

“Everything tastes different”

The impact of changes in chemosensory perception
on food preferences, food intake and quality of life
during chemotherapy in cancer patients

“Everything tastes different”

Yfke Carlijn de Vries

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Propositions

1. Chemosensory changes during chemotherapy in cancer patients are a matter of taste.
(this thesis)
2. Objective measures of taste and smell are not relevant for cancer patients.
(this thesis)
3. Clinical guidelines are outpaced by clinical practice.
4. Personalized nutrition does not exist.
5. Preserving cultural diversity should be as self-evident as preserving biodiversity.
6. You don't need to speak Frisian to be Frisian.

Propositions belonging to the thesis entitled:

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Yfke Carlijn de Vries
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Thesis

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Chapter 1

General introduction



Introduction

In the Netherlands, one in three persons is diagnosed with cancer at some point in their lives.¹ Because of earlier detection and further developments in cancer treatment, cancer survival rates have increased in the past decades and the number of cancer survivors is growing. Therefore, long term side effects of cancer treatment are becoming more and more important. There are several known long term effects after cancer treatment, like fatigue, pain and cognitive complaints.^{2, 3} Weight gain has also been described as a possible long term concern in breast cancer patients that were treated with chemotherapy.^{4, 5} This gain in weight is associated with a decreased quality of life and an increased risk of comorbidities like cardiovascular disease and diabetes.⁵ Moreover, there are studies that suggest that this gain in weight in breast cancer patients is characterised by a change in body composition, with an increase in fat mass, and no change or decrease of lean mass.^{6, 7} It is currently unknown whether this increase in weight is due to lower energy expenditure, higher energy intake, a combination of the two, or influenced by other factors.

One frequently observed side effect of chemotherapy is a change in taste and smell perception, with a prevalence of 45% to 85% for taste changes and 5% to 60% for smell changes.⁸ Possibly, these changes lead to a change in food preferences, and can thereby contribute to a changed dietary intake and play a role in weight gain and changing body composition in breast cancer patients (figure 1.1). However, the nature of these chemosensory changes and their impact on food preferences and dietary intake are not well documented in cancer patients undergoing chemotherapy. Furthermore the impact of chemosensory changes may go beyond nutritional consequences, as taste and smell also play an important role in everyday functioning and quality of life.



Figure 1.1 Hypothetical chain of events for how taste and smell changes could contribute to weight change and body composition.

Although weight gain may occur in breast cancer, not all cancer patients gain weight during chemotherapy. The way chemosensory changes impact food preferences and

dietary intake may potentially be different for different types of cancer. Patients with cancer in the upper gastrointestinal tract, like oesophagogastric cancer patients, receive different types of chemotherapy than breast cancer patients, and may possibly experience different chemosensory alterations and food preferences. Moreover, oesophagogastric cancer patients are mostly diagnosed when the disease is already in an advanced stage and are often malnourished when they are diagnosed.⁹ In this thesis, chemosensory changes and food preferences will be investigated in two different patient groups, thereby possible differences and similarities will indicate to what extent chemosensory and food preference changes are patient group specific, and if these might play a differential role in nutritional status in cancer patients undergoing chemotherapy.

This general introduction starts with an overview on the senses of taste and smell, after which taste and smell changes, food preferences and intake, and quality of life in patients with cancer undergoing chemotherapy will be discussed. The introduction ends with the aim and outline of this thesis.

Taste

The sense of taste, or gustation, is involved in the enjoyment and evaluation of nutritional content of food, and prevention of ingesting potentially toxic foods.¹⁰ Humans can perceive five distinct basic tastes: sweet, salt, bitter, sour and umami. Sweet and umami taste function to signal sugars and amino acids, salt functions to maintain electrolyte balance and bitter and sour signal potential poisonous and unripe foods.¹¹ Furthermore, there are indications that fat could also be a basic taste, but this is still under debate.¹²

Tastes are signalled when they activate taste receptor cells mostly on the tongue, soft palate, or oropharynx. These receptor cells constantly regenerate and are renewed every 9 to 15 days.¹³ Taste receptor cells are clustered in taste buds, which are in turn located in gustatory papillae.¹³ Tastes are signalled through different types of receptors. Salty and sour tastes are signalled through ion channels, while sweet, bitter and umami are detected by G-protein-coupled receptors. When tastes are signalled, signals travel to the brain through the facial, glosso-pharyngeal and vagus nerve. Signals are first sent to the solitary tract of the brain stem after which signals are then synapsed to the thalamus, anterior insula and frontal operculum (primary taste cortex), and the orbitofrontal cortex (secondary taste cortex).^{14, 15}

Smell

The sense of smell, or olfaction, is much more complex than the sense of taste. Whereas there are five basic tastes, it was calculated that humans are able to detect and discriminate more than a trillion of different odorants.¹⁶ The olfactory system is not only important for food and flavour perception, but is also important in identifying potential hazards and interpersonal communication.¹⁷

There are two routes whereby odorants can reach the olfactory epithelium, orthonasally and retronasally.¹⁸ The orthonasal route goes through the nose and gives information on ambient odours in the outside world. Before eating, the orthonasal route signals whether something is edible or not. Furthermore, external olfactory cues can stimulate appetite in the anticipatory phase of eating.^{19, 20} The retronasal route refers to foods present in the mouth. During eating and drinking, volatiles aromas from food are released and travel through the oral cavity and pharynx to the olfactory epithelium at the top of the nasal cavity, where olfactory receptor neurons are located. Olfactory receptor neurons also regularly regenerate, renewing approximately every month.²¹ When olfactory stimuli reach the olfactory receptors, action potentials are sent through the olfactory nerve through the cribriform plate to the olfactory bulb in the brain. Different from other senses, olfactory signals travel directly to the brain and do not relay through the thalamus. From the olfactory bulb, signals are further processed in amongst others the piriform cortex and orbitofrontal cortex.¹⁴

When a food is eaten, the gustatory, olfactory and somatosensory (irritation, texture, temperature) signals of a food together determine the flavour of the food.²² Flavour is therefore a multimodal experience. In everyday life, it is difficult for humans to distinguish between the sense of taste and smell as they are so much intertwined. The “taste” of food, for most humans, is therefore strongly related to the flavour of a food and this also encompasses an olfactory component.

Taste and smell during chemotherapy in cancer patients

Many cancer patients undergoing chemotherapy report that their food does not taste the same.⁸ These chemosensory alterations have been reported as an absence of taste or smell, reduced or increased sensitivity, distortion of taste or smell, phantom tastes or odours and metallic sensations.⁸

There are several possible mechanisms through which chemotherapy could affect taste and smell function. The most generally accepted hypothesis is that as chemotherapy targets rapidly dividing cells, besides the tumour, taste and smell receptor cells can be affected as well. This may lead to a lower number of receptor cells, but possibly also to an altered cell structure, changed receptor surface or interrupted neural coding.²³ Taste and smell changes can start during the first infusion of chemotherapy⁸, but longitudinal studies also show that these changes are transient and mostly recover after chemotherapy.^{24, 25} However, there are also reports of taste and smell changes well beyond the end of chemotherapy.^{26, 27} It is suggested that the nature of taste and smell changes may vary among different types of cancer and chemotherapy.²⁸ However, often studies have used heterogeneous study populations in terms of types of cancer, types of chemotherapy and stage of disease. Therefore systematic reviews failed to draw firm conclusions on whether there are specific target groups that suffer most from chemosensory changes.^{8, 29} Therefore it is important to assess taste and smell changes in homogeneous groups in terms of types of cancer and chemotherapy, and identify potential (clinical) determinants.

Many studies address taste and smell changes by self-report. However it should be noted that for most persons it is difficult to accurately judge their taste or smell function^{30, 31}, let alone to actually distinguish taste and smell. As mentioned before, when one is asked about taste, the response will mostly involve flavour as a whole. Therefore, to understand more on what actually changes during chemotherapy, it is also important to measure taste and smell function objectively. In this thesis, we use both objective and subjective measures of taste and smell, to get insight on whether actual taste and/or smell function is affected through chemotherapy and to get understanding of what patients actually experience during chemotherapy.

The taste and smell of foods are important predictors for food preferences and food intake. Therefore, when a patient's taste or smell perception is altered, this may have consequences for food preferences and intake. The next part of this introduction will go further into these factors.

Food preferences and food intake

Taste preferences form early in life. Humans have an innate preference for sweet taste, while having an innate aversion for sour and bitter.³² However, food preferences are subject to change upon life experience. E.g. although we have an innate aversion for

bitter, persons can learn to like coffee. In daily life, food preferences can differ depending on factors like the time of the day, the appropriateness of foods within a meal context and the meal or food eaten previously.³³⁻³⁵

Taste and food preferences are related to macronutrient balance. There are studies that show that, when humans are brought in a protein-depleted status, their preferences shift towards more savoury, protein-rich products to meet the metabolic needs.^{36, 37} Potentially, when taste and/or smell function are changed, this elicits shifts in food preferences and thereby can influence food intake during chemotherapy. Assessment of food preferences during chemotherapy in cancer patients to date have mostly focussed on reporting food products that are experienced as aversive. Products that are frequently reported as aversive are meat, caffeinated foods and drinks, and citrus fruits.²⁹ As breast cancer patients seem to gain weight, mainly in fat mass and stay stable, or decrease in muscle mass, in this thesis, we hypothesise that food preferences may shift from more protein rich (savory) products towards fat and carbohydrate rich (sweet) products in breast cancer patients.

Liking of foods measured on a scale is often used as a measure for food preferences, this can range from rating one product, to a questionnaire that includes over 100 food items.^{38, 39} However, it could be that two foods are liked the same, but a specific preference becomes apparent when being forced to choose. In addition, in daily life humans are exposed to many foods, and have the possibility to choose one product over the other. There are methods that assess food preferences with a forced-choice paradigm, like the Leeds Food Preference Questionnaire (LFPQ).⁴⁰ The LFPQ uses food pictures from different categories (high or low fat and savoury or sweet). During the task participants choose their preferred food between two food products from different categories. This method has its limitations, as it only includes one macronutrient (e.g. high and low fat). In order to measure shifts for multiple macronutrients and tastes, we developed a new method to assess food which is described in **chapter 2**, and then used as a method to assess food preferences in **chapter 3 and 4**.

Although food preferences are important predictors for food intake, it is not always directly related to food intake. Intake studies in breast cancer patients undergoing chemotherapy show conflicting results, with studies showing increases⁴¹, decreases^{42, 43}, and no changes^{6, 7, 44} of total energy intake during chemotherapy. Potentially because of different methods used to assess dietary intake, and differences in the moment of

assessing dietary intake during chemotherapy. Furthermore, studies focussing on dietary intake in cancer patients undergoing chemotherapy are limited to reporting total energy intake, but information on macronutrient intake, or specific food groups is often lacking. Therefore, in **chapter 5**, the dietary intake of breast cancer patients before and during chemotherapy is described, in relation to symptom burden, including subjective taste and smell perception.

Daily life and quality of life

Taste and smell play a role in eating and drinking, but these senses also play a role in identifying potential hazards and social communication.⁴⁵ Therefore these senses are important for everyday functioning, pleasure and enjoyment. Studies have shown that individuals who suffer from olfactory dysfunction have more depression and anxiety symptoms, feel more isolated and can have relationship difficulties.^{46, 47} Therefore, chemosensory dysfunction can have a serious impact on quality of life.

Quality of life outcomes are becoming more and more important in oncology research. In clinical trials, quality of life outcomes give additional information to the clinical endpoints used for determining the patients' benefits and toxicity of treatment.⁴⁸ Several studies have shown that in cancer patients undergoing chemotherapy, patients that experience taste and/or smell changes have a lower quality of life.^{28, 49} However, studies are mostly conducted in heterogeneous study populations, while experiences may vary in different patient groups. To get a better understanding on how taste and smell changes may impact daily life and quality of life, we assess the impact of taste and smell changes on quality of life in this thesis, both in oesophagogastric cancer patients (**chapter 6**) and in breast cancer patients (**chapter 7**).

Aim and thesis outline

Taste and smell changes during chemotherapy in cancer patient can have an impact on food preferences, food intake, daily life and quality of life. However, the direction of these relations is hardly studied and needs further investigation in specific cancer populations. The overall aim of this thesis is to assess how the sense of taste and smell change upon treatment with chemotherapy in two specific cancer populations, and to investigate their consequences in terms of food preferences, food intake and quality of life. For that, four research questions were defined:

1. How can we systematically measure food preferences in terms of macronutrients and tastes?
2. How do (objective and subjective) taste and smell perception change over the course of chemotherapy?
3. How do food preferences and food intake change over the course of chemotherapy, and are they related to taste and smell perception?
4. What are the consequences of chemosensory changes during chemotherapy for daily life and quality of life?

The first research question is addressed in **chapter 2**, which shows the development and validation of the Macronutrient and Taste Preference Ranking Task (MTPRT). In **chapter 3 and 4**, research question 2 and 3 are addressed, with two studies assessing objective and subjective taste and smell function, as well as food preferences assessed with the MTPRT, during chemotherapy in both oesophagogastric cancer patients and breast cancer patients. **Chapter 5** investigates the actual dietary intake in detail during chemotherapy in breast cancer patients, and the association between chemotherapy related symptoms (including taste and smell) and dietary intake (question 3).

To get more insight into the consequences of taste and smell changes during chemotherapy on daily life and quality of life (question 4), **chapter 6** describes a qualitative study on the experience of chemosensory and food-related changes and their impact on daily life in oesophagogastric cancer patients. Then in **chapter 7**, we assess the association between taste and smell changes and quality of life after chemotherapy in breast cancer patients.

Finally, in **chapter 8** of this thesis, the main findings of the studies are summarized and discussed. This discussion puts the findings in perspective and gives implications for practice and directions for future research.

The chapters involving breast cancer patients (**chapter 4, 5 and 7**) were done within the COBRA-study (see box 1).

Box 1. The COBRA-study stands for Change of Body composition in Breast cancer: All-in Assessment. In this prospective cohort, breast cancer patients are followed over the course of chemotherapy treatment, with measurements before, during, shortly after and 6 months after chemotherapy. These patients are compared to a similar group of women without cancer, who are followed over a similar time frame. Overall, the aim of the COBRA-study is to assess changes in body composition during and after treatment for breast cancer, and to study whether lifestyle, sensory perception, hormone levels, personal characteristics and treatment related factors have an impact on those changes. The study also includes a qualitative arm, to get insight into the perceptions of breast cancer patients on why potential changes in dietary intake, physical activity and quality of life occur.

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Chapter 2

The reliability and validity of the Macronutrient and Taste Preference Ranking Task: A new method to measure food preferences

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Abstract

Food preferences are for a large part determined by the macronutrient content and taste of foods, but may change depending on internal and external factors. Here, we discuss a newly developed food preference task, the Macronutrient and Taste Preference Ranking Task (MTPRT), in which participants rank groups of four food products according to how much they desire to eat the products. The MTPRT includes pictures of sweet and savoury food products from four categories: high-carbohydrate, high-fat, high-protein and low-energy. A within-subjects study on sensory-specific satiety was conducted to assess the task's reliability and validity. Sixty-nine healthy participants performed two test sessions that were at least one week apart. Participants ate either a sweet or a savoury meal, which were similar in macronutrient content. Before and after eating the meal participants rated appetite and completed the MTPRT. In hungry state, preference scores for all food categories were significantly correlated between the two test sessions (all $r > 0.68$, all $p < 0.001$). Preference for sweet decreased after the sweet meal and increased after the savoury meal. In addition, preference for protein decreased more after consuming the savoury meal than it did after consuming the sweet meal. Preference for carbohydrate and fat decreased after meal consumption, regardless of taste. Preference for low-energy increased after meal consumption. These results show the MTPRT is a reliable and valid task for measuring food preferences. The MTPRT can be used for both hypothesis-driven and exploratory studies to examine the influence of different factors on changes in food preferences.

Introduction

Sensory properties of foods play an important role in the preferences for and intake of food.¹ The basic tastes seem to have specific signalling functions for the body, in that sweet taste signals carbohydrates, and salty and savoury taste signals protein and electrolytes.² Indeed, various studies have demonstrated relations between sugar content and sweetness, and between protein content and salty and umami taste.³⁻⁵ The body uses these signalling cues to maintain macronutrient balance. Studies have shown that a protein-depleted state elicits a higher preference and reward for and intake of savoury foods in order to restore protein status.^{6, 7} Energy and macronutrient balance may be challenged in certain people, which may be related to changed preferences for foods. For instance after gastric bypass surgery preference for sweet and high-fat foods decreases^{8, 9}, while other studies report an increased preference for high-protein foods.¹⁰ In cancer patients undergoing chemotherapy, a reduced taste and smell function is frequently reported, which has consequences for food preferences and food intake.¹¹⁻¹³ However, it is important to note that also in the general population food preferences are influenced by many factors including the time of the day, the appropriateness of foods within a meal context and the meal eaten previously.¹⁴⁻¹⁶ This multitude of factors that influence food preferences makes measuring food preferences a challenge. To better understand how food preferences can shift in different situations, it is essential to include macronutrient and taste composition when measuring food preferences. However, few methods are available that capture both macronutrient and taste composition and that are able to assess shifts in food preferences by these factors.

A questionnaire that takes both macronutrient and taste composition into account is the macronutrient preference checklist (MPC). The MPC is a list of foods divided over four macronutrient categories, including both sweet and savoury products. Participants are instructed to check off all foods in the MPC that one would like to eat right at that moment.¹⁷⁻¹⁹ This method results in frequencies of selected products from specific macronutrient or taste categories. Another method that includes different macronutrient and taste categories is the Leeds Food Preference Questionnaire (LFPQ).²⁰ The questionnaire uses food pictures rather than words, which is of importance as visual cues are important factors in food selection and give input on the edibility, palatability and satiating properties of a food.¹ The LFPQ is a computer-based food preference task in which participants make forced choices between two food products from four different

food categories. Thereby, products are not just rated on their own. Instead, products from different product categories are directly compared and relative preferences for food categories are measured. These relative preferences provide insight in motivation for the chosen food category over the non-chosen food category.²¹ However, the LFPQ includes only two macronutrient-based categories divided over sweet and savoury taste. In the original LFPQ, Finlayson and colleagues used high- and low-fat foods.^{20, 21} Later studies adapted this to include high- and low-protein²² and to high- and low-energy.²³ As it is essential to be able to assess preferences for a full range of macronutrients, we developed the Macronutrient and Taste Preference Ranking Task (MTPRT), which includes both macronutrient and taste categories. The task was developed based on the following criteria (1) foods included should be from multiple macronutrient categories and tastes, (2) the foods should be presented as pictures rather than words, and (3) should consist of a ranking paradigm in order to assess relative food preferences.

