____140_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____141_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____140_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____142-144___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____N/A_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___N/A_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____139____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____141_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____141_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____N/A_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____N/A_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____N/A_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____N/A_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___144_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____N/A_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____144_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____144-145__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____N/A_____

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Note: DMC is not required because there is no external sponsor and this is a low risk intervention.	____N/A_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____N/A_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____146____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___141-142____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____144_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____N/A_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____144_____

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____N/A_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Appendix E. Brochure containing the study information

We would like to hear from you!

Please contact us if you would like to participate or you want to know more about the study.

Blanca Enriquez
Research coordinator .

benrique@ualberta.ca
780- 432- 8962

Study approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-18-0061)

For questions regarding ethical issues, please contact Health Research Ethics Board of Alberta-Cancer Committee contact: 780-423-5727 or toll-free 1-877-423-5727

Research opportunity for head and neck cancer patients

14-day consumption of a nutrient-rich oat beverage

Did you know?

Inadequate nutrition is common among head and neck cancer patients.

The addition of nutrient rich foods to your diet might help you meet the recommendations for calories and protein. However, few nutrient-rich products suitable for head and neck cancer are available.

Purpose of the study

This research study is being done to assess if the consumption of a nutrient-rich oat beverage over 14 days is feasible for head and neck cancer patients.

The contribution of the product to your intake of total calories and protein will also be evaluated.

Who can participate?

You may be eligible to participate in this study if you a you have a diagnosis of Head & Neck cancer and you are:

- over 18 years old
- capable of oral intake
- not allergic or sensitive to the product ingredients, which include oats

What will you be asked to do?

Baseline

Complete baseline surveys about foods consumed, symptoms, quality of life and food preferences as well as liking of the oat beverage.

14-day oat beverage consumption

- Consume one serving of the oat beverage per day
- Complete surveys at different time points regarding product liking, consumption, symptoms and foods consumed.

Day 14

Repeat baseline surveys

What type of product would you consume?

A commercially available oat-based beverage powder that can be mixed with hot or cold milk or water, or with yogurt or fruits to create a smoothie.

It contains the nutrients protein, dietary fibre and ß-glucan and it has probiotics.

Your experience is very valuable for future patient care.

This study may help us improve the current programs that we have for patients to promote healthy food choices.

Appendix F. Informed Consent Form for Participation in a Research Study

DEPARTMENT OF AGRICULTURAL, FOOD AND NUTRITIONAL SCIENCE

FACULTY OF AGRICULTURAL, LIFE & ENVIRONMENTAL SCIENCES

410 Agriculture/Forestry Centre
Edmonton, Alberta, Canada T6G 2P5
Tel: 780.492.3239
Fax: 780.492.4265
afns-chair@ualberta.ca
www.afns.ualberta.ca

Informed Consent Form for Participation in a Research Study

Consumption of oat-based beverages by cancer patients – a 14-day feasibility study (Oat-based beverages 14 days consumption study)

Researcher: *Wendy V. Wismer, PhD*
Associate Professor
University of Alberta

Co-Investigators:

- *Blanca E. Enríquez-Fernández, PhD Candidate, University of Alberta*
Phone: 780-492-3833
- *Rufus A. Scrimger, MD, Department of Oncology. Division of Radiation Oncology*
- *Brock Debenham, MD, Department of Oncology. Division of Radiation Oncology*

Sponsor: University of Alberta

WHY AM I BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being invited to participate in this research study because maintaining adequate nutrition might be challenging after your diagnosis and/or treatment for head and neck cancer and the consumption of nutrient rich oat-based beverages could represent a way to increase your caloric and nutrient intake. The purpose of this study is to help understand if the daily consumption of this product over 14 days is feasible, if daily consumption changes your liking for the product, and if product consumption increases your protein and caloric consumption.