The MTPRT consists of pictures of products from four macronutrient categories, i.e., high-carbohydrate, high-fat, high-protein and low-energy, including both sweet and savoury products. Participants are asked to make rankings of four products based on how much they desire to eat the different products at that moment. These rankings are used to assess relative preferences for the four macronutrient categories and the two tastes sweet and savoury. In the current study we aim to show that the MTPRT is a reliable and valid task to measure food preferences: to demonstrate reliability of the task, we assessed test-retest reliability. To demonstrate validity of the task, we assessed the discriminative ability of the task by assessing sensory-specific satiety; after eating a food to satiety, the pleasantness of sensory properties of that food is decreased more than of foods that have not been eaten.²⁴ Based on previous studies we expect preference for sweet products to decrease after a sweet test meal and to increase after a savoury test meal. Furthermore we expect decreased preferences for high-carbohydrate and high-fat products after eating a meal in general, a decreased preference for high-protein products after a savoury test meal and an increased preference for low-energy products after eating a meal in general.

Materials and methods

Products and categories of the MTPRT

A total of 32 food products from four macronutrient categories, i.e., high-carbohydrate, high-fat, high-protein and low-energy was used in the MTPRT. Each category contained eight products, of which four products were sweet and four were savoury. The high-protein category formed an exception and consisted of eight savoury products, as no products met all requirements to be included as high-protein sweet. A product had to meet the following requirements to be included in the MTPRT:

- Commercially available.
- High-fat, high-protein and high-carbohydrate foods contained at least 50% of total energy from their respective macronutrient category classification.
- Low energy products contained less than 60 kcal/100 gram.

Hill's European MPC^{17, 18} and Brisbois-Clarkson's North American MPC¹⁹ were used as starting point to select the food products. Products were replaced based on commercial availability in the Netherlands when needed. The Dutch Food Composition table was used to ensure appropriate macronutrient composition.²⁵ The final list of products including their respective nutritional values can be found in Supplementary Table 2.1.

For the products that were included in the MTPRT, standardized pictures were provided by the Image Sciences Institute, UMC Utrecht, and created as part of the Full4Health project (www.full4health.eu), funded by the European Union Seventh Framework Program (FP7/2007-2013) under grant agreement nr. 266408, and the I.Family project (<http://www.ifamilystudy.eu>), grant agreement nr. 266044.²⁶ Pictures of foods were standardized by means of the plate on which products are presented, background colour, contrast, camera distance and angle (see Fig. 2.1 for examples).

Task procedure

The MTPRT consisted of three parts: practicing, liking and ranking.

The practicing part was designed to familiarize participants with the ranking task. Participants were presented with four combinations of four pictures and asked to rank these pictures according to "what they most desire to eat at this moment". The pictures

used in the practicing part were not used in the main task and did not necessarily fit within one of the macronutrient categories.

The liking part was designed to introduce participants to each product by name and picture. Liking was assessed by presenting pictures of all 32 products with the question: 'How much do you like [product name]?' which was rated on a 100 point visual analogue scale (VAS) anchored by 'do not like at all' and 'like extremely'.

The ranking part consisted of two sections, one focused on macronutrients the other on taste, i.e., sweet and savoury. In both sections, participants were presented with four different pictures, which they had to rank according to "what they most desire to eat at this moment" (Fig. 2.1). Participants first clicked on the product they most desired to eat at the moment of completing the task, then they clicked on the second most desired product, followed by the third and the product they least desired to eat at the moment of completing the task. In the macronutrient section, each of the four pictures represented one of the macronutrient categories. In total sixteen combinations of pictures were presented, in which each picture was shown twice. In the taste section, the four pictures that were presented came from two macronutrient categories. Within each category, one picture represented a sweet food item, and the other a savoury one. For example, one sweet product and one savoury product were high in carbohydrate and one sweet product and one savoury product were high in fat. In the taste section, products from the high-protein category were excluded, as this category only contained savoury products. In total twelve rankings were made in the taste section. As in the macronutrient section, each picture was shown twice.

For both sections, the order in which categories were presented on the screen was randomized and balanced across trials. For the macronutrient section, this meant that each macronutrient appeared four times on each of the four available positions. The same picture never appeared on the same position within this section. In the taste section, both tastes appeared six times on each of the four available positions. All pictures were presented twice, on two different positions.

The task took approximately 10 minutes to complete and was executed in E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). The MTPRT can also be executed in EyeQuestion software (Logic8 BV), which facilitates participants to complete the task online.

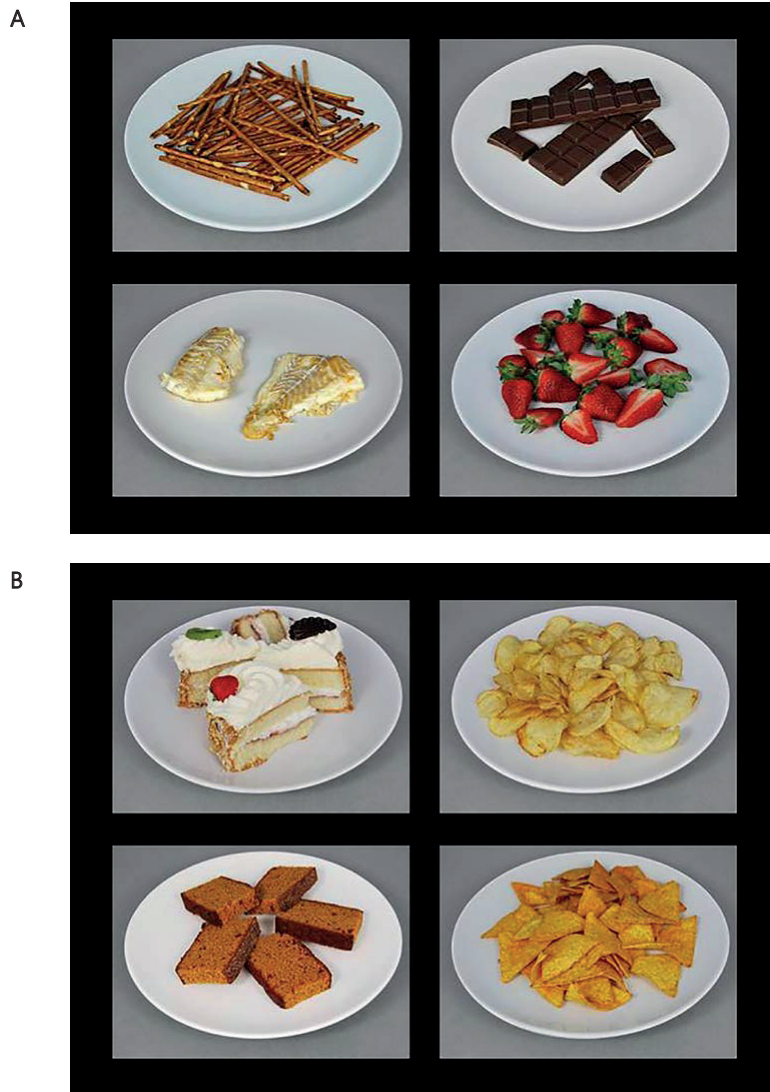


Figure 2.1. Lay-out of the macronutrient section (A) and taste section (B) of the MTPRT.

Participants

Healthy participants aged 18-35 years with a normal weight (BMI 18.5-25 kg/m²) were recruited. Exclusion criteria were restraint eating (DEBQ: men: >2.9, women >3.4)²⁷, lack of appetite, difficulties swallowing or eating, having taste or smell disorders (self-report), energy restricted diet two months prior to the study, weight loss or gain >5 kg during the two months prior to the study, being allergic or intolerant for the products under study, smoking, being vegetarian or vegan, and for women: being pregnant or lactating.

Seventy-four participants were included in the study. Five participants were excluded from the analyses because they did not comply with study procedures. Analyses were done on data of the remaining 69 participants (16 male/53 female) with an average age of 21.3 years (SD ± 2.9) and average BMI of 21.6 kg/m² (SD ± 1.8). All participants received a financial compensation for participating. The study was exempt from formal ethical approval by the Medical ethical Committee of Wageningen University. All participants signed an informed consent form.

Study design

We used a randomized crossover design, in which participants were invited to attend two test sessions that were at least seven days apart. Participants were told that the purpose of the study was to examine the effect of a sweet and savoury lunch on preference for different food products. During both test sessions, participants were presented with either a sweet or a savoury test meal, the order of which was randomized and balanced across the participants. When participants arrived they were instructed to first fill out an appetite questionnaire with 5 questions, i.e., hunger, fullness, prospective consumption, appetite for something sweet and appetite for something savoury. Questions were rated on a 100 point visual analogue scale (VAS) anchored by 'not at all' and 'extremely', except for prospective consumption which was anchored by 'nothing at all' and 'a very large amount'. Next, participants completed the MTPRT, as described under 'task procedure'. After finishing the MTPRT, participants were presented with the test meal and 150 ml water. They were instructed to finish the meal and water within 30 minutes. Next, participants rated the test meal for liking on a 100 point VAS anchored by 'not at all' and 'extremely' and completed the appetite ratings and MTPRT again.

To standardize hunger feelings for all participants in both test sessions, participants were instructed to standardize their breakfast and morning physical activity on both test days.

They were asked to refrain from eating and to drink only water or tea without sugar during the three hours prior to the test session. Test sessions started at 11:30, 11:45, 12:00, 13:00, 13:15 and 13:30 and lasted approximately one hour. Both test sessions started at the same time for each individual participant.

Test meals

Participants received a standard amount of each test meal based on their energy requirements as calculated by the Schofield formula²⁸ with a physical activity level of 1.6. The test meal contained 18% of participant's daily required energy intake, rounded to the nearest 50 kcal, which is 81% of the amount of energy provided by an average lunch in the Netherlands.²⁹

Energy and macronutrient composition were similar for both meals and are shown in Table 2.1. The savoury meal consisted of risotto rice (Lassie, Wormer, The Netherlands) (65%), semi-skimmed milk (17%), crème fraîche (11%), bouillon (0.3%), garlic powder (0.02%), salt (0.8%) and maltodextrin (Fantomalt, Nutricia, The Netherlands) (6%). The sweet meal consisted of risotto rice (64%), semi-skimmed milk (21%), water (4%), margarine (4%), cinnamon (0.08%), sucralose (0.05%) and maltodextrin (7%). A standard protocol was used to make fresh meals on each test day. Meals were kept warm with an average temperature of 81 °C (range 69–89 °C).

Table 2.1. Nutritional composition per 100 g of the sweet and savoury meal

	Savoury meal	Sweet meal
Energy (kcal)	91	89
Energy (kJ)	381	375
Protein (g)	2	1.9
Fat (g)	3.2	3.2
Carbohydrates (g)	13.2	13.1
Fiber (g)	0.2	0.2

Data analysis

Each product received a macronutrient preference score based on the place the product was ranked. The higher the rank, the higher the score. Scores for all 16 presentations added up to a total score that was divided by the 16 times a product from each category was presented. Preference scores can range from 1 to 4:

relative preference score macronutrient

$$= \frac{4 * (\# \text{rank } 1) + 3 * (\# \text{rank } 2) + 2 * (\# \text{rank } 3) + 1 * (\# \text{rank } 4)}{16}$$

Similarly a preference score was calculated based on taste rankings. As both sweet and savoury products were presented twice in all 12 rankings the ranks-based score is divided by 24 and this preference score can range from 1.5 to 3.5:

relative preference score sweet

$$= \frac{4 * (\# \text{rank } 1) + 3 * (\# \text{rank } 2) + 2 * (\# \text{rank } 3) + 1 * (\# \text{rank } 4)}{24}$$

In case of no apparent preference for a specific category, all macronutrients would be ranked on each position twice and preference scores are 2.5.

As the preference scores for sweet and savoury are each other's opposites, i.e., savoury score = 5 - sweet score, we report only sweet preference scores in this article.

Data are presented as means with standard deviation (SD) unless otherwise specified. Data was analysed using IBM SPSS 21 (IBM Corporation, Armonk, New York, USA). Results were considered statistically significant at $p < 0.05$.

To compare liking of both test meals a paired-samples T-test was conducted. Repeated measures ANOVA was used to analyse appetite ratings and the preference scores with hunger state (before and after a meal) and taste of the test meal (sweet and savoury) as factors.

Non-parametric tests were used to determine relative preference for the different macronutrient and taste categories. To compare preference scores for macronutrient categories within conditions, e.g., before the sweet meal, Friedman ANOVA was used. Post-hoc analyses were done using Wilcoxon signed rank tests with Bonferroni correction. To determine relative preference for taste, sweet and savoury preference scores were compared using Wilcoxon signed rank tests. Pearson's correlations were determined to assess reproducibility of food preferences measured with the MTPRT.

Liking scores were calculated by using the average liking rating within a category. These were analysed with repeated measures ANOVA to compare liking scores before and after the two different test meals. Post-hoc analyses were done using Bonferroni correction.

Results

Liking of test meals

Average liking of the sweet test meal was 40.7 (SD = 27.7), compared to 45.3 (SD = 23.2) for the savoury meal. Liking of both meals did not differ significantly, $T(1,68) = 1.12$, $p = 0.27$.

Appetite ratings

Regardless of taste, eating a test meal decreased hunger, prospective consumption, appetite for something sweet and appetite for something savoury, but increased fullness (all $p < 0.001$, Table 2.2). The interaction between hunger state and taste of the test meal showed that appetite for something sweet decreased more after eating the sweet test meal than after eating the savoury test meal, $F(1,68) = 27.92$, $p < 0.001$. Similarly, appetite for something savoury decreased more after eating the savoury test meal than after eating the sweet test meal, $F(1,68) = 34.31$, $p < 0.001$.

Table 2.2. Pre and post meal appetite ratings per type of meal

	Sweet meal		Savoury meal	
	Pre	Post*	Pre	Post*
Hunger	71±16	19±19	67±15	20±18
Fullness	22±13	72±20	28±17	76±18
Prospective consumption	66±14	27±20	64±15	25±19
Appetite for sweet ¹	58±23	21±26	55±23	44±28
Appetite for savoury ¹	73±15	48±24	68±18	23±22

Ratings performed on a 100-unit VAS. Values are means±SD.

*Post meal ratings are significantly different from pre meal ratings.

¹Significant difference between post meal ratings between sweet and savoury meal.

Test-retest reliability of preference scores

The preference scores in hungry state on the two test days did not significantly differ from each other (all $p > 0.05$). In addition, these preference scores significantly correlated with each other within all macronutrient categories and the sweet category, $r = 0.77, 0.68, 0.78, 0.69, 0.74$ for high-carbohydrate, high-fat, high-protein, low-energy, and sweet respectively, all $p < 0.001$ (Fig. 2.2).

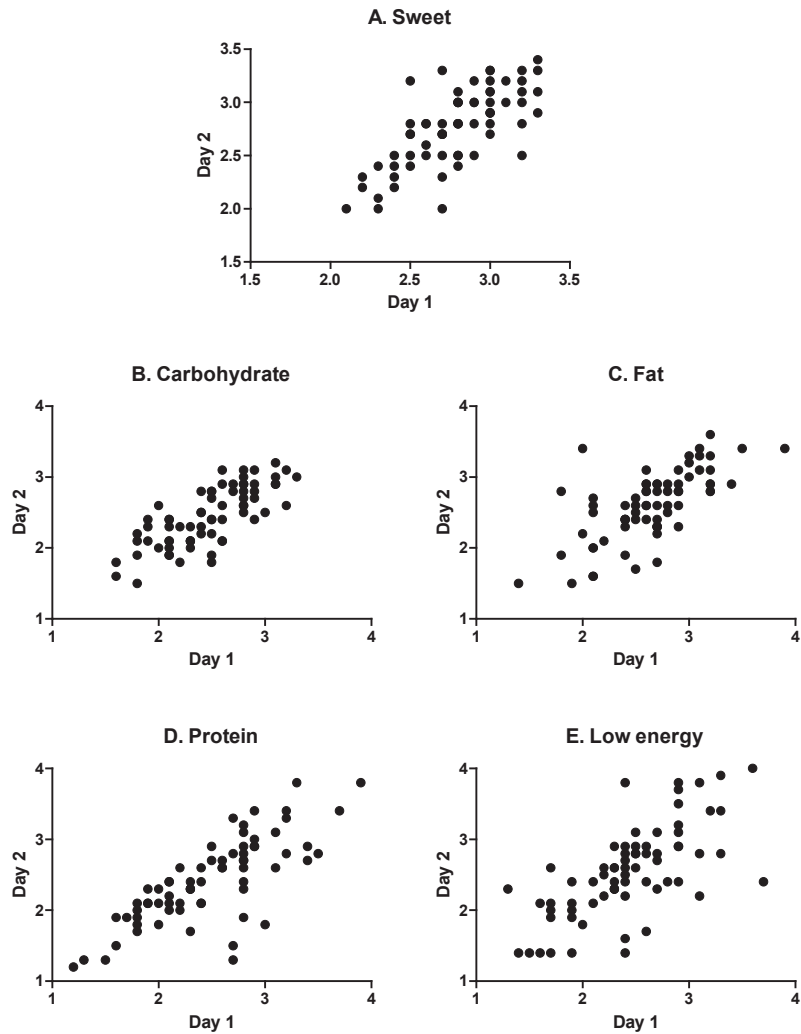


Figure 2.2. Correlation preference scores for sweet (A), high-carbohydrate (B), high-fat (C), high-protein (D) and low-energy (E) products in hungry condition between test day 1 and test day 2.

Food preferences

Before consumption, preference scores for all categories did not differ between the sweet and savoury test meal conditions (all $p > 0.05$). In both conditions, participants showed a relative preference for sweet over savoury (both $p < 0.001$), but no relative preference for one of the macronutrient categories (Fig. 2.3).

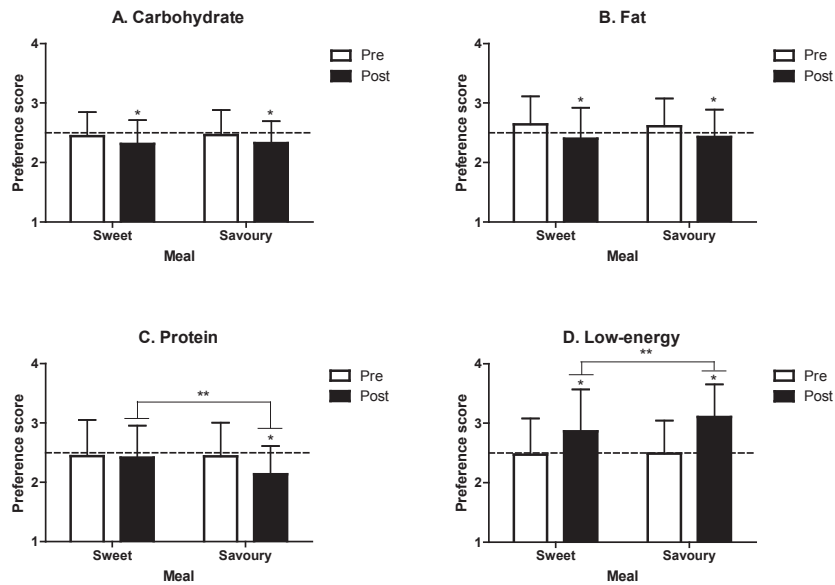


Figure 2.3. Preferences for high-carbohydrate (A), high-fat (B), high-protein (C) and low-energy (D) products (mean \pm SD). Dotted line represents chance level. * indicates significant change compared to pre meal at $p < 0.05$ level, ** indicates significant difference at $p < 0.05$ level.

After consumption of the test meal, sweet preference shifted dependent on taste of the meal as shown by the interaction between hunger state and taste of the test meal: $F(1,68) = 53.26$, $p < 0.001$, partial $\eta^2 = 0.44$. Sweet preference decreased after the sweet meal and increased after the savoury meal (Fig. 2.4). After consumption of the sweet test meal, participants lost their relative preference for sweet products over savoury products, $Z = -1.53$, $p = 0.127$.

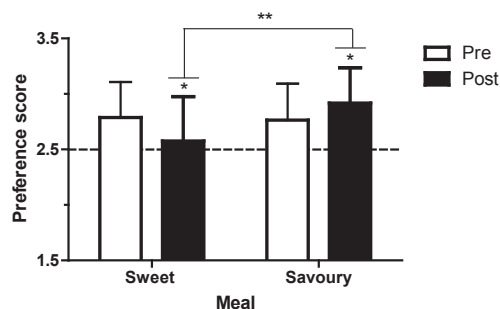


Figure 2.4. Preferences for sweet products before and after the sweet and savoury meal (mean \pm SD). Dotted line represents chance level. * indicates significant change compared to pre meal at $p < 0.05$ level, ** indicates significant difference at $p < 0.05$ level.

Fig. 2.3 shows the preferences for the four macronutrient categories. Preference for high-carbohydrate and for high-fat products decreased after meal consumption, regardless of taste, main effect carbohydrate: $F(1,68) = 18.87$, $p < 0.001$, partial $\eta^2 = 0.22$; fat: $F(1,68) = 38.92$, $p < 0.001$, partial $\eta^2 = 0.36$. Hunger state interacted with taste of the test meal for high protein foods, $F(1,68) = 22.13$, $p < 0.001$, partial $\eta^2 = 0.25$. This was explained by a decrease for high protein products after the savoury meal, but no change in preference for high protein products after the sweet meal. Preference for low-energy products increased after eating a meal, main effect: $F(1,68) = 85.30$, $p < 0.001$, partial $\eta^2 = 0.56$. Hunger state interacted with taste of the test meal; low-energy preference increased more after the savoury meal than after the sweet meal $F(1,68) = 22.13$, $p < 0.001$, partial $\eta^2 = 0.11$. After both meals, participants showed a relative preference for low-energy products compared to the other macronutrient categories (all $p < 0.01$). After the savoury meal, high-fat products were preferred over high-protein products ($p < 0.05$).

Liking of food categories

Fig. 2.5 shows the liking ratings for the different food categories. After eating both test meals, liking of the sweet, savoury, high-carbohydrate, high-fat and high-protein products decreased (all $p < 0.05$), but liking of the low-energy products did not change ($p = 0.832$). For savoury, $F(1,68) = 10.96$, $p = 0.001$, and for high-protein, $F(1,68) = 8.49$, $p = 0.005$, hunger state interacted with taste of meal. For both categories, liking decreased more after the savoury meal than after the sweet meal.

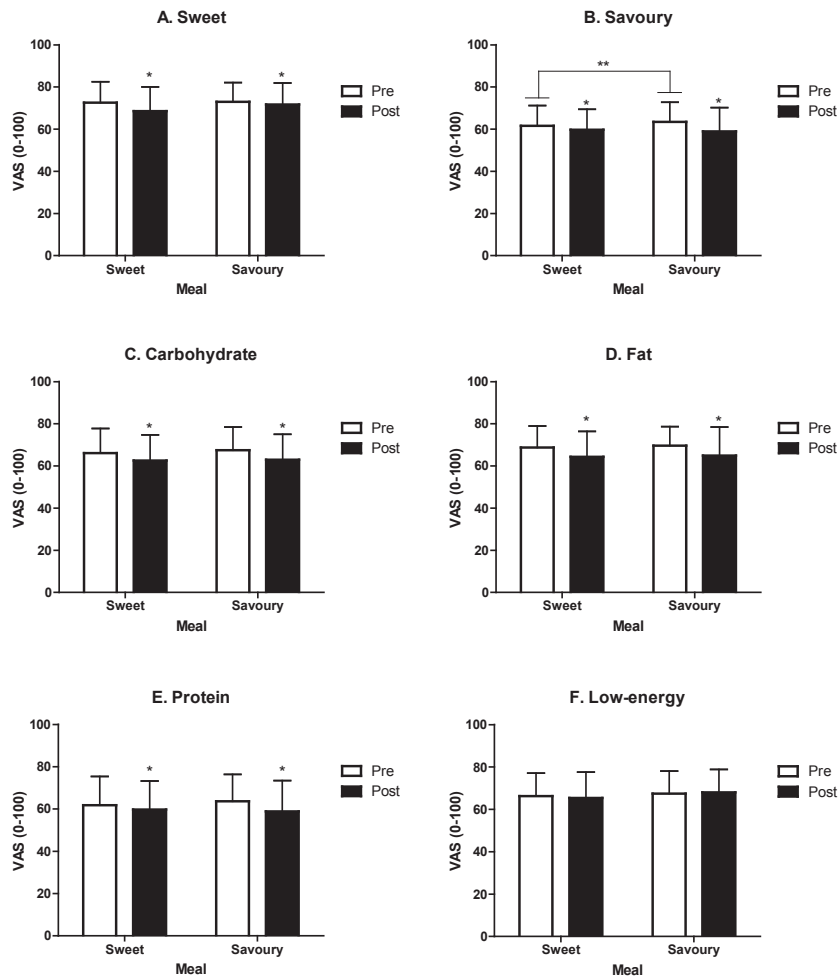


Figure 2.5. Liking ratings (0-100 VAS) for sweet (A), savoury (B), high-carbohydrate (C), high-fat (D), high-protein (E) and low-energy (F) products (mean \pm SD). * indicates significant change compared to before meal at $p < 0.05$ level. ** indicates significant difference at $p < 0.05$ level.

Discussion

The current study demonstrates the reliability and validity of the Macronutrient and Taste Preference Ranking Task, the first food preference ranking task that includes both taste and four macronutrient dimensions. First, we showed that food preference scores for all categories in a hungry condition were highly correlated over two test sessions indicating test-retest reliability. Second, we showed a decreased preference for sweet products after eating a sweet meal and an increased preference for sweet products after eating a savoury meal. Preference for high-protein products decreased more after eating a savoury meal than it did after eating a sweet meal. Preferences for high-carbohydrate and high-fat products decreased after eating a meal, regardless of the taste of the meal. Preferences for low energy products increased after eating a meal, and this increase was most pronounced after the savoury meal. These results indicate that the MTPRT is a valid task to detect changes in food preferences.

Food preferences as measured with the MTPRT were shown to be reproducible. Correlations of preference scores for the different food categories as measured under similar circumstances were comparable to those found in previous studies that assessed test-retest reliability of methods to measure food preferences.^{19, 30, 31} Given the reproducibility and the high variation in individual food preference scores between participants, the MTPRT may be able to identify individuals with specific preferences. Further studies are needed to assess whether there are specific individual characteristics that determine these individual food preferences.

In addition, the discriminative ability of the MTPRT was successfully demonstrated by assessing the effect of sensory-specific satiety. Similar to other methods used in previous studies, preferences for sweet decreased after the sweet meal and increased after the savoury meal.^{16, 32} Moreover, we were able to discriminate preferences between four different macronutrient categories, i.e., high-carbohydrate, high-fat, high-protein and low-energy. Preferences for high-carbohydrate and high-fat products decreased after eating a meal, regardless of the taste of the meal. Conversely, preference for low-energy products increased after meal consumption. This increased preference for low-energy products can be explained by the fact that participants were feeling full after the meal. This induced a shift from energy-dense to low-energy products and is consistent with other studies.^{23, 33} Preferences for high-protein products decreased after consumption of the savoury meal, but not after consumption of the sweet meal. This finding can be

explained by the fact that savoury products are generally associated with high protein content.^{3, 5} Contrarily, a previous study into the effects of taste of a 24-hour diet on food preferences did not find a difference in preference for protein.³⁴ However in that study, protein content of high-protein products was at most 26 energy percent and included both sweet and savoury products. This difference between high-protein products could explain these different findings. Another possible explanation could be that the preference for protein was confounded by preference for savoury. In that case, we would have expected an increased preference for protein after the sweet meal, similar to the increased preference for savoury. However, preference for protein did not change after the sweet meal. We therefore consider this explanation unlikely.

The meals in our study were carefully composed to be similar with regard to nutritional content, and only differed in the taste, sweet and savoury. Therefore we mainly observe effects which can be explained by the taste and detect less differentiation on the macronutrients. Most likely, when varying meals in macronutrient content pronounced changes in macronutrient preferences would become apparent.^{31, 35, 36} Compared to the LFPQ, the MTPRT has more macronutrient categories and can therefore be used in a wide range of studies that assess the influence of different factors on changes in preferences for different macronutrients and tastes in a variety of populations.

By using a ranking procedure, we can assess food preferences for categories of foods relative to other categories. In our study, we detected changes in preference for all food categories included in the MTPRT, while we did not detect these for all categories in the liking part. One important difference is that liking of sweet products decreased in a similar fashion after both the sweet and the savoury meal, whereas the preference score for sweet increased after the savoury meal. Furthermore, the ranking showed an increased preference for low-energy products after eating the meals, while liking of low-energy products did not change. Therefore, the ranking procedure is more sensitive compared to the liking procedure, and is thus able to detect more subtle shifts in food preferences.

The ranking method makes the MTPRT an easy and quick tool for evaluating food preferences over a wide range of food categories, i.e., high-carbohydrate, high-fat, high-protein and low-energy, both sweet and savoury. Because of this range, the food preference task can be used in a variety of studies without changing food categories based on the research question. In the current study the experiment was focused on assessing sensory-specific satiety in a controlled setting and within subjects. However

food preferences are influenced by many factors and further research is needed to assess the use of the task in a less controlled, more natural setting, and to assess the effect of time of day, meal context and person characteristics like gender, age and eating type.

The current study did not measure actual food intake and thus cannot compare preference scores with actual intake. No conclusions can be drawn, therefore, on how food preferences as assessed with the MTPRT translate into actual behaviour. Based on previous comparisons of a forced-choice procedure with actual food intake,^{16, 22} where strong correlations were found between relative food preference and food intake, we would hypothesize that the preference scores as measured with the MTPRT correlate with actual food choice behaviour.

It is important to note that the MTPRT does not include sweet high-protein products. Within the range of products that contain at least 50 energy percent of protein, there are no sweet products. The same applies to other food preference measures^{19, 36} and therefore we do believe that the products in the high-protein category are a good representation of this macronutrient. In addition, the food products currently included in the task are chosen based on their commercial availability in the Netherlands. As Dutch consumption patterns may differ from consumption patterns in other countries, it might be necessary to exchange a few individual food products in the MTPRT when using the task in other countries.

The MTPRT is the first food preference task that uses a ranking procedure and can detect shifts in preferences for both taste and macronutrients. The MTPRT was shown to be a reliable and valid method to measure food preferences, as results were reproducible under similar conditions, and differentiated food preferences based on macronutrients and taste in an experimental setting. The task can be used to examine the effect of internal and external factors that influence food preferences.

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Supplementary table 2.1. Nutritional values for the selected 32 products

		Energy (kJ/100 grams)	Energy (kcal/100 grams)	Protein (en%)	CHO (en%)	Fat (en%)
High carbohydrate						
Sweet	Ginger bread	1346	318	3.4	88.9	5.9
	Syrup waffles (Dutch: Stroopwafels)	1985	473	3.1	59.4	36.7
	Pancakes	826	196	16.9	59.6	22.5
	Wine gums	1481	349	6.3	92.8	0.8
Savoury	Tortilla chips	2039	487	5.7	51.3	41.2
	French fries	1282	306	5.9	50.1	42.1
	Nibbitts	1989	475	3.4	53.9	41.7
	Salty sticks	1654	395	9.4	81.0	8.2
High fat						
Sweet	Chocolate bar (milk chocolate)	2278	546	5.1	40.2	53.6
	Cream pie	1465	350	4.0	33.1	64.3
	Apple turnover (Dutch: Appelflap)	1506	361	3.9	39.3	55.8
	Large chocolate eclair (Dutch: Bossche bol)	1275	307	5.9	23.6	70.1
Savoury	Salted peanuts	2390	577	16.6	7.6	73.3
	Sausage roll	1596	382	12.4	35.8	51.4
	Chips (salted)	2254	541	4.7	37.9	55.7
	Cheese cubes	1508	363	25.0	0.0	73.4
High protein						
	Chicken satay	667	158	78.2	0.0	21.6
	Cod fillet	498	118	72.9	2.0	25.2
	Pork chop	743	177	64.0	0.0	35.6
	Turkey fillet (cold cut)	479	113	69.7	11.0	19.1
	Roast beef	656	156	69.7	0.5	29.4
	Gammon (cold cut)	569	136	53.5	7.1	38.4
	Shrimps	397	94	84.3	0.4	15.3
	Steak	616	146	80.3	0.0	19.7
Low energy						
Sweet	Peach	172	41	9.8	77.1	0.0
	Strawberries	123	29	9.7	70.3	0.0
	Apple	254	60	1.3	86.7	3.0
	Melon galia	107	25	0.0	96.0	0.0
Savoury	Tomato	96	23	12.2	53.9	19.6
	Cucumber	55	13	18.5	58.5	13.8
	Pickles	44	11	36.4	36.4	0.0
	Celery sticks	60	14	28.6	57.1	0.0



Chapter 3

Low reported taste function is associated with low preference for high protein products in advanced oesophagogastric cancer patients undergoing palliative chemotherapy

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Submitted

Abstract

Background & aims: Cancer patients undergoing palliative chemotherapy can experience a variety of chemosensory and food preference changes which may impact their nutritional status and quality of life. However, evidence of these changes in oesophagogastric cancer patients is currently mostly qualitative and not supported by quantitative data. The aim of this study was to assess the influence of palliative chemotherapy on both objective and self-reported taste and smell function and food preferences in oesophagogastric cancer patients.

Methods: This observational study included 15 advanced oesophagogastric cancer patients planned for first line treatment with capecitabine and oxaliplatin. Participants completed two test sessions scheduled before start of cytotoxic treatment and after two cycles. Objective tests and self-reported taste and smell function and the macronutrient and taste preference ranking task were conducted at each test session.

Results: Self-reported taste and smell did not change upon chemotherapy. Objective smell function did not change, but objective taste function decreased during chemotherapy, although this was not statistically significant ($p=0.06$). Before and during chemotherapy, high protein foods were preferred over high carbohydrate and over low energy products, but food preferences did not change over time. A lower self-reported taste function correlated with a lower preference for high-protein products ($p=0.526$, $p=0.003$).

Conclusion: This study suggests that objective taste function decreases during chemotherapy in OGC patients, but not olfactory function. A low reported taste function was related to a lower preference for high-protein products. This highlights the importance of monitoring chemosensory function when giving nutritional advice in advanced OGC patients.

Introduction

Oesophagogastric cancer (OGC) is a highly lethal disease. The overall 5-year survival rate for OGC is approximately 26%, as the majority of patients is diagnosed with advanced disease. For these patients, the benefit of palliative chemotherapy compared with best supportive care has been established both in terms of overall survival and quality of life.¹⁻³ However, cytotoxic treatment is often accompanied by side effects including alterations in taste and smell that may impact food preferences and quality of life.⁴⁻⁷ A previous qualitative study of our group in OGC patients undergoing chemotherapy showed a large variation in the experience and impact of changes in taste and smell perception.⁴ These chemosensory changes had consequences in terms of food preferences, with a change in food preferences and avoidance of specific products like meat. Taste and smell changes, and eating problems related to the location of the tumour affected daily life and social life. For humans it is difficult to distinguish taste and smell, as these systems are highly related in the perception of food. Therefore it is important to objectively assess taste and smell function to understand the nature of these changes. Thus far, it is unknown how reported *subjective* chemosensory changes and changes in food preferences relate to actual *objective* measures of taste, smell and food preferences in oesophagogastric cancer patients undergoing chemotherapy. Therefore, the aim of the current study is to measure the influence of chemotherapy on both objective and self-reported taste and smell function and food preferences in OGC patients.

Materials and methods

Patients

Twenty-three patients with metastatic or irresectable carcinoma of the stomach or oesophagus were included. All patients were scheduled to start cytotoxic treatment with capecitabine (Xeloda®) 1000 mg/m² days 1-14 and oxaliplatin (Eloxatin®) 130 mg/m² day 1 of three-weekly cycles and had a WHO performance status of 0 - 2. Treatment and tumour characteristics were obtained from medical records.

Study design

This observational study included test sessions before the first chemotherapy cycle (baseline) and shortly before the third chemotherapy cycle (follow-up). Objective and self-reported chemosensory function and food preferences were assessed during each test

session. The study was exempted from formal ethical approval by the medical ethics committee of the Academic Medical Centre.

Measurements

Taste function was assessed using the Taste Strips (Burghart, Wedel, Germany) to assess sensitivity for sweet, salty, bitter and sour. Scores for each taste ranged from 0 to 4, and total taste scores range from 0-16, which was the sum of the four basic taste scores.^{8, 9} Olfactory function was measured using the Sniffin' Sticks. The test consists of three parts: odour threshold (THR, range 1-16), odour discrimination (DIS, range 0-16) and odour identification (ID, range 0-16). Overall olfactory function (TDI) was the sum of the three subtests.^{10, 11} The Appetite Hunger and Sensory Perception questionnaire (AHSP) was used to assess reported taste, smell, appetite and hunger feelings.¹² Food preferences were assessed using the Macronutrient and Taste Preference Ranking Task, a computer-based food preference task with food pictures from four food categories high-protein, high-carbohydrate, high-fat and low-energy, divided over sweet and savoury products.¹³ Relative preferences were calculated for each category.

Data analysis

Differences for olfactory, gustatory scores and food preferences within macronutrient and taste categories between baseline and follow up were analysed with Wilcoxon's Signed Rank test. Preferences between food categories at baseline and follow-up were assessed using Friedman ANOVA with Dunn-Bonferroni test to assess post hoc differences. Spearman correlations were done to correlate reported taste and smell perception with objective taste and smell function, and to correlate reported and measured taste and smell with food preferences. Data were analysed using IBM SPSS version 23.0, a p-value of <0.05 was considered statistically significant.

Results

Twenty-three patients were included, of which 8 dropped out because of early discontinuation of treatment (n=3), feeling too ill to undergo the tests (n=3), and death before the second measurement (n=2). Table 3.1 shows demographic and clinical characteristics of the 15 OGC patients who completed baseline and follow-up measurements.