This consent form provides information about the study to assist you with making an informed decision. The researcher will discuss this study with you and will answer any questions you may have. You are encouraged to ask questions. When all your questions have been answered to your satisfaction, you can decide if you want to be in the study or not.

Taking part in this study is voluntary. You may choose whether or not you take part. If you choose to participate, you may leave the study at any time without giving reason or without penalty. Deciding not to take part or deciding to leave the study early will not result in any penalty or effect current or future care or employment.

If you decide to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 55 people will take part in this study. We plan to enroll all participants at the

Head and Neck cancer clinic of the Cross Cancer Institute.

WHAT WILL HAPPEN DURING THIS STUDY?

This study should take about 21 days for you (3-7 days for baseline assessment and 14 days of product consumption). The total study (recruitment and completion of all participants´ involvement) will take one year to complete and the final results should be known in about one year.

The following study visit table shows the questionnaires to be completed:

Table 1. Study visit table.

Study Questionnaires	Day 0	Day 3	Day 7	Day 10	Day 14
Sociodemographic information	X				
3-day food record	X				X
24 hour diet recall			X		
Food aversions/ preferences questionnaire	X				X
Head and Neck symptom checklist (HNSC®)	X				X
Appetite, Hunger and Sensory Perception (AHSP) questionnaire					
Patient-Generated Subjective Global Assessment (PG-SGA) sections 1, 2, 4	X				X
University of Washington quality of life	X		X		X

Satisfaction with food-related quality of life (SWFL)					
Product liking and consumption tracking	X	X	X	X	X

WHAT ARE MY RESPONSIBILITIES SHOULD I DECIDE TO PARTICIPATE IN THIS STUDY?

If you participate in this study, you will be asked to consume the oat-based product (20g per day) daily for 14-days. You will also be asked to complete questionnaires at the beginning, throughout and the end of the study.

When signing this informed consent form, you will receive a three-day food record to be completed at home and returned at a later date. It may take up to 30 minutes per day to complete it. Another three-day diet record will be requested after about 11 days of consuming the product. These food records will be reviewed for clarity by the study staff. At your next visit to the CCI you will be asked to hand in the initial three-day food record and you will complete the following baseline questionnaires:

- Sociodemographic information.
- Product liking using a 9-points scale.
- Food aversions/preferences questionnaire: short survey to obtain information about your food preferences, aversions and eating patterns.
- Head and Neck Symptom Checklist (HNSC) to indicate the presence and frequency of 17 symptoms known to interfere with eating.
- Nutritional status will be assessed using some sections of the Patient-Generated Subjective Global Assessment.
- University of Washington quality of life and Satisfaction with food-related quality of life (SWFL) questionnaires, both used to assess quality of life.

When signing this consent form, you will receive samples of the oat-based product, so you can consume them at home. During that 14-day period, you will be asked to consume one serving (20g of the powdered product) per day. Each week, you will receive the oat beverage product for the next 7 days. Any unused product will be returned at the next week during your visit.

On day 7 you will be asked to complete a 24-hour food recall to list all food and drink consumed in the past 24 hours and the quality of life questionnaires. Additionally, on days 3, 7, 11 and 14, you will also be asked to tell us about how the oat-based product was prepared (e.g. mixed with milk, water or yogurt) and consumed (time of day, amount). At the end of the trial, you will be asked to repeat the baseline questionnaires. The questionnaires will be completed at time of regular appointments. The time required to complete the questionnaires will be about 30 minutes.

If you decide to participate in this study, you will receive two grocery store gift cards of $ 25 each (one on day 0 and one on day 7) to purchase milk or the ingredients you want to mix the product with.

WHAT WILL HAPPEN IF I CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to end your participation in this research study (called early withdrawal) at any time without having to provide a reason and without penalty. If you choose to withdraw early from the study without finishing the procedures, you are encouraged to contact the researcher or study staff. The research may also withdraw you from the study if he/she feels it is in your best interest.

Information that was recorded before you withdrew will be used by the researcher for this study, but no additional information will be collected after you withdraw your permission.