Table 3.1. Sociodemographic and tumour characteristics of the included OGC patients (n=15)

		n (%) or mean \pm SD
Gender	Male	14 (93)
	Female	1 (7)
Age (years)		61 \pm 9.3
BMI (kg/m²)		24.4 \pm 2.7
WHO performance status ¹	0	8 (53)
	1	5 (33)
	2	2 (13)
Tumour characteristics		
Location	Oesophagus	10 (67)
	Gastroesophageal junction	2 (13)
	Stomach	3 (20)
Tumour type	Adenocarcinoma	13 (87)
	Large cell undifferentiated carcinoma	2 (13)
Stage	I-II	2 (13)
	III	8 (53)
	IV	5 (33)
Resectable status	Locally resectable	6 (40)
	Locally irresectable	4 (26)
	Metastatic disease	5 (33)

¹ World Health Organisation(WHO) performance status is a tool to assess a patient's general health.

We observed no differences in the objective measurements of olfactory function (TDI), threshold, discrimination or identification of odours between baseline and follow up (table 3.2). Objective taste function at follow up was lower than at baseline (median 9 vs. 6), which was borderline statistically significant ($p=0.06$). For the separate tastes, salt taste decreased the most, although all tastes (salt, sweet, sour and bitter) were not statistically significantly different (table 3.2). Self-reported taste, smell, appetite and hunger feelings did not differ between baseline and follow-up.

Table 3.2. Median (IQR) scores of taste and smell function in oesophagogastric cancer patients before chemotherapy (baseline) and after two cycles chemotherapy (follow up), n=15.

	Baseline	Follow up	P-value
Objective taste function			
Total taste	9 (5-12)	6 (5-11)	0.06
Sweet	3 (1-4)	3 (2-4)	0.21
Sour	1 (1-2)	1 (1-2)	0.71
Salty	3 (2-4)	2 (1-4)	0.08
Bitter	1 (0-3)	1 (0-2)	0.45
Objective smell function			
TDI	28.3 (22.0-34.8)	27.3 (21.7 – 34.5)	0.57
Threshold	6.3 (4-7)	6.5 (5-8)	0.09
Discrimination	10 (9-14)	10 (7-13)	0.23
Identification	12 (9-13)	11 (8-14)	0.15
Self-report			
Taste	28 (23-29)	28 (27-28)	0.42
Smell	22 (19-22)	22 (20-22)	0.78
Appetite	21 (19-22)	22 (20-22)	0.59
Hunger	35 (33-38)	34 (30-40)	0.45

IQR = Interquartile range, TDI =Threshold Discrimination Identification score

Both at baseline and at follow-up, high protein products were preferred over high carbohydrate and low energy products (all $p < 0.05$), but no differences were observed in preferences for the macronutrient categories between baseline and follow up (figure 3.1a). There were no differences in preferences for sweet and savoury products between baseline and follow up, nor was there a specific preference for either sweet or savoury products (figure 3.1b).

A lower self-reported taste perception was correlated with a lower preference for high-protein products ($p = 0.526$, $p = 0.003$). Reported taste and smell perception were not significantly correlated with objective taste and smell function.

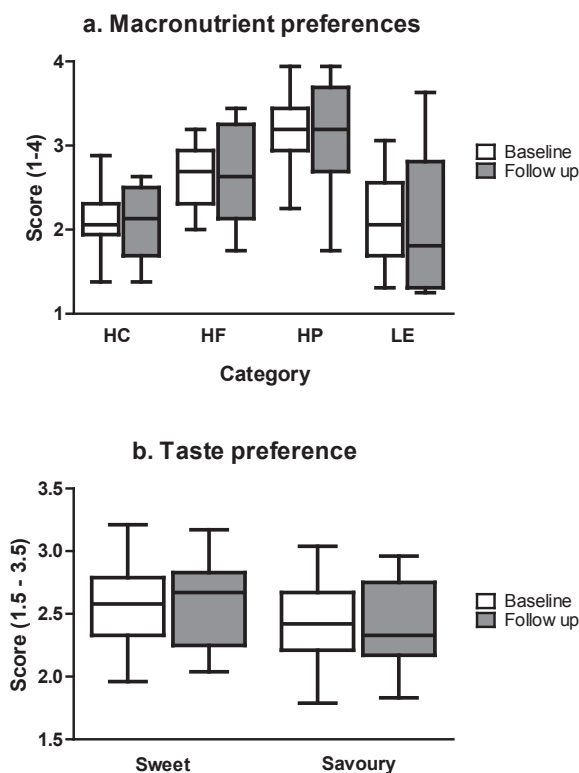


Figure 3.1. Boxplot of baseline and follow-up measurements a. macronutrient preferences and b. taste preferences. Whiskers represent minimum and maximum. (HC: high carbohydrate; HF: high fat; HP: high protein; LE: low energy)

Discussion

This is the first study that used both self-reported and objective methods to assess olfactory and gustatory sensitivity and food preferences in oesophagogastric cancer patients undergoing palliative chemotherapy. Although the sample size of the study is small, our results suggest that objective taste function decreases during chemotherapy in OGC patients, while objective olfactory function remains unchanged. Furthermore, self-reported taste and smell function did not change upon chemotherapy treatment. A recent qualitative study of our group in this patient group showed that OGC patients undergoing chemotherapy do experience chemosensory changes.⁴ It could be argued that the reported changes in the qualitative study are more hedonic in nature, related to the appreciation of tastes or smells, rather than reflecting an actual decrease in chemosensory function.⁵

Although food preferences did not change during chemotherapy, there was a preference for high protein products over low energy and high carbohydrate products both before and during chemotherapy. This preference for high-protein products was not seen previously in a sample of young healthy adults.¹³ Weight loss and malnutrition prevails in the majority of patients with oesophageal cancer before treatment.¹⁴ This weight loss is often accompanied with a loss of muscle mass, indicating a poor protein status. Studies have shown that humans develop compensatory preferences for protein-rich food when being brought into a low protein status by a low-protein diet.^{15, 16} Therefore, the preference for high-protein products in our study could be the result of a low protein status in oesophagogastric cancer patients. Unfortunately, no data were available on weight loss of the patients before start of the study. Studies on the relation between body composition and food preferences should be done to further explore the potential relationship between weight change, protein status and food preferences in cancer patients.

Importantly, we observed that a low self-reported taste function was correlated with a low preference for high-protein products. Dietary advice in oesophagogastric cancer patients is directed at enhancing protein intake.¹⁷ Potentially, patients with a lower reported taste function have more difficulties to comply to a higher protein intake, as their preference for high-protein products is lower. Therefore it is important to consider the patient's taste function, when providing dietary advice to OGC patients.

Conclusion

This study suggests that olfactory function in oesophagogastric cancer patients undergoing palliative chemotherapy does not change, but objective taste function decreases. A low reported taste function was related to a lower preference for high-protein products. Given the importance of maintaining a good nutritional status, these findings highlight the importance of asking about chemosensory function when giving nutritional advice in advanced OGC patients.

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Chapter 4

Altered food preferences and
chemosensory perception during
chemotherapy in breast cancer patients:
a longitudinal comparison with
healthy controls

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Abstract

Changes in food preferences and chemosensory function are frequently reported during chemotherapy, but the nature of these changes are largely unknown. We aimed to follow and characterize food preferences, taste and smell function over treatment with chemotherapy in breast cancer patients and compared to women without cancer. Furthermore, we assessed associations between taste and smell function and food preferences in breast cancer patients.

Women with newly diagnosed breast cancer (n=28) completed test sessions before, halfway, shortly after, and six months after chemotherapy. Twenty-eight women without cancer were tested at similar time points as control. During each test session, food preferences were assessed with the Macronutrient and Taste Preference Ranking Task (MTPRT). Self-reported taste and smell function were tested on a visual analogue scale. Objective taste and smell function were assessed with Taste Strips and Sniffin' Sticks.

Breast cancer patients liked high-protein, high-fat, sweet, and savoury products less during chemotherapy, which returned to baseline half a year after chemotherapy, while the control group was stable over time. Chemotherapy led to a decreased taste and smell function which recovered six months after chemotherapy. A better self-reported taste was associated with higher liking of high-protein, low-energy, savoury and sweet products.

Breast cancer patients undergoing chemotherapy have altered food preferences for macronutrients, but not specifically for sweet or savoury tastes. Chemotherapy has a transient influence on food preferences and chemosensory function, of which patients should be informed prior to treatment, and which should be monitored during treatment due to the consequences for nutritional intake and quality of life.

Introduction

Cancer patients undergoing chemotherapy treatment experience many side effects, including changes in taste, smell and food preferences. The prevalence of these changes vary from 45 to 84% for self-reported taste and 5 to 60% for smell.¹ These changes are amongst the most troublesome side effects of chemotherapy,^{2, 3} and can have a substantial impact on the daily life of cancer patients by reducing food enjoyment, nutritional intake and quality of life.⁴⁻⁷ However, the nature of changes in food preferences and changed chemosensory function is largely unknown.

Our recent study showed that breast cancer patients have a lower intake of total energy, protein and fat during chemotherapy compared to a group of women without cancer, but a similar intake of carbohydrates.⁸ A lower self-reported taste perception was associated with this decreased intake of energy, protein and fat. Possibly, this association reflects the nutrient-signalling function of taste, where sweet taste signals carbohydrates, salt taste signals sodium content which is important for the bodies electrolyte balance, and savoury (umami) taste signals protein content.⁹ The body uses these signals to maintain macronutrient balance. Experimental studies have shown that in humans, a protein-depleted state elicits a higher preference for savoury foods to restore protein status.^{10, 11} Possibly a dysfunctional taste system might elicit different preferences for food and thereby influence food intake during chemotherapy in cancer patients. However, there is little known on macronutrient preferences during chemotherapy and whether this is influenced by actual changes in taste or smell function.

Several studies have assessed food preferences during chemotherapy, but mostly in terms of food aversions, with foods such as meat, coffee and chocolate frequently being reported as aversive.¹²⁻¹⁵ However, there are no quantitative studies available that specifically assessed food preferences in terms of macronutrients in breast cancer patients. Recently, the Macronutrient and Taste Preference Ranking Task (MTPRT) was developed in our group.¹⁶ This task assesses food preferences for four macronutrient categories (high-fat, high-protein, high-carbohydrate and low-energy) and two tastes (sweet and savoury), with both liking and relative preferences (ranking) of these food categories. This task could therefore give more systematic insights in how food preferences might change over chemotherapy treatment.

To explore the possible relation between taste, smell and food preferences, it is important to assess chemosensory function both subjectively and objectively. As reported

chemosensory changes do not always correspond to objective measures of taste or smell function,¹⁷ these measures give information on the actual changes during chemotherapy. Studies using objective measures thus far suggest that chemotherapy lowers taste sensitivity in cancer patients.¹⁸ For objective olfactory function studies have different findings, some suggesting a decreased olfactory function, while others report unchanged olfactory function during chemotherapy.¹⁸ This heterogeneity in findings is partly attributed to studies that are performed in populations with different types of cancer, treatments and disease phases.¹² Interestingly, to date there are no prospective studies in cancer patients that included a control group that was followed over the course of the study, thus excluding the effect of normal fluctuations or repeated testing over time.

To better understand the relation between altered food preferences and chemosensory function over chemotherapy treatment, we followed and characterized food preferences, taste and smell function before, during and after chemotherapy in breast cancer patients and compared women without cancer. Furthermore, in breast cancer patients, we assessed the associations between subjective and objective taste and smell and food preferences.

Materials and Methods

Study population

This study involves a sub-group of an ongoing observational multi-centre study among breast cancer patients during chemotherapy and a control group of women without cancer of similar age (COBRA-study).⁸ In the COBRA-study, women with newly diagnosed, stage I-IIIb, operable breast cancer, who were scheduled for 2nd or 3rd generation chemotherapy were compared with women without cancer of similar age (range within 2 years). Eligible patients were recruited by the staff of 11 participating hospitals in the Netherlands prior to commencement of chemotherapy. The control group was recruited via patients, who were asked to distribute information about the study to friends, acquaintances and colleagues. Women without cancer could contact the researchers if they were interested in participating in the study. All study participants needed to be at least 18 years old and be able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, pregnancy or the intention to get pregnant during the study period, dementia or other mental conditions that made it impossible to comply with study procedures. The protocol was approved by the Medical Ethical Committee of Wageningen University (ABR NL40666.081.12). All participants

provided written informed consent before enrolment. For the current sub-study we included 33 breast cancer patients and 30 controls between February 2014 and December 2015. There were no additional in- or exclusion criteria to participate in this sub-study. Five patients and two controls dropped out for various reasons: lack of sufficient time to participate (n=1), participants wanted to focus solely on treatment (n = 1), receiving palliative treatment (n=1), medical reasons (n=2) or no specific reason (n=2).

Study design

Assessment of taste and smell function, and food preferences was done at four time points for all study participants. For patients this was before start of chemotherapy (T1), during chemotherapy (T2), 1-3 weeks after the last chemotherapy cycle (T3) and 6 months after end of chemotherapy (T4). The measurement during chemotherapy was scheduled halfway the scheduled chemotherapy cycles, mostly in the week before administration of the next cycle. For the comparison group measurements were done over a similar time frame; baseline (T1), 3 months (T2), 6 months (T3) and 12 months (T4) after baseline. All tests were done at participants' homes by trained researchers. Measurements took place at approximately the same time of the day for each participant, either in the morning or during the afternoon. Participants were instructed not to wear perfume, not to smoke, and not to eat or drink anything other than water or unsweetened tea 15 minutes prior to testing. The measurements were completed in the same order during each test session: subjective taste and smell perception, olfactory function, taste function, hedonic taste intensity ranking and food preference task. Demographic information regarding age, BMI, education level and smoking status was derived from a questionnaire at study onset. Information regarding disease stage and treatment was derived from medical records.

Measurements

Macronutrient and Taste Preference Ranking Task

Food preferences were assessed using the Macronutrient and Taste Preference Ranking Task, a computer-based preference task with food pictures from four food categories: high-protein, high-carbohydrate, high-fat and low-energy products.¹⁶ Each macronutrient category consisted of 8 products, with both sweet and savoury products, except the high-protein category, which only consisted of savoury products. First, liking was assessed for each product on a 100 point VAS anchored: 'do not like at all' and 'like extremely'. Next, participants were presented with the ranking procedure of the MTPRT, which

consisted of a macronutrient and a taste section. In both sections, participants were presented with four different pictures which they had to rank according to “what they most desire to eat at this moment”. In the macronutrient section, each of the four pictures represented one of the macronutrient categories, with 16 combinations in total. In the taste section, the four pictures that were presented came from two macronutrient categories, with twelve combinations in total. Within each category, one picture represented a sweet food item, and the other a savoury one. In this section, products from the high-protein category were excluded. Liking for the macronutrient and taste categories were calculated by using the mean liking for each category. Relative preferences were calculated for the macronutrient and taste categories as described elsewhere.¹⁶ Preference scores for the macronutrient categories can range from 1-4, with a higher score indicating a higher preference for a category. Preference scores for sweet and savoury can range from 1.5 to 3.5. Because preference scores for sweet and savoury are each other’s opposite in this task, we only report preference scores for savoury in this article.

Taste intensity preferences

Taste intensity preferences were evaluated with lemonade and tomato juice, with five different concentrations of sucrose and salt^{19, 20}. Sucrose was added to peach mango flavoured beverage (Kool-Aid® drink mix, Kraft Foods Canada Inc., Ontario, Canada), prepared in water according to manufacturer’s instructions. The sucrose concentrations ranged from 0.0625 M to 1M, with a twofold increase between every concentration. Tomato juice was made by diluting tomato paste without added sodium chloride (Albert Heijn, Zaandam, Netherlands) in water (215g/L). Sodium chloride was added to the tomato juice, with a concentration range of 0.3125 M to 0.5 M with a twofold increase between every concentration. Solutions were stored frozen in lidded containers (30ml) and brought to room temperature on the day of testing. For each taste, the five concentrations were presented in random order. Participants had to taste the concentrations, with a sip of water in between, and rank order the samples from least liked to most liked. Scores were ranged 1-5, with 1 being the least liked and 5 the most liked sample.

Self-reported taste and smell perception

Self-reported taste and smell function were assessed by asking response to the following statements: ‘At this moment I can taste’ and ‘At this moment I can smell’. Responses were

measured on a 100 point visual analogue scale (VAS), anchored from 'not good at all' to 'very good'.

Taste

Taste function was assessed using the Taste Strips (Burghart, Wedel, Germany). This validated test uses filter-paper taste strips impregnated with different concentrations of the basic tastes sweet, salty, bitter and sour^{21, 22}. The filter papers are impregnated with four concentrations of sweet (0.05, 0.1, 0.2 or 0.4 g/ml sucrose), salty (0.016, 0.04, 0.1 or 0.25 g/ml sodium chloride), sour (0.05, 0.09, 0.165 or 0.3 g/ml citric acid) or bitter (0.0004, 0.0009, 0.0024, 0.006 g/ml quinine hydrochloride) taste. After placing a paper on the tongue, patients were asked to identify the taste stimulus with five possible answers (sweet, sour, salty, bitter or no taste). Taste strips were presented in a semi-randomized forced choice procedure. Patients rinsed their mouth with water before each taste strip. Scores for each taste range from 0 to 4, and total taste scores range from 0-16, which is the sum of the four basic taste scores. Higher scores indicate a better taste function.

Smell

Olfactory function was measured using the Sniffin' Sticks.²³ This validated test battery examines nasal chemosensory performance using pen-like odour devices. The test consists of three parts: a detection threshold (THR), discrimination (DIS) test and odour identification (ID) test. The THR was measured with a standard series of pens with different concentrations of n-butanol. With a staircase procedure, three pens were presented to participants in a randomized order. Of these pens, one contained the odour and two contained solvent. Participants had to indicate which pen contained the odorant. To measure DIS ability, 16 triplets of odorants were presented to participants. The triplet contained two pens with the same odour and one with a different odour. Participants had to discriminate which pen smelled differently. During the ID test, 16 pens with common odours were presented. Participants had to choose the correct descriptor from a list of four descriptors for each pen. For the THR, scores range from 1 to 16, for the ID and DIS test scores ranged from 0 to 16. A score for overall olfactory function (TDI) was calculated by taking the sum of the THR, DIS and ID. Higher scores indicate a better olfactory function. To limit potential learning effects over the sessions, the extended version of the Sniffin' Sticks was used, which contains 32 odour combinations for the DIS-test and 32 odours for the ID-test.²⁴ Combinations of pens were randomized across participants and test sessions.

Data analysis

Baseline characteristics (age, BMI, smoking and education level) are presented as mean \pm SD or percentages. For 8 out of 28 patients, baseline measurements of taste and smell and food preferences were missing because the inclusion date was too close to the start of the first chemotherapy cycle to schedule the first test session.

Linear mixed models were used to analyse liking and ranking of high-fat, high-protein, high-carbohydrate, low-energy, sweet and savoury products, reported and measured taste and smell function, over time and differences between groups. Test session (T1-T4) and group (patient and control) and their interaction were included as fixed factors in the model and participants were included as random factors. When significant main effects or a significant interaction was found, post hoc analyses were performed to further explore the effects. For the liking of high-protein and savoury products, and ranking of the four macronutrient categories, vegetarian and vegan participants (n=3.) were excluded from the analyses.

Differences in preference for each lemonade and tomato juice concentration between the four test sessions were assessed for patients and controls separately with Friedman ANOVA and Dunn-Bonferroni test to assess post hoc differences. Pearson correlations were done to correlate self-reported taste and smell function with objectively measured taste and smell function, and to correlate reported and measured taste and smell with liking food preferences in patients. All time points were included in these analyses. Statistical analyses were performed using SPSS statistics version 23 (IBM Corporation, Armonk, New York, USA). A p-value ≤ 0.05 was considered statistically significant.

Results

Twenty eight breast cancer patients and 28 women in the control group completed all four test sessions (table 4.1). The two groups were similar in age and BMI, while there were more smokers and less former smokers in the patient group than in the control group. The control group had a higher education level than the patient group. Most patients had a stage II tumour and received adjuvant chemotherapy containing anthracyclines and taxanes.

Table 4.1. Demographic and clinical characteristics of the participants in the study presented as mean (SD) or n (%)

	Control n=28	Patients n=28
Age (years)	51.8 ± 7.6	51.0 ± 8.1
BMI (kg/m ²)	25.0 ± 4.8	25.1 ± 4.5
Smoking		
Current	0 (0)	5 (18)
Former	17 (61)	13 (46)
Never	11 (39)	10 (36)
Education		
Lower	0 (0)	4 (14)
Middle	8 (29)	11 (39)
Higher	20 (71)	13 (47)
Adjuvant chemotherapy		22 (79)
Neo-adjuvant chemotherapy		6 (21)
Stage		
I		9 (32)
II		17 (61)
III		2 (7)
Chemotherapy		
Taxanes		1 (4)
Anthracyclines + taxanes		26 (92)
Platinum containing		1 (4)

Food preferences

Macronutrient and Taste Preference Ranking Task

For all analyses on the MTPRT, liking and ranking the control group did not significantly change over time unless specified otherwise.

In patients, liking of high-fat products was significantly lower shortly after chemotherapy (T3) compared to baseline, but not for other time points (T1: 60 ± 17.3 , T2: 56 ± 15.7 , T3: 54 ± 16.9 , T4: 59 ± 16.7). For high-protein products (figure 4.1b), liking was higher in the patient group compared to the control group at baseline (67 ± 12.1 vs. 60 ± 14.8). Furthermore, patients liked high-protein products less during (T2) and shortly after chemotherapy (T3) compared to baseline (T1: 67 ± 12.1 , T2: 62 ± 14.2 , T3: 60 ± 14.8 , T4: 66 ± 12.2). There were no significant differences between the groups and over time for liking of high carbohydrate products and low energy products (figure 4.1c-d).

Patients liked savoury products more than controls at baseline (65 ± 7.6 vs. 58 ± 10.6) and T4 (64 ± 9.7 vs. 58 ± 9.4) (figure 4.1e). Furthermore, patients liked savoury products less shortly after chemotherapy compared to baseline (T1: 65 ± 7.6 , T2: 62 ± 10.5 , T3: 58 ± 10.1 , T4: 64 ± 9.7). Sweet products were liked less during and shortly after chemotherapy compared to baseline in the patient group (T1: 64 ± 14.3 , T2: 61 ± 13.1 , T3: 60 ± 12.3 , T4: 64 ± 12.8) (figure 4.1f).

For all data of the liking and ranking scores of the MTPRT, see Supplementary material 4.1. Ranking scores for high-fat, high-protein, high-carbohydrate and low-energy products did not differ over time within or between the groups. Preferences for savoury products changed over time in both the patient and the control group. In the patient group, preference for savoury products was significantly higher during chemotherapy compared to baseline (T1: 2.4 ± 0.4 , T2: 2.5 ± 0.37 , T3: 2.4 ± 0.33 , T4: 2.4 ± 0.39). In the control group preference for savoury products was significantly higher at T2 and T3 compared to T1 (T1: 2.2 ± 0.34 , T2: 2.3 ± 0.34 , T3: 2.3 ± 0.38).

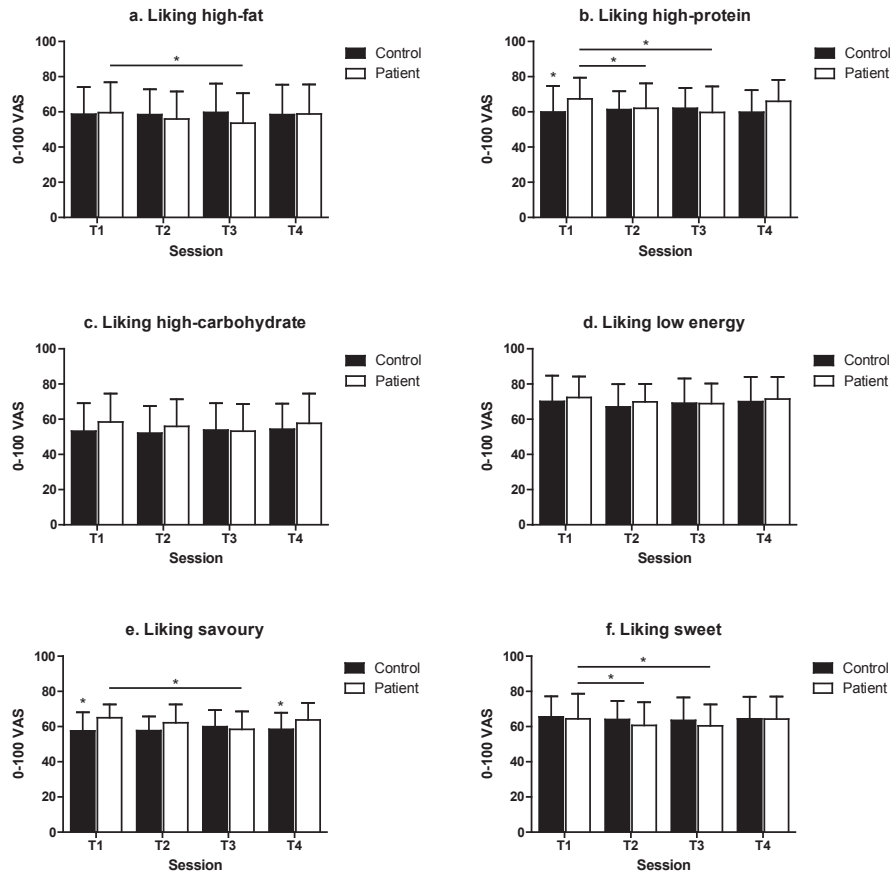


Figure 4.1. Liking of high-fat (a), high-protein (b), high-carbohydrate (c) and low energy (d), savoury (e) and sweet (f) products over time in breast cancer patients and controls (mean \pm SD). T1 represents before chemotherapy (patients) or baseline (control), T2 halfway chemotherapy (patients) or three months (controls), T3 shortly after chemotherapy (patients) or six months (controls) and T4 represents $\frac{1}{2}$ year after chemotherapy (patients) or 12 months (controls). * indicates a significant difference at $p < 0.05$.

Taste intensity preferences

Preferences for the lemonades with different concentrations of sucrose were similar over time in the control group (figure 4.2a). In the patient group, the lemonade with the second lowest concentration was less preferred during chemotherapy compared to baseline (figure 4.2b). Furthermore, the sweetest lemonade was more preferred, indicating a greater preference for highly intense sweet, albeit not statistically significant.

For the tomato juices, there were significant differences in salt intensity preferences over time, but mainly in the control group (figure 4.2c). In the patient group there were no significantly changed preferences for the different concentrations of salt in tomato juice (figure 4.2d).

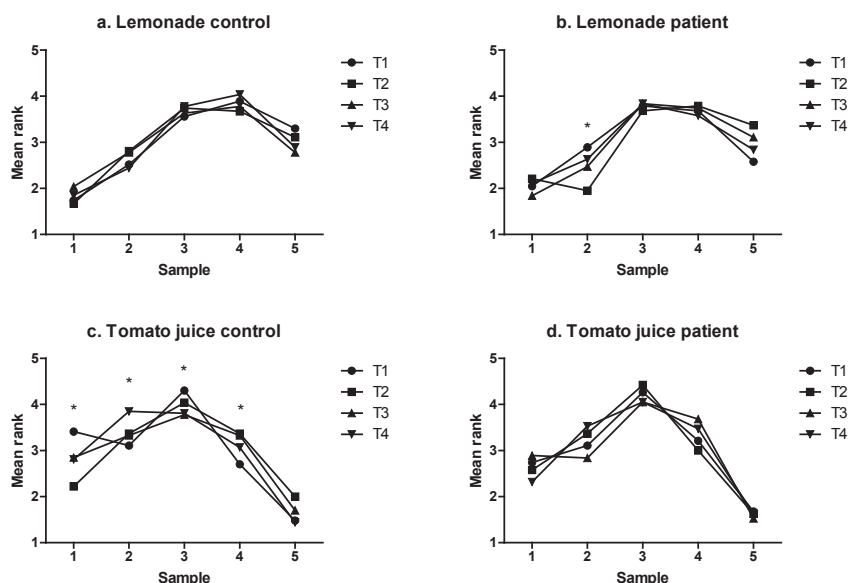


Figure 4.2. Hedonic ranking of lemonades and tomato juice over time in breast cancer patients and control group. T1 represents before chemotherapy (patients) or baseline (control), T2 halfway chemotherapy (patients) or three months (controls), T3 shortly after chemotherapy (patients) or six months (controls) and T4 represents ½ year after chemotherapy (patients) or 12 months (controls). Sample 1 presents the lowest concentration of sugar or salt, sample 5 the highest concentration.

Taste and smell function

For reported and objective taste and smell function measures, the control group remained stable over time.

Taste

Patients reported their taste function significantly lower during (T2) and shortly after chemotherapy (T3) compared to baseline (T1: 78 ± 19.2 , T2: 56 ± 25.1 , T3: 55 ± 27.4 , T4: 76 ± 17.1) and compared to the control group (T2: 74 ± 15.5 , T3: 76 ± 15.8) (figure 4.3a). The self-reported taste function of breast cancer patients was recovered half a year after chemotherapy (T4).

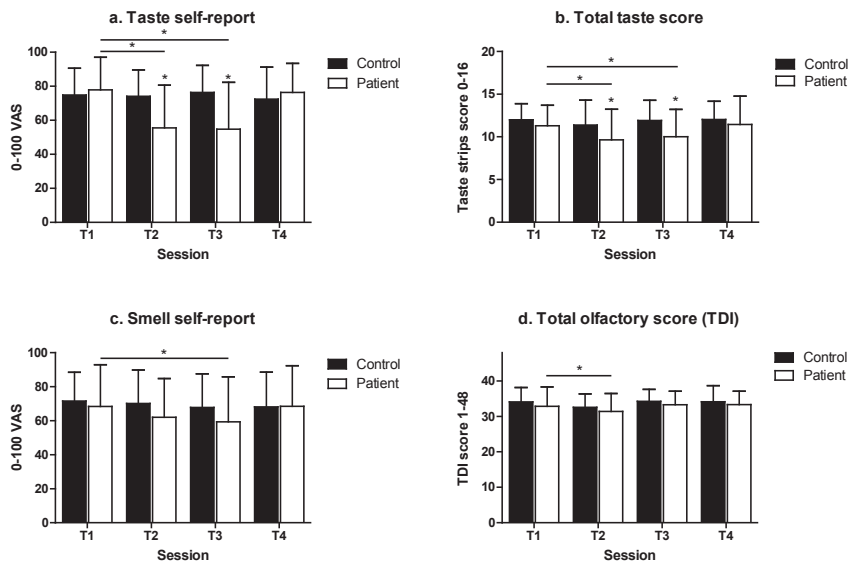


Figure 4.3. Self-reported taste (a), objective taste (b) and self-reported and objective smell function (c-d) over time in breast cancer patients and controls (mean \pm SD). T1 represents before chemotherapy (patients) or baseline (control), T2 halfway chemotherapy (patients) or three months (controls), T3 shortly after chemotherapy (patients) or six months (controls) and T4 represents ½ year after chemotherapy (patients) or 12 months (controls). * indicates a significant difference at $p < 0.05$.

Objective taste function (figure 4.3b) was lower during and shortly after chemotherapy compared to baseline, and also recovered half a year after chemotherapy (T1: 11.3 ± 2.41 , T2: 9.6 ± 3.6 , T3: 10.0 ± 3.22 , T4: 11.5 ± 3.32). Similarly, during and shortly after chemotherapy objective taste function was significantly lower than the control group (T2: 11.4 ± 2.92 , T3: 11.9 ± 2.36).

For data on the separate tastes in both groups see supplementary material 4.2. Patients had a significantly lower sensitivity for sweet during chemotherapy (T2) compared to baseline (T1: 3.2 ± 1.1 , T2: 2.7 ± 1.3 , T3: 2.9 ± 1.2 , T4: 3.4 ± 1.1).

During (T2) and shortly after chemotherapy (T3) the patient group had a significantly lower sensitivity for sweet compared to the control group (T2: 3.4 ± 0.6 , T3: 3.5 ± 0.6). Similarly, sensitivity for salt taste was lower during (T2) and shortly after chemotherapy (T3) compared to baseline in the patient group (T1: 3.1 ± 0.8 , T2: 2.4 ± 1.4 , T3: 2.3 ± 1.2 , T4: 2.8 ± 1.2). Shortly after chemotherapy this was significantly different from the control group (T3: 3.0 ± 1.1). Sensitivity for sour and bitter taste were not significantly different over time, nor between the groups.

Smell

Patients reported their smell function significantly lower shortly after chemotherapy (T3) (T1: 68 ± 24.5 , T2: 62 ± 22.8 , T3: 59 ± 26.5 , T4: 69 ± 23.8) (figure 4.3c). For overall olfactory function (TDI, figure 4.3d), patients scored lower during chemotherapy (T2) compared to baseline (T1: 32.9 ± 5.46 , T2: 31.4 ± 5.06 , T3: 33.3 ± 3.82 , T4: 33.4 ± 3.74). For odour thresholds (THR), patients had the lowest THR during chemotherapy, which was significantly different from shortly after chemotherapy and half a year after chemotherapy, but not from baseline (T1: 7.5 ± 2.41 , T2: 6.4 ± 2.16 , T3: 7.5 ± 2.08 , T4: 7.9 ± 1.66). The DIS and ID test did not show changes over time within or between the groups. For all data on separate olfactory tests in both groups see Supplementary material 4.2.

Correlations between subjective, objective taste and smell function, and food preferences

Subjective taste was significantly correlated with subjective smell function in both the patient and the control group (patients: $r=0.73$, $p<0.001$; control: $r=0.59$, $p<0.001$). Furthermore, subjective smell function was significantly correlated with objective smell function in both groups (patients: $r=0.31$, $p=0.001$; control: $r=0.25$, $p<0.01$), while

subjective and objective taste function were not significantly correlated in either of the groups (patients: $r=0.12$, $p=0.22$; control: $r=-0.06$, $p=0.54$). Objective taste function was significantly correlated with objective smell function in the patient group ($r=0.21$, $p=0.03$), but not in the control group ($r=0.05$, $p=0.60$).

A higher rating of taste function was significantly correlated with a higher liking of high protein ($r=0.32$, $p<0.01$), low energy ($r=0.27$, $p<0.01$), savoury ($r=0.32$, $p<0.01$) and sweet products ($r=0.21$, $p=0.04$), but not with liking of high carbohydrate or high fat products. A higher rating of subjective smell function was significantly correlated with a higher liking of low energy ($r=0.29$, $p<0.01$) and sweet products ($r=0.24$, $p=0.01$), but not with liking of high carbohydrate, high fat, high protein and savoury products. Objective taste and smell function were not significantly correlated with any of the liking of the macronutrient and taste categories (all $p>0.05$).

Discussion

In this study we assessed food preferences, taste and smell function before, during and after chemotherapy in breast cancer patients and compared women without cancer. Furthermore, in breast cancer patients, we assessed the associations between subjective and objective taste and smell and food preferences.

Altered preferences for macronutrients were expressed in a lower liking of high-fat and high protein products during chemotherapy, but was not shown in changed ranking scores in the MTPRT. The changed liking for these macronutrient categories are in line with the actual dietary intake of breast cancer patients during chemotherapy, where we found a lower intake of protein and fat, but not for carbohydrates.⁸ Probably, the lower liking for high-protein and high-fat products results in a lower intake of protein and fat during chemotherapy. This corresponds to literature frequently reporting meat as being aversive during chemotherapy, as it is high in protein and fat.¹²⁻¹⁴

Our results for sweet and savoury preferences do not suggest a specific change in preference for either of the tastes, as the results for sweet and savoury preferences were not consistent over the different methods used. Liking of both sweet and savoury products in the MTPRT decreased during chemotherapy. In the ranking procedure of the MTPRT, we found a higher preference of savoury products over sweet products during chemotherapy. However, the control group showed a similar change in preference during the study period. Therefore the shift in ranking of sweet and savoury products in breast cancer patients cannot specifically be attributed to chemotherapy. Furthermore, the intensity preference ranking of the lemonades suggest a higher preference for more intense sweet taste during chemotherapy, but the results from the salt intensity preferences were difficult to interpret, as there were also fluctuations of preferences in the control group. Possibly, the preferences for the tomato juices were more difficult to assess, as tomato juice is less frequently consumed in the Netherlands and was less liked in general. These results highlight the importance of including a control group in these types of observational studies. Without a control group, changes in cancer patients could be falsely attributed to influences of chemotherapy, while these could also be natural fluctuations in eating behaviour.

Generally, the ranking methods used for tastes in our study indicated fluctuations in both the patient and the control group, while the liking scores indicated a stable pattern over time in the control group, and changes in the patient group during chemotherapy.

Possibly, the liking measures give information on liking over a longer period of time, while the ranking measures are more susceptible to daily fluctuations, like time and previous meals, which was difficult to standardize in our study setting.

Our study shows that chemotherapy induced taste changes, both measured subjectively and objectively. These changes were transient and recover after the end of chemotherapy, which has also been reported by several other studies.^{13, 25, 26} However, it should be noted that on average objective taste function during chemotherapy was still considered to be within the normal range.²² With regard to specific tastes, changes were mostly measured for sweet and salt taste, but not for sour and bitter taste. However, other studies investigating separate tastes during chemotherapy show varying results, with all tastes affected during chemotherapy¹³, only salt, umami and sour²⁵, only sweet and bitter²⁷ and only salt being affected.²⁶ Results may vary with methods used to assess taste sensitivity, but also due to variations in the moment of assessing taste function during chemotherapy. Recent studies show that taste changes are largest early in the chemotherapy cycle^{25, 26}, while most studies, including ours, assess taste function later in the cycle. Potentially, the taste changes we found would be greater when measurements were done early cycle.