WHAT ARE THE RISKS/DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

There are no risks other than the everyday risks of consuming water and oat-based products.

If you have any allergies, sensitivities or intolerances to the foods or ingredients used, you should not participate in this study.

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING IN THIS STUDY?

Participation in this study may or may not be of personal benefit to you. You may enjoy the experience of consuming the product and you may be better able to meet the recommended consumption amounts for protein and calories.

Based on the results of this study, it is hoped that in the long-term, patient care can be better understood or improved. The results of the study will allow us to confirm if this product can be consumed daily over 14-days and possibly a longer time by other patients with head and neck cancer as a food to increase caloric and nutrient consumption.

HOW WILL MY PERSONAL INFORMATION BE KEPT PRIVATE?

If you decide to participate, the researcher and study staff will only collect information they need for this study. They will do everything that they can to make sure that this data is kept private/ confidential by maintaining any study files in a locked cabinet.

Some study data will be collected and managed using REDCap (Research electronic data capture), an electronic data capture tool designed to protect patient privacy and confidentiality in clinical research. Computer files will be encrypted. No data relating to this study that includes your name will be released outside of the study site nor will it be published by the researcher. Sometimes, by law, the researcher may have to release information including names and therefore absolute confidentiality cannot be guaranteed. However, every effort will be made to make sure that your information is kept confidential.

The researcher or study staff may need to look at your medical files/records or at those kept by other health care providers that you may have seen in the past (e.g., your family doctor). Any information that they get from these records will be only what is needed for the purpose of this study. It will be kept confidential to the extent permitted by the applicable laws and will not be

disclosed or made publicly available, except as described in this consent document. In some circumstances, researchers are required by law to release information about participants to local authorities such as positive HIV or Hepatitis results.

Individuals of the following organizations may look at your medical records, including your name, for quality assurance purposes and/or to verify that the information collected for this study is correct and follows proper laws and/or guidelines: University of Alberta, the Health Research Ethics Board of Alberta (HREBA) or Health Canada.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

By signing this consent form you are allowing the study team to collect, use and disclose information about you from your personal medical records. After the study is done, we will still need to securely store your data that was collected as part of the study. We will keep your data and study records stored for 5 years after the end of the study.

A copy of the consent form that you sign to enter this study may be included in your medical record/hospital chart.

WILL THERE BE COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

There could be a cost associated with purchasing milk or other items (e.g. yogurt, fruit) to mix the product with. Therefore, if you decide to participate in this study, you will receive two grocery store gift cards of $25 each (one on day 0 and one on day 7) to purchase these products.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the researcher.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the hospital, researchers, sponsor, institutions or their agents involved for compensation, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE ANY CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the researcher and funder(s) of this study.

WHO DO I CONTACT FOR QUESTIONS RELATED TO THIS STUDY?

If you have questions about taking part in this study you should talk to the researcher, co-investigator or study nurse. These person(s) are:

Wendy V. Wismer	780-492-2923
Name	Telephone
Blanca Enríquez-Fernández	780-492-3833
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta.

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

UNDERSTANDING AND SIGNATURES PAGE

	Yes	**No**
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits and risks/discomforts of taking part in this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason or without penalty?	☐	☐
Do you understand that we will be collecting information about you for use in this study only?	☐	☐
Do you understand that by signing this consent form you are allowing the study team to collect, use and disclose information about you from your personal medical records?	☐	☐

Do you understand who can potentially see your medical /study records, including those that identify you?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Do you feel that you had enough time and opportunity to consider the information provided to you by way of asking questions, having conversations with others and considering your options?	☐	☐

By signing this form I agree to participate in this study.

Signature of Participant	Printed Name	Date

STUDY TEAM ACKNOWLEDGEMENT

I believe the person signing this form understands what is involved in this research study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	Printed Name	Date

You will be given a copy of this signed and dated consent form prior to participating in this optional research.