Smell function was less affected by chemotherapy than taste function. The decrease in total olfactory function score was small (1.5), and is not considered a clinically relevant difference.²⁸ Furthermore, the odour threshold score was decreased, while odour identification and discrimination were unaffected by chemotherapy. This suggests that olfactory function is mostly affected by chemotherapy on peripheral level, but that supra-threshold perception and cognitive processing of odours remain unaffected.²⁹ Chemotherapy targets rapidly dividing cells and as a consequence, next to tumour cells, also smell and taste receptor cells are likely to be affected. This also explains why the effects on chemosensory perception are transient and recover after the end of chemotherapy.

In terms of self-reported taste and smell function, there was a more prominent decrease during chemotherapy for taste than for smell, in line with the objectively measured data. However, it is difficult for humans to distinguish between taste and smell. When people are asked about taste, they mostly refer to the overall flavour of food which also includes a large olfactory component.³⁰ This was also reflected in the lack of correlation between self-reported taste and objective taste function, while self-reported smell was significantly

correlated with objective smell function. Furthermore, self-reported taste may also reflect hedonic changes, rather than an actual taste change. Which means that food is not enjoyed anymore, but it might taste the same. This could also explain the lack of associations between objective measures of taste and smell and the liking measures of the MTPRT, while subjective measures were associated. Subjective taste function was most often correlated to liking of foods. Self-reported measures may therefore be more relevant in a clinical context, as a lower self-reported taste function was related to a lower liking of foods in this study, and a lower dietary intake in our previous study.⁸

In conclusion, this is the first study that longitudinally assessed food preference and chemosensory perception in breast cancer patients undergoing chemotherapy and a healthy control group. Breast cancer patients undergoing chemotherapy have altered food preferences for macronutrients, but not specifically for sweet or savoury tastes. Chemotherapy has a transient influence on food preferences and chemosensory function, on which patients should be informed prior to treatment, and monitored during treatment due to the consequences for nutritional intake and quality of life.

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Supplementary table 4.1. Liking and ranking scores of the MTPRT in breast cancer patients and controls over time (mean \pm SD). T1 represents before chemotherapy (patients) or baseline (control), T2 halfway chemotherapy (patients) or three months (controls), T3 shortly after chemotherapy (patients) or six months (controls) and T4 represents ½ year after chemotherapy (patients) or 12 months (controls).

Liking	Control				Patients			
	T1	T2	T3	T4	T1	T2	T3	T4
Carbohydrate	53 \pm 15.9	52 \pm 15.4	54 \pm 15.3	54 \pm 14.5	58 \pm 16.2	56 \pm 15.4	53 \pm 15.3	58 \pm 16.9
Fat	59 \pm 15.4	58 \pm 14.4	60 \pm 16.3	58 \pm 17.1	60 \pm 17.3	56 \pm 15.7	54 \pm 16.9	59 \pm 16.7
Protein	60 \pm 14.8	61 \pm 10.5	62 \pm 11.6	60 \pm 12.6	67 \pm 12.1	62 \pm 14.2	60 \pm 14.8	66 \pm 12.2
Low energy	70 \pm 14.6	67 \pm 13	69 \pm 14	70 \pm 14.1	72 \pm 12	70 \pm 10.2	69 \pm 11.5	71 \pm 12.5
Savoury	58 \pm 10.6	58 \pm 8.2	60 \pm 9.4	58 \pm 9.4	65 \pm 7.6	62 \pm 10.5	58 \pm 10.1	64 \pm 9.7
Sweet	66 \pm 11.5	64 \pm 10.6	63 \pm 13.1	64 \pm 12.4	64 \pm 14.3	61 \pm 13.1	60 \pm 12.3	64 \pm 12.8
Ranking								
	T1	T2	T3	T4	T1	T2	T3	T4
Carbohydrate	2.2 \pm 0.5	2.2 \pm 0.55	2.3 \pm 0.42	2.3 \pm 0.54	2.2 \pm 0.34	2.3 \pm 0.4	2.3 \pm 0.39	2.2 \pm 0.47
Fat	2.6 \pm 0.57	2.5 \pm 0.56	2.5 \pm 0.57	2.5 \pm 0.51	2.4 \pm 0.35	2.3 \pm 0.42	2.4 \pm 0.39	2.5 \pm 0.39
Protein	2.5 \pm 0.63	2.5 \pm 0.61	2.6 \pm 0.56	2.4 \pm 0.63	2.7 \pm 0.51	2.6 \pm 0.49	2.6 \pm 0.52	2.6 \pm 0.51
Low energy	2.7 \pm 0.64	2.8 \pm 0.73	2.6 \pm 0.71	2.8 \pm 0.66	2.7 \pm 0.63	2.8 \pm 0.66	2.7 \pm 0.69	2.7 \pm 0.69
Sweet	2.8 \pm 0.34	2.7 \pm 0.34	2.7 \pm 0.38	2.7 \pm 0.34	2.6 \pm 0.4	2.5 \pm 0.37	2.6 \pm 0.33	2.6 \pm 0.39
Savoury	2.2 \pm 0.34	2.3 \pm 0.34	2.3 \pm 0.38	2.3 \pm 0.34	2.4 \pm 0.4	2.5 \pm 0.37	2.4 \pm 0.33	2.4 \pm 0.39

Supplementary table 4.2. Self-reported and objective taste and smell in breast cancer patients and controls over time (mean \pm SD). T1 represents before chemotherapy (patients) or baseline (control), T2 halfway chemotherapy (patients) or three months (controls), T3 shortly after chemotherapy (patients) or six months (controls) and T4 represents ½ year after chemotherapy (patients) or 12 months (controls).

	Control				Patient			
	T1	T2	T3	T4	T1	T2	T3	T4
Taste self-report	75 \pm 15.7	74 \pm 15.5	76 \pm 15.8	72 \pm 18.8	78 \pm 19.2	56 \pm 25.1	55 \pm 27.4	76 \pm 17.1
Smell self-report	72 \pm 16.9	70 \pm 19.7	68 \pm 19.8	68 \pm 20.5	68 \pm 24.5	62 \pm 22.8	59 \pm 26.5	69 \pm 23.8
TDI score	34.1 \pm 4.09	32.6 \pm 3.75	34.2 \pm 3.42	34.1 \pm 4.58	32.9 \pm 5.46	31.4 \pm 5.06	33.3 \pm 3.82	33.4 \pm 3.74
THR score	7.4 \pm 2.01	7.2 \pm 1.68	8.3 \pm 2.48	8.1 \pm 2.67	7.5 \pm 2.41	6.4 \pm 2.16	7.5 \pm 2.08	7.9 \pm 1.66
DISC score	13 \pm 2.0	12 \pm 2.0	13 \pm 1.4	13 \pm 2.0	12 \pm 2.7	12 \pm 2.3	13 \pm 2.0	12 \pm 2.5
ID score	14 \pm 1.5	13 \pm 1.8	13 \pm 1.4	13 \pm 1.8	13 \pm 1.9	13 \pm 1.9	13 \pm 2.1	13 \pm 1.7
Taste strips total	12.0 \pm 1.89	11.4 \pm 2.92	11.9 \pm 2.36	12 \pm 2.13	11.3 \pm 2.41	9.6 \pm 3.6	10.0 \pm 3.22	11.5 \pm 3.32
Sweet	3.6 \pm 0.6	3.4 \pm 0.6	3.5 \pm 0.6	3.8 \pm 0.5	3.2 \pm 1.1	2.7 \pm 1.3	2.9 \pm 1.2	3.4 \pm 1.1
Sour	2.4 \pm 1.1	2.3 \pm 1.2	2.4 \pm 1.0	2.4 \pm 0.8	2.4 \pm 0.9	2 \pm 1.0	2.4 \pm 0.7	2.5 \pm 0.8
Salt	3.1 \pm 1	2.9 \pm 1.1	3 \pm 1.1	2.8 \pm 1.2	3.1 \pm 0.8	2.4 \pm 1.4	2.3 \pm 1.2	2.8 \pm 1.2
Bitter	2.8 \pm 1.3	2.8 \pm 1.4	3.1 \pm 1.2	3.1 \pm 1.1	2.8 \pm 1.1	2.6 \pm 1.3	2.4 \pm 1.5	2.9 \pm 1.1



Chapter 5

Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer

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Abstract

Purpose: Breast cancer patients receiving chemotherapy often experience symptoms such as nausea, vomiting and loss of appetite that potentially affect dietary habits. This study assessed the intake of energy, macronutrients and food groups before and during chemotherapy in breast cancer patients compared with women without cancer, and determined the association between symptoms and energy and macronutrient intake.

Methods: This study included 117 newly diagnosed breast cancer patients scheduled for chemotherapy and 88 women without cancer. Habitual intake before chemotherapy was assessed with a food frequency questionnaire. Two 24h dietary recalls were completed on random days for each participant during the whole chemotherapy treatment for patients and within 6 months after recruitment for women without cancer. Shortly after the dietary recall, participants filled out questionnaires on symptoms.

Results: Before chemotherapy, habitual energy and macronutrient intake was similar for breast cancer patients and women without cancer. During chemotherapy, breast cancer patients reported a significantly lower total energy, fat, protein and alcohol intake than women without cancer, as shown by a lower intake of pastry and biscuits; cheese; legumes; and meat products. A decline in subjective taste perception, appetite, hunger, and experiencing a dry mouth, difficulty chewing, lack of energy and nausea were associated with a lower energy intake.

Conclusions: Symptoms induced by chemotherapy are associated with lower dietary intake, and manifested by a lower intake of specific food groups. To ensure an optimal dietary intake during chemotherapy, it is important to monitor nutritional status and symptom burden during chemotherapy in breast cancer patients.

Introduction

The majority of women with breast cancer is treated with chemotherapy.¹ Treatment with cytotoxic drugs is often accompanied with symptoms such as nausea, vomiting, loss of appetite, dry mouth and changes in taste or smell perception. These symptoms can be very disturbing and can significantly impact quality of life.^{2, 3} In types of cancer where the gastro-intestinal tract is affected, such as head and neck cancer, the impact of these symptoms on dietary intake and nutritional status is well established.^{4, 5} However, for breast cancer patients the experience of symptoms during cancer treatment may differ and the extent to which symptoms specifically affect dietary intake in breast cancer patients is less clear.

Previous studies that investigated whether dietary intake changed during chemotherapy in breast cancer patients are inconsistent in their findings. They either showed increases,⁶ decreases^{7, 8} or no changes⁹⁻¹¹ in energy intake during chemotherapy, possibly because different studies used different methods and different time points during the course of chemotherapy to assess dietary intake. Most studies in breast cancer patients assessed dietary intake only in the week prior to a next chemotherapy cycle, while dietary intake is suggested to vary during a cycle.¹² Most importantly, earlier studies did not compare dietary intake in breast cancer patients to a comparable group of women without breast cancer, limiting the possibility to assess whether changes in intake deviate from normal fluctuations in intake over time. Additionally, most studies are limited by only focussing on energy and macronutrient intake, and not on food items or food groups. Thereby it is unknown whether changes in dietary intake during chemotherapy are due to changes in intake of specific food groups.

There are studies that suggest that breast cancer patients gain weight during and after chemotherapy, which may be associated with an increased risk of comorbidities like cardiovascular disease and diabetes.^{13, 14} Therefore it is important to give breast cancer patients well-grounded advice on their lifestyle and dietary habits before, during and after treatment. Especially since breast cancer patients have expressed a need for dietary support during treatment with chemotherapy,¹⁵ unmet supportive care needs in cancer patients are highest during treatment.¹⁶ However, in order to give specific dietary advice it is important to first know what the actual change in dietary intake of breast cancer patients is and which symptoms are associated with dietary changes during chemotherapy.

Therefore, the aim of this observational study was to assess the intake of energy, macronutrients and food groups before and during chemotherapy in breast cancer patients in comparison with a group of women without cancer, and to determine the association between the experience of specific symptoms and energy and macronutrient intake.

Materials and Methods

Participants

This study is part of an ongoing observational multi-centre study among breast cancer patients during chemotherapy and a comparison group of women of similar age without cancer (COBRA-study). Women with newly diagnosed, incident, stage I-IIIb, operable breast cancer, scheduled for 2nd or 3rd generation chemotherapy were compared with women without cancer of similar age (range within 2 years). Eligible patients were recruited by the staff of 11 participating hospitals prior to commencement of chemotherapy. The comparison group was recruited via the women with breast cancer, who were asked to distribute information about the study to female friends, acquaintances and colleagues. This approach was chosen to maximize the comparability of groups with respect to possible confounding factors, and thus to minimize the risk that other factors than chemotherapy influenced our findings on dietary intake. Women without cancer contacted the researchers if they were interested in participating in the study. All study participants needed to be at least 18 years old and be able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, pregnancy or the intention to get pregnant during the study period, dementia or other mental conditions that made it impossible to comply with the study procedures. The protocol was approved by the Medical Ethical Committee of Wageningen University (ABR NL40666.081.12). All participants provided written informed consent before enrolment.

Measurements

Dietary intake

Upon recruitment, all participants filled out a food frequency questionnaire (FFQ) to assess habitual intake before chemotherapy (patient group) or start of the study (comparison group).^{17, 18} During chemotherapy, actual dietary intake was assessed using

two telephone-based 24h dietary recalls, because of the expected high day to day variation during chemotherapy. The recalls were planned on two random days during chemotherapy, during all weeks within a chemotherapy cycle and over all chemotherapy cycles administered. Recalls were planned between the day of the first chemotherapy infusion and three weeks after the last chemotherapy infusion. Women in the comparison group also completed two recalls, which were planned on two random days within 6 months after recruitment. This was a comparable time-frame, as current oncological guidelines for chemotherapy for breast cancer in the Netherlands encompass schemes which mostly take 4.5 to 6 months to complete. Randomization of the recall days was done for each participant separately. The two recalls were scheduled at least 7 days apart. If it was not possible to complete the recall on the scheduled day, a new day was planned randomly within 2 weeks. The 24h-recalls were performed using a standardized protocol and conducted by trained dietitians. The recalls were at least one week apart and were conducted both on week and weekend days. Dietary recall data were coded and entered, after which the intake of total energy, protein, carbohydrate, fat, alcohol and fibre were calculated in the computation module of Compl-eat™ using the Dutch food composition table 2013.¹⁹ A data check was performed by the dietitians. The highest and lowest ten values for energy, macronutrients, and fruit and vegetables intake were checked for errors in coding or amounts. Food items were grouped into food groups for both the food frequency questionnaire and 24h dietary recall.¹⁹ These food groups were: bread; cereal and cereal products; fruit; vegetables; legumes; nuts, seeds and snacks; soups; soy products and vegetarian products; pastry and biscuits; sugar, candy sweet toppings and sweet sauces; milk and dairy products; cheese; eggs; meat and meat products; and fish.

Symptoms

After being called for each 24-h recall, participants were instructed to fill out questionnaires on sensory perception and experienced symptoms. The Appetite, Hunger feelings and Sensory Perception (AHSP) questionnaire was used to assess self-judgement of taste, smell and appetite.²⁰ The questionnaire consisted of 29 questions answered on a 5 point Likert scale, concerning four categories; taste (8 items, score range 8-40), smell (6 items, range 6-30), appetite (6 items, range 6-30) and hunger (9 items, range 9-45). An example of a question for taste was: In former days the taste of food was: 1. much better than nowadays, 2. better than nowadays, 3. the same as nowadays, 4. worse than nowadays, 5. much worse than nowadays. For the patient group, 'former days' was referenced as the situation before chemotherapy and for the comparison group as the

situation one year ago. A higher score corresponds to a more positive judgement about current taste and smell perception, appetite and hunger. The severity of 13 additional symptoms was assessed: pain; dry mouth; feeling depressed; thick saliva; diarrhoea; sore mouth; lack of energy; nausea; difficulty chewing; difficulty swallowing; anxiety; constipation and vomiting. For each symptom the question was asked: 'How often have you experienced this symptom during the past three days?', scored on a 5 point Likert scale, ranging from 1="not at all" to 5="a lot". If participants did not answer the symptoms questionnaires within 3 days after complete the 24h dietary recall, we did not include their data in the analyses. In total, we collected n=274 recalls from patients and n=205 recalls from women without breast cancer. A number of n=205 recalls from breast cancer patients and n=152 recalls from women without cancer were used in the analyses in this paper. Excluding participants who did not complete the questionnaires within 3 days from analysis did not significantly influence the results on energy and macronutrient intake.

Demographics and medical information

All participants filled out a baseline questionnaire for demographic information, including age, smoking status and educational level. Information on stage of cancer at diagnosis and treatment were obtained from reviewing patients' medical records. Dates of chemotherapy cycles were compared with the dates of the 24h-recalls to classify the recalls into the week within a chemotherapy cycle and to the number of cycles that was administered at the date of the 24h recalls.

Data analysis

Population characteristics were described as medians with interquartile range (IQR) or percentages of the patient and comparison group separately. To assess differences in the population characteristics between the groups, the Mann-Witney U-test was used for continuous data and the Chi Square test for categorical data. Differences in dietary intake at study onset (FFQ) between the women with and without breast cancer were analysed with Linear Regression. Mixed Model analysis was used to assess differences in energy, macronutrient and food group intake between the patient and comparison group. For the analysis of differences in dietary intake within a chemotherapy cycle for patients receiving a three weekly scheme of chemotherapy, recalls were classified according to the week within a chemotherapy cycle a 24h-recall was administered (week 1, week 2 or week 3) and to the number of cycles administered. Patients with weekly chemotherapy cycles were excluded from this analysis (n=22 recalls). Mixed models were also used to assess the

association between symptoms and energy intake. Interactions between each symptom and group (patient and comparison group) were evaluated to test whether associations between symptoms and energy intake were different between the two groups. For significant interactions (p -value ≤ 0.1), stratified results for patients and the comparison group are shown. For symptoms with a significant association with energy intake, data was also analysed for the macronutrients protein, carbohydrates and fat. Covariates considered as potential confounders were included in the regression and mixed models analyses based on literature and change of regression coefficient. Variables that changed the regression coefficient $\geq 10\%$ in the adjusted model compared to the crude model were included in the final model. Final regression and mixed models analyses were adjusted for: age at inclusion, BMI at inclusion, education level, and smoking status at inclusion. Statistical analyses were performed using SPSS, version 21 (SPSS inc. Chicago, IL). A p -value < 0.05 was considered as statistically significant.

Results

Patient characteristics

Data were collected for 117 breast cancer patients and 88 women in the comparison group, see table 5.1. BMI was higher in women with breast cancer than in women without breast cancer. In the patient group, fewer women had a high educational level than in the comparison group. There were no differences for age, smoking status and menopausal status between the groups. The majority of the breast cancer patients had a stage 2 tumour, and received adjuvant chemotherapy combining taxanes and anthracyclines.

Dietary intake at study onset

At study onset, mean energy, protein, fat and carbohydrate intakes were similar between the patient and comparison group as assessed with a food frequency questionnaire (table 5.2). Women with breast cancer reported to consume less alcohol than women in the comparison group. Intake for the various food groups was similar between the two groups, with the exception of cheese intake, which was slightly higher in breast cancer patients compared to the women without cancer.

Table 5.1. Demographic and clinical characteristics of the patient and comparison group included in the study.

Characteristic	Comparison group (n=88)	Patient group (n=117)
Demographics		
Age, years (median, IQR)	53.5 (46.1 – 60.9)	51.0 (46.8 – 55.3)
Education level (n, %) *		
<i>Low</i>	4 (4.5)	12 (10.4)
<i>Medium</i>	18 (20.5)	35 (30.4)
<i>High</i>	66 (75.0)	68 (59.1)
Lifestyle		
BMI, kg/m ² (median, IQR) *	23.8 (22.1 – 26.7)	25.2 (22.3 – 28.4)
Smoking status (n, %)		
<i>Current</i>	9 (10.2)	21 (18.1)
<i>Former</i>	40 (45.5)	49 (42.2)
<i>Never</i>	39 (44.3)	46 (39.7)
Medical profile		
Tumor Stage (n, %)		
<i>I</i>		25 (21.4)
<i>II</i>		70 (59.8)
<i>III</i>		22 (18.8)
Adjuvant chemotherapy (n, %)		68 (58.1)
Neo adjuvant chemotherapy (n, %)		49 (41.9)
Chemotherapy regimen (n, %)		
<i>Taxanes only</i>		4 (3.4)
<i>Anthracyclines only</i>		4 (3.4)
<i>Taxanes + Anthracyclines</i>		109 (93.2)

Abbreviations: IQR, Interquartile range;

Missings per variable : education, 2; smoking, 1.

* p <0.05

Table 5.2. Habitual intake of energy, macronutrients and food groups for the patient and comparison group (mean \pm SE) and differences in intake between the groups at study onset, assessed by a food frequency questionnaire.

	Intake in kcal (mean \pm SE)		Difference ^a [95% CI]
	Comparison group (N=88)	Patient group (N=114)	
Energy	2069 \pm 69.2	2070 \pm 59.7	1 [-181 ; 184]
Protein	318 \pm 10.1	315 \pm 8.7	-3 [-30 ; 24]
Carbohydrate	859 \pm 31.3	870 \pm 27.0	11 [-71 ; 93]
Fat	761 \pm 32.3	779 \pm 27.8	18 [-67 ; 103]
Alcohol*	75 \pm 7.5	51 \pm 6.5	-24 [-44 ; -4]
Fibre	46 \pm 1.6	45 \pm 1.4	-1 [-5 ; 3]
Food groups			
Bread	256 \pm 16.7	256 \pm 14.4	0 [-44 ; 44]
Cereal and cereal products	139 \pm 10.9	131 \pm 9.4	-8 [-37 ; 21]
Fruit	134 \pm 8.3	118 \pm 7.2	-16 [-37 ; 7]
Vegetables	50 \pm 3.5	53 \pm 3.0	3 [-6 ; 12]
Legumes	10 \pm 1.6	11 \pm 1.4	1 [-4 ; 5]
Nuts, seeds and snacks	168 \pm 15.7	146 \pm 13.5	-22 [-63 ; 19]
Soups	24 \pm 3.3	22 \pm 2.8	-2 [-11 ; 6]
Soy products and vegetarian products	18 \pm 5.3	16 \pm 4.5	-2 [-15 ; 12]
Pastry and biscuits	119 \pm 11.3	136 \pm 9.7	17 [-13 ; 47]
Sugar, candy, sweet toppings and sweet sauces	110 \pm 10.6	120 \pm 9.2	10 [-18 ; 38]
Milk and dairy products	195 \pm 13.9	173 \pm 12.0	-22 [-58 ; 15]
Cheese*	105 \pm 13.8	145 \pm 11.9	40 [3 ; 76]
Eggs	25 \pm 2.6	24 \pm 2.3	-1 [-8 ; 6]
Meat, meat products and poultry	153 \pm 9.3	159 \pm 8.0	6 [-19 ; 30]
Fish	36 \pm 3.1	29 \pm 2.7	-7 [-15 ; 1]

^a Adjusted for age, BMI, education level, smoking status * p < 0.05

Dietary intake during chemotherapy

In total, 357 recalls were collected, 205 in the patient group and 152 in the comparison group. During chemotherapy, breast cancer patients had a significantly lower energy intake than the women without cancer as assessed with 24-h dietary recalls, 1779 ± 56 vs 1993 ± 68 kcal (table 5.3). Breast cancer patients reported a significant lower absolute intake of protein, fat, and alcohol, but not of carbohydrates and fibre than women without cancer. Expressed as energy percentages, during chemotherapy women with breast cancer consumed relatively more energy from carbohydrates and less energy from alcohol compared to women without cancer.

During chemotherapy, women with breast cancer consumed less energy from the food groups legumes; pastry and biscuits; cheese; and meat than the women without cancer (table 5.4). The intake of other food groups: bread; cereal and cereal products; fruit; vegetables; nuts, seeds and snacks; soups; soy and vegetarian products; sugar, sweets, sweet toppings and sweet sauces; milk and dairy products; cheese; eggs; and fish was similar between breast cancer patients during chemotherapy and women without cancer. Results expressed in grams/day can be found in Supplementary table 5.1. The main sources of total protein, fat and carbohydrate intake were similar for the patient and the comparison group. The main sources of protein intake were meat, bread and milk and dairy products. For fat the main sources were fats, oils and savoury sauces, cheese and meat. Carbohydrates came mostly from the food groups bread, alcoholic and non-alcoholic drinks, milk and dairy products and fruit.

Dietary intake in the patient group was lower compared to the women without cancer in all three weeks after chemotherapy was administered, and was lowest in each first week. However, there were no statistically significant differences in energy and macronutrient intake between the first, second and third week within a chemotherapy (Supplementary table 5.2). In addition, there was no association between dietary intake and the number of chemotherapy cycles administered.

Table 5.3. Energy and macronutrient intake in kcal and energy percentages (en%) for the breast cancer patients during chemotherapy and comparison group during follow up (mean \pm SE) and the differences in intake between the groups.

	Intake in kcal* (mean \pm SE)		Difference ^a [95% CI]
	Comparison group	Patient group	
Energy*	1993 \pm 68.3	1779 \pm 55.7	-214 [-353 ; -76]
Protein*	313 \pm 10.7	270 \pm 8.8	-43 [-64 ; -21]
Carbohydrate	844 \pm 34.4	815 \pm 28.0	-29 [-99 ; 41]
Fat*	734 \pm 32.0	633 \pm 26.1	-101 [-166 ; -37]
Alcohol*	54 \pm 9.4	17 \pm 7.7	-37 [-57 ; -19]
Dietary fibre	38 \pm 1.8	35 \pm 1.4	-3 [-7 ; 1]
	Intake in en%* (mean \pm SE)		
	Comparison group	Patient group	
Protein	16.3 \pm 0.45	15.5 \pm 0.37	-0.8 [-1.6 ; 0.2]
Carbohydrate*	41.9 \pm 1.0	46.2 \pm 0.82	4.3 [2.2 ; 6.3]
Fat	36.6 \pm 0.85	35.0 \pm 0.70	-1.6 [-3.4 ; 0.1]
Alcohol*	2.8 \pm 0.47	0.8 \pm 0.38	-2.0 [-2.9 ; -1.0]
Dietary fibre	2.0 \pm 0.09	2.0 \pm 0.07	0.0 [-0.1 ; 0.2]

Table 5.4. Intake per food group for the breast cancer patients during chemotherapy and comparison group during follow up (mean \pm SE) and the differences in intake between the groups in kcal.

	Intake in kcal* (mean \pm SE)		Difference [95% CI] ^a
	Comparison group	Patient group	
Bread	332 \pm 39.5	291 \pm 37.2	-41 [-81 ; 2]
Cereal and cereal products	68 \pm 29.4	67 \pm 27.7	-1 [-32 ; 31]
Fruit	98 \pm 26.5	86 \pm 24.9	-121 [-40 ; 16]
Vegetables	41 \pm 9.4	33 \pm 8.9	-8 [-17 ; 3]
Legumes*	136 \pm 39.2	83 \pm 36.9	-53 [-95 ; -12]
Nuts seeds and snacks	7 \pm 11.8	9 \pm 11.1	2 [-11 ; 14]
Soups	35 \pm 28.5	22 \pm 26.8	-13 [-43 ; 18]
Soy products and vegetarian products	29 \pm 14.9	31 \pm 14.0	2 [-14 ; 18]
Pastry and biscuits*	131 \pm 36.6	84 \pm 34.4	-47 [-86 ; -8]
Sugar, candy, sweet toppings, and sweet sauces	90 \pm 28.7	86 \pm 27.0	-4 [-34 ; 26]
Milk and dairy products	164 \pm 36.6	170 \pm 34.5	6 [-33 ; 44]
Cheese*	140 \pm 22.4	112 \pm 21.1	-28 [-52 ; -4]
Eggs	35 \pm 9.1	39 \pm 8.6	4 [-6 ; 14]
Meat, meat products and poultry*	190 \pm 31.8	150 \pm 29.9	-40 [-74 ; -6]
Fish	25 \pm 22.3	42 \pm 20.95	17 [-8 ; 40]

^a Adjusted for age, BMI, education level, smoking status

*p < 0.05

Symptoms

During chemotherapy, the patient group scored significantly lower on their self-reported taste, smell, appetite and hunger, compared to the women without cancer (table 5.5). Furthermore, breast cancer patients undergoing chemotherapy experienced more often anxiety, dry mouth, constipation, feeling depressed, thick saliva, diarrhoea, sore mouth, lack of energy, nausea, difficulty chewing and difficulty swallowing than women in the comparison group (table 5.6). Scores were not different for the symptoms pain and vomiting between the patient and the comparison group. Only 3 women with breast cancer and 1 woman without breast cancer reported vomiting as a symptom they experienced that day, therefore vomiting was not analysed for its association with energy intake.

Table 5.5. Taste, smell, appetite and hunger scores from AHSP questionnaire for the breast cancer patients during chemotherapy and comparison group during follow up (mean \pm SE) and the association of AHSP categories with energy intake (kcal). Higher scores indicate a more positive self-judgement on the categories of the questionnaire. β for energy intake is the difference in energy intake (kcal) per 1 unit higher score within ASHP category.

Category	Range	Score questionnaire (mean \pm SE)		Difference	Estimate (β) for energy intake (kcal) ^a [95% CI]
		Comparison group	Patient group		
Taste	8-40	30.9 \pm 0.71	22.0 \pm 0.57	-8.9* [-10.4 ; -7.5]	16.4* [7.0 ; 25.8]
Smell	6-30	23.3 \pm 0.42	20.6 \pm 0.42	-2.7 * [-3.7 ; -1.8]	11.9 [-5.0 ; 28.7]
Appetite	6-30	24.7 \pm 0.40	18.7 \pm 0.50	-6.0* [-7.0 ; -5.0]	26.5* [14.4 ; 38.5]
Hunger	9-45	38.3 \pm 0.70	32.5 \pm 0.70	-5.8* [-7.4 ; -4.3]	24.5* [15.1 ; 33.9]

^a Adjusted for age, BMI, education level, smoking status

*p < 0.05

Symptoms and dietary intake

A higher self-judgement of taste perception, better appetite and more hunger were significantly associated with a higher energy intake (table 5.5). Self-judgement of smell was not significantly associated with energy intake.

Having a dry mouth, lack of energy, nausea and having difficulty chewing were significantly associated with a lower energy intake (table 5.6). The associations between anxiety and energy intake and between constipation and energy intake were different for the patient and the comparison group (interaction anxiety $p=0.02$, constipation $p=0.03$): anxiety was not associated with energy intake in breast cancer patients, while it was associated with a lower energy intake in the comparison group. Constipation was associated with a higher energy intake in the patient group and with a lower energy intake in the comparison group, but these associations were not statistically significant (table 5.6).

For the symptoms that were significantly associated with energy intake, we additionally assessed whether those symptoms were associated with protein, carbohydrate and fat intake. Briefly, those associations were in the same direction as how the intake of macronutrients differed during chemotherapy between the patients and the comparison group: symptoms were associated with a lower protein and fat intake, and not associated with the intake of carbohydrates (Supplementary table 5.3).

Table 5.6. Results of the symptom questionnaire for the breast cancer patients during chemotherapy and comparison group during follow up (mean \pm SE) and the association between symptoms and energy intake (kcal). Symptom severity was assessed on a 5 point Likert scale (1=not at all, 5=a lot). β for energy intake indicates the difference in energy intake (kcal) per 1 unit higher score in the symptom.

Symptom	Score questionnaire (mean \pm SE)		Difference	Estimate (β) for energy intake (kcal) ^a [95%CI]
	Comparison group	Patient group		
Pain	1.6 \pm 0.13	1.9 \pm 0.11	0.3 [-0.005 ; 0.520]	54.2 [-2.8 ; 111.2]
Dry mouth	1.3 \pm 0.15	2.9 \pm 0.12	1.6 [1.3 ; 1.9]*	-47.1* [-92.5 ; -1.8]
Depressed	1.3 \pm 0.1	1.6 \pm 0.08	0.3 [0.1 ; 0.5]*	5.4 [-68.4 ; 79.1]
Thick saliva	1.1 \pm 0.12	1.9 \pm 0.10	0.8 [0.6 ; 1.1]*	-56.3 [-114.1 ; 1.5]
Diarrhoea	1.0 \pm 0.09	1.5 \pm 0.07	0.5 [0.2 ; 0.6]*	-3.1 [-75.9 ; 69.6]
Sore mouth	1.3 \pm 0.13	2.2 \pm 0.11	0.9 [0.7 ; 1.2]*	-35.7 [-86.0 ; 14.6]
Lack of energy	1.6 \pm 0.14	3.3 \pm 0.12	1.7 [1.5 ; 2.0]*	-55.5* [-99.0 ; -12.1]
Nausea	1.1 \pm 0.1	1.7 \pm 0.08	0.6 [0.4 ; 0.8]*	-77.7* [-139.4 ; -16.0]
Difficulty chewing	1.1 \pm 0.09	1.5 \pm 0.07	0.4 [0.2 ; 0.6]*	-102.6* [-180.3 ; -24.9]
Difficulty swallowing	1.1 \pm 0.08	1.5 \pm 0.06	0.4 [0.2 ; 0.6]*	-33.6 [-117.1 ; 49.8]
Constipation ^b	1.3 \pm 0.12	1.8 \pm 0.09	0.5 [0.2 ; 0.7]*	
Constipation control				-103.3 [-228.8 ; 22.3]
Constipation patient				42.1 [-34.1 ; 118.5]
Anxiety ^b	1.2 \pm 0.08	1.5 \pm 0.07	0.3 [0.1 ; 0.4]*	
Anxiety Control				-208.7* [-384.1 ; -33.3]
Anxiety Patient				83.1 [-18.2 ; 184.5]
Vomiting ^c	1.0 \pm 0.04	1.1 \pm 0.03	0.04 [-0.04 ; 0.12]	

^a Adjusted for age, BMI, education level, smoking status

^b For anxiety and constipation significant interactions were found on the association with energy intake, therefore stratified results are shown.

^c For vomiting only 1 control and 3 patients reported a score of 2 or higher on the questionnaire, therefore this symptom was not analysed for the association with energy intake.

Discussion

To date, this is the largest study that examined energy, macronutrient and food group intake in breast cancer patients during chemotherapy compared to a group of women without cancer. We showed that breast cancer patients had a significantly lower energy intake during chemotherapy compared with a group of women without cancer. Since habitual intake of breast cancer patients before start of chemotherapy was comparable to the women without cancer in our study, we can assume that the differences found between the groups were mostly due to the consequences of chemotherapy. These findings are in accordance with two other studies that observed a lower energy intake in breast cancer patients during chemotherapy compared to before chemotherapy.^{7, 8} Only one previous study, published in 1987, suggested a higher dietary intake during chemotherapy in breast cancer patients compared with controls.⁶ However, that study had a control group which already had a lower intake at baseline, limiting the reliability of those conclusions.

The lower energy intake that we observed during chemotherapy was not caused by a lower intake of all macronutrients. The intakes of fat, protein and alcohol were lower during chemotherapy in breast cancer patients than in women without cancer, while intakes of carbohydrates and dietary fibre were similar. The lower protein and fat intake can be explained by the food groups that were consumed less during chemotherapy: meat and cheese are mostly high in protein and fat, and may thereby partially account for the different intakes of macronutrients. Habitual alcohol intake was lower in breast cancer patients before chemotherapy than women without cancer, and the intake remained lower during chemotherapy. As alcohol is a known risk factor for breast cancer,²¹ a higher or comparable alcohol intake could be expected in the patient group compared with the women without cancer. Possibly, breast cancer patients underreported their alcohol intake due to social desirability bias. However, it is also possible that breast cancer patients changed their dietary habits due to cancer diagnosis. Cancer diagnosis has been referred to as a 'teachable moment' for lifestyle changes and may motivate patients to change their dietary habits.²²

Patients in our study experienced a variety of symptoms during chemotherapy, but not all were associated with energy intake. Specifically, the symptoms of lower self-reported taste, lower appetite, less hunger, dry mouth, lack of energy, nausea and difficulty chewing were associated with a lower energy intake. These symptoms are known to limit

the enjoyment of eating as they make eating more difficult. It is thus not surprising that they have been previously related to a lower energy intake.^{4, 23} Interestingly, self-judgement of taste was significantly associated with energy intake, but self-judgement of smell was not, while smell function is generally recognized as an important factor for food intake.²⁴ We must consider that humans are generally not well able to rate their own smell sensitivity.²⁵ Therefore, we cannot exclude that reduced smell function influences energy intake. The experience of symptoms does not only have an effect on dietary intake, symptoms also negatively impact quality of life.²⁶ Therefore it is important to monitor symptoms during chemotherapy, and to treat symptoms where possible. Furthermore, given the associations of symptoms with dietary intake, it is important to monitor nutritional status to ensure an adequate intake of energy and nutrients during chemotherapy.

In addition to experienced symptoms, changed preferences for foods may be related to the changed food choices we observed during chemotherapy. Aversions for meat are commonly reported during chemotherapy,^{27, 28} and may thereby underlie the lower intake of this food group that we observed in breast cancer patients during chemotherapy compared to the women without cancer. However, research on food preferences during chemotherapy is mostly anecdotal and scarcely measured quantitatively and should be taken into account in future studies.

Studies suggest that breast cancer patients gain weight during and after chemotherapy.^{13, 14} To date, it is not clear which factors underlie these weight changes. However, our study does not suggest nutritional intake as a contributing factor for this weight gain, as we observe a decreased energy intake of patients during chemotherapy. However, breast cancer patients may have a lower energy requirement, as physical activity may be lower.^{9, 29} Additionally, reductions in resting energy expenditure have been reported during and after chemotherapy.^{13, 14} Therefore, studies assessing weight change during chemotherapy should take changes in dietary intake, physical activity and resting energy expenditure into account to assess the contribution of these factors on weight change.

Previous studies investigating dietary intake during chemotherapy in breast cancer patients were heterogeneous in the time points dietary intake was assessed. Mostly, it was assessed the week before a next cycle would be administered. In our study, we deliberately chose to assess dietary intake at random days during the full cycle of chemotherapy, thereby capturing the full variation in dietary intake over chemotherapy.

Although there were no significant differences between the weeks within chemotherapy cycles, there was variation within the weeks; dietary intake was lowest in the first week after a cycle was administered. This renders the importance to take into account all weeks within chemotherapy cycles to give a correct representation of dietary intake during chemotherapy.

It cannot be excluded that differential reporting of dietary intake between patients and the comparison group influenced the results of our study. Differential reporting may be influenced by differences in BMI.³⁰ BMI was slightly higher in the patient group than the comparison group at the start of our study. As persons with higher BMI tend to underestimate dietary intake, the patient group may have underestimated their intake, explaining the difference in intake between women with breast cancer and women without cancer observed during chemotherapy. However, habitual intake was similar between patients and the comparison group at baseline and analyses were adjusted for BMI. Therefore, we do not expect that differential reporting substantially influenced our results.

In conclusion, our study is the largest study to date showing that breast cancer patients have a lower dietary intake during chemotherapy, which is expressed in a lower intake of specific food groups. The lower intake was associated with specific symptoms. These finding can guide clinicians to inform patients about the potential impact of chemotherapy and related symptoms on dietary intake and to ensure an adequate intake of energy and nutrients during chemotherapy.

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Chapter 5

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Supplementary table 5.1. Intake per food group for the breast cancer patients during chemotherapy and comparison group during follow up (mean \pm SE) and the differences in intake between the groups in grams.

	Intake in gram* (mean \pm SE)		Difference [95% CI] ^a
	Comparison group	Patient group	
Bread	124 \pm 15.3	110 \pm 14.4	-14 [-31 ; 2]
Cereal and thickeners	35 \pm 17.4	37 \pm 16.4	2 [-16 ; 21]
Fruit	131 \pm 34.8	125 \pm 32.8	-6 [-43 ; 31]
Vegetables	152 \pm 29.1	125 \pm 27.4	-27 [-58 ; 4]
Legumes*	33 \pm 10.4	19 \pm 9.8	-14 [-25 ; -3]
Nuts seeds and snacks	14 \pm 18.1	8 \pm 17.1	-6 [-25 ; 13]
Soups	25 \pm 19.5	21 \pm 18.4	-4 [-25 ; 17]
Soy products and vegetarian products	76 \pm 29.9	77 \pm 28.1	1 [-31 ; 33]
Pastry and biscuits*	40 \pm 11.2	25 \pm 10.5	-15 [-27 ; -3]
Sugar, candy, sweet toppings, and sweet sauces	22 \pm 6.4	21 \pm 6.0	-1 [-7 \pm 6]
Milk and dairy products	260 \pm 54.8	247 \pm 51.7	-13 [-70 ; 44]
Cheese*	39 \pm 6.5	31 \pm 6.1	-8 [-15 ; -1]
Eggs	27 \pm 6.6	30 \pm 6.2	3 [-5 ; 9]
Meat, meat products and poultry*	92 \pm 14.4	76 \pm 13.6	-16 [-32 ; -1]
Fish	18 \pm 12.4	20 \pm 11.7	2 [-11 \pm 16]

^a Adjusted for age, BMI, education level, smoking status

*p < 0.05

Supplementary table 5.2. Energy and macronutrient intake per week within the chemotherapy cycle. Week 1: n=90 recalls, week 2: n= 60 recalls, week 3: n=42 recalls.

	Intake in kcal* (mean \pm SE)	Difference [95% CI] ^a
Energy		
Week 1	1751 \pm 74.1	Ref
Week 2	1883 \pm 84.0	132 [-54 ; 318]
Week 3	1861 \pm 95.6	110 [-96 ; 315]
Protein		
Week 1	267 \pm 12.6	Ref
Week 2	286 \pm 14.4	19 [-14 ; 52]
Week 3	283 \pm 16.5	16 [-21 ; 53]
Fat		
Week 1	621 \pm 34.2	Ref
Week 2	665 \pm 39.0	43 [-44 ; 130]
Week 3	671 \pm 44.3	50 [-47 ; 146]
Carbohydrate		
Week 1	816 \pm 38.1	Ref
Week 2	863 \pm 42.9	47 [-45 ; 139]
Week 3	847 \pm 48.1	30 [-71 ; 131]

^a Adjusted for age, BMI, education level, smoking status

Supplementary table 5.3. The association of AHSP and symptom categories and intake of protein, carbohydrate and fat (kcal) for the categories that were significantly associated with energy intake.

Symptom	Estimate (β) for protein intake (kcal) ¹ [95%CI]	Estimate (β) for carbohydrate intake (kcal) ^a [95%CI]	Estimate (β) for fat intake (kcal) ^a [95%CI]
Taste ^b	3.5* [2.0 ; 5.0]	2.6 [-2.1 ; 7.3]	7.7* [3.3 ; 12.1]
Appetite ^b	5.1* [3.1 ; 7.1]	5.5* [0.6 ; 11.5]	12.6* [6.9 ; 18.3]
Hunger ^b	4.2* [2.7 ; 5.7]	8.5* [3.8 ; 13.2]	10.2* [5.7 ; 14.7]
Dry mouth ^c	-8.0* [-15.7; -0.4]	-7.9 [-30.3; 14.5]	-21.0 [-42.6; 0.7]
Lack of energy ^c	-12.2* [-19.5 ; -4.8]	-12.0 [-33.5 ; 9.5]	-22.6* [-43.4 ; -1.8]
Nausea ^c	-11.1* [-21.9 ; -0.2]	-8.6 [-39.1 ; 21.9]	-42.4* [-72.3 ; -12.5]
Difficulty chewing ^c	-14.9* [-28.4 ; -1.3]	-20.2 [-58.6 ; 18.2]	-61.6* [-99.0 ; -24.2]

^a Adjusted for age, BMI, education level, smoking status^b β for macronutrient intake is the difference in macronutrient intake (kcal) per 1 unit higher score within ASHP category.^c β for macronutrient intake indicates the difference in macronutrient intake (kcal) per 1 unit higher score in the symptom.* $p < 0.05$



Chapter 6

The impact of chemosensory and food-related changes in patients with advanced oesophagogastric cancer treated with capecitabine and oxaliplatin: a qualitative study

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Abstract

Purpose: Chemosensory changes are frequently observed side effects of cytotoxic treatment and have an impact on daily life by altering food-related behaviour and daily practices. For oesophagogastric cancer patients these changes can be particularly important as they may have specific needs with regard to eating, due to obstruction of the upper intestinal tract. The purpose of this study was to gain insight into the impact of chemosensory and food-related changes in oesophagogastric cancer patients undergoing chemotherapy and how this may influence the practical and social aspects of food-related behaviour of patients and their relatives.

Methods: We used a qualitative interview approach with a cross-sectional design using semi-structured interviews. Template analysis was used to analyse patients' experiences with and the impact of chemosensory changes on daily life. Thirteen advanced oesophagogastric cancer (OGC) patients treated with capecitabine and oxaliplatin were included by convenience sampling, recruited from one academic hospital, and interviewed at home or in the hospital.

Results: There was a large variation in the impact of chemosensory changes in OGC patients, though daily life was impacted substantially when chemosensory and/or food-related changes were experienced. Three main themes emerged from the interviews: altered food preferences, practical constraints in daily life, and impact on social functioning.

Conclusion: Chemosensory and food-related changes significantly influenced food preferences and had practical and social consequences in daily life of patients and their relatives. Specific nutritional care for these patients should be directed towards enhancing food enjoyment and should take the specific needs, related to the location of the tumour, into account.

Introduction

Taste and smell alterations are among the most common side effects in cancer patients undergoing cytotoxic treatment.¹⁻³ Studies have reported a prevalence of 45 to 84% for self-reported taste changes and 5 to 60% for smell changes among cancer patients undergoing chemotherapy.² These changes can lead to a decreased appetite, liking and enjoyment of food, food avoidance, altered food preferences, food aversions, a reduction in food intake and eventually malnutrition in cancer patients.^{1, 4-10} These different alterations in taste and smell may seriously impact patients' daily life and quality of life.¹¹⁻¹³ For instance, taste and smell changes can affect daily living, change practical routines and may also have an impact on social functioning related to cooking and rituals of eating, such as eating together with family and friends.^{11, 14, 15} In order to support patients in the course of their anti-cancer treatment, it is important to further explore these experienced chemosensory changes.

To date, most studies assessing chemosensory changes during chemotherapy were executed in heterogeneous study populations undergoing a variety of chemotherapeutic regimens.² However, it has been suggested that the experience of taste and smell changes may depend on specific cytotoxic agents used.¹⁶ Additionally, patients with certain cancer types may experience specific difficulties with respect to eating. For instance, in patients with oesophagogastric cancer (OGC), eating may be particularly complicated by obstruction of the upper intestinal tract, potentially resulting in a poor nutritional status.¹⁷ Therefore, it is of specific interest to study how patients and their families experience the interactions of these complications with chemosensory alterations resulting from cytotoxic treatment.

So far, no studies have focussed on the impact and consequences of chemosensory changes within advanced OGC patients receiving chemotherapy. In order to improve supportive care, in particular nutritional advice and management strategies for OGC patients with chemosensory changes, a better understanding of the experiences of patients is needed. Not only the experience of chemosensory changes and dietary itself are of interest, but also the impact of these experiences and the consequences of these changes in daily life.

In this study, we use a qualitative approach to explore the impact of chemosensory and food-related changes in advanced oesophagogastric cancer patients undergoing chemotherapy with two specific cytotoxic agents, capecitabine and oxaliplatin, and study

how this influences the practical and social aspects of food-related behaviour of patients and their relatives.

Methods

Study design

We adopted qualitative approach, applying template analysis to describe and interpret the lived experience of patients in order to get a deep understanding of these experiences at both a general and individual level.¹⁸ The study was exempt from formal ethical approval by the institutional medical ethics committee of the Academic Medical Centre (W14_010).

Participants

We included a convenience sample of patients with OGC diagnosed in the Academic Medical Centre (AMC) in Amsterdam, the Netherlands. The following inclusion criteria were applied: patients with diagnosed oesophageal and stomach cancer who had a metastatic or irresectable carcinoma at the time of diagnosis with a WHO performance status of 0 to 2,¹⁹ who were currently receiving palliative chemotherapy with capecitabine (Xeloda®) and oxaliplatin (Eloxatin®) (CAPOX) and had completed at least two cycles of chemotherapy. We considered convenience sampling to be adequate for broadly exploring the experiences of chemosensory changes following chemotherapy. Patients were not purposefully selected on reporting an altered chemosensory perception.

Data collection

MK, a clinical dietician and MSc student Nutrition and Health at the time of the study, carried out semi-structured interviews. She had no prior relationship with the participants. Interviews were held at home or in the hospital, following patients' preference, and lasted approximately 15 - 60 minutes. In the hospital, rooms could be private or shared with other patients. During the interviews, patients were often accompanied by a close relative or friend, who was allowed to participate in the conversation. The interview guide was developed based on key topics from literature and investigators' knowledge and experiences from clinical practice, and further adapted in the course of the study. Interviews covered changes in taste and smell, appetite, enjoyment of food, food preferences, practical and social consequences, strategies to handle changes, the impact

of changes in smell, taste on daily life and the impact of such changes upon diagnosis. Interviews were audio recorded.

Data analysis

Interviews were transcribed and coded according to the template analysis as described by King.²⁰ Template analysis is a thematic analysis where, to analyse the data, the researcher identifies a number of codes or themes that summarize key ideas, concepts, actions or experiences extracted from the interviews by reading and re-reading the text. Codes are organized hierarchically with the highest level codes representing broad themes in the data and lower-level codes representing more narrow or specified themes in the data. When patients did not experience any changes in chemosensory function, interviews were not or only partly transcribed, although all interviews were reviewed for the final template. The first two interviews were coded for main themes by MK, together with and YV, a PhD student in the field of sensory science and eating behaviour and studies chemosensory changes during chemotherapy in cancer patients. The template was further developed in discussion with EH, an elderly care physician with specific expertise in qualitative research, who was working on separate transcripts. MK and YV constructed the final template on the basis of detailed re-reading of the full set of transcripts and discussed their interpretations with EH and HvL, a medical oncologist specialized in the treatment of OGC patients.

Results

Thirteen patients were interviewed for this study, of whom demographic and diagnostic data are summarized in Table 6.1. We defined nine themes, each divided into further sub-themes (Table 6.2). Three main themes pertained strongly to the experience of patients and are fully described: altered food preferences, practical constraints in daily life and the meaning of chemosensory and food-related changes for social life.

General findings

We found a large individual variation in the perceived degree and impact of chemosensory changes and other side effects of chemotherapy in patients. Patients who experienced mild or few side effects mostly did not experience alterations in their sense of smell or taste either. In contrast to other side effects of chemotherapy, patients did not always mention changes in taste and smell spontaneously. Nevertheless, these changes

were described as important or as having a substantial impact on their daily lives. Some patients reported that their daily lives were greatly impacted by chemosensory changes, while others experienced the impact as less significant. Two extremes are mentioned; Sam, a patient with only minor chemosensory complaints, said:

'I do find them noticeable [changes in taste and smell], but I think it's more important to live than to hand in some of the sensory stimuli.' (Sam)

Charles, a patient with severe complaints, believes that these chemosensory changes do not outweigh the benefits of chemotherapy.

'I would not do it again [chemotherapy] if I knew what I know now. (...) Should I be severely ill for nine or ten weeks for just a few months extension of my life?' (Charles)

Patients found it difficult to describe changes in taste and smell perception as distinct features and referred to changes in flavour as a whole or instead jointly ascribed these to changes in taste perception. They were, however, perfectly able to articulate what these changes entailed:

'I used to love cheese, but if I eat cheese now, I cannot taste it. I only taste the saltiness. I also used to love quark with blueberries.(...) If you would close your eyes and take a bite it just doesn't taste the way that it used to do.' (Nicole)

Patients described changes in taste or smell in terms of having a reduced enjoyment of food.

'You just hope that it's over soon, because you don't enjoy food whatsoever. You just eat because you have to, but there is no pleasure in it. You just hope that it will improve soon.' (Jacob)

Table 6.1. Patient characteristics and interview settings

Pseudonym	Gender	Age	BMI	WHO status ^a	Diagnosis	Previous treatment	Interview location	Interview timepoint ^b	Accompanied during interview ^c	Chemosensory complaints
Sam	male	56	23,6	0	oesophageal cancer	no previous treatment	hospital: private room	4	yes	yes
Charles	male	78	23,4	0	oesophageal cancer	no previous treatment	hospital: private room	3	yes	yes
Nicole	female	58	17,1	1	gastroesophageal junction cancer	no previous treatment	hospital: private room	4	yes	yes
Alvord	male	64	23,8	1	oesophageal cancer	neoadjuvant chemoradiation	hospital: shared room	2	no	no
Jervis	male	56	26,1	1	stomach cancer	neoadjuvant chemotherapy	hospital: shared room	2	yes	no
Jacob	male	64	24,2	0	oesophageal cancer	neoadjuvant chemoradiation	hospital: private room	3	yes	yes
Harold	male	58	26,4	1	oesophageal cancer	neoadjuvant chemoradiation	hospital: shared room	4	yes	yes
Lambert	male	67	29,0	0	stomach cancer	neoadjuvant chemotherapy	hospital: private room	3	no	yes
Wilford	male	64	22,4	1	stomach cancer	no previous treatment	at patients' home	3	no	yes
Ralph	male	55	24,6	0	gastroesophageal junction cancer	single palliative radiotherapy	at patients' home	2	yes	yes
Abraham	male	61	33,0	1	oesophageal cancer	neoadjuvant chemoradiation	at patients' home	3	no	yes
Chadd	male	60	24,8	2	oesophageal cancer	neoadjuvant chemoradiation	hospital: private room	3	no	yes
Nixon	male	62	24,4	0	oesophageal cancer	no previous treatment	hospital: private room	4	no	yes

^a WHO (World Health Organisation) performance status: a tool to assess general health and level of physical functioning of patients.¹⁹^b Interview timepoint: number of fully administered chemotherapy cycles at time of interview.^c Patients could be accompanied during the interview by a relative or close friend

Table 6.2. Template

-
1. **Changes in taste**
 - 1.1. Reduced taste perception
 - 1.2. Enhanced taste perception
 - 1.3. Altered taste perception
 - 1.4. Constant taste without the presence of food (phantom)
 2. **Changes in smell**
 - 2.1. Reduced odour perception
 - 2.2. Enhanced odour perception
 - 2.3. Altered odour perception
 3. **Appetite**
 - 3.1. Decreased appetite
 - 3.2. Improved appetite
 4. **Nutritional advice (dietician)**
 - 4.1. Adding more fat to the diet/ eating products that contain more fat
 - 4.2. Eating more protein-rich foods
 - 4.3. Eating more frequently
 5. **Altered food preferences**
 - 5.1. Need for a more intense flavour
 - 5.1.1. Addition of condiments
 - 5.1.2. Choose products with a more distinctive flavour
 - 5.2. Need for a less intense flavour
 - 5.2.1. Less addition of seasonings
 - 5.3. Changed food choices
 - 5.3.1. Favouring warm food
 - 5.3.2. Taking into account patients' food preferences
 - 5.3.3. Food for easy passage oesophagus
 - 5.3.3.1. Liquid and smooth food
 - 5.3.3.2. Avoiding dry and grainy food
 - 5.3.3.3. Drink while eating
 - 5.4. Food aversions
 - 5.4.1. Decreased enjoyment in eating food
 - 5.4.1.1. Not liking anything anymore
 - 5.4.1.2. Counting nutrients
 - 5.4.2. Aversion to specific foods
 - 5.4.2.1. Aversion towards fried food and hot meals
 - 5.4.2.2. Aversion towards meat
 6. **Practical constraints in daily life**
 - 6.1. Not being able to eat / drink
 - 6.1.1. Not being able to eat / drink cold products
 - 6.2. Not being able to swallow the food
 - 6.3. Planning meals and dinners
 - 6.4. Adapting to what is still possible to eat
 - 6.4.1. Liquid and smooth food
 - 6.4.2. Avoiding dry and grainy food
 - 6.4.3. Drink while eating
 - 6.4.4. Trying different foods
 - 6.4.5. Eating more frequently
 - 6.4.6. Eating less (frequently)
 - 6.4.7. Eating smaller portions

7. **Social functioning in daily life**
 - 7.1. Eating (together) less sociable
 - 7.1.1. Fewer dinners with family and friends
 - 7.1.2. Planning of meals
 - 7.2. Role of partners and family
 - 7.2.1. Taking into account patients' food preferences
 - 7.2.2. Family is motivating (forcing?) patient to eat
 - 7.2.3. Change of family roles
 - 7.3. Decreased pleasure in eating
 8. **Significance of chemosensory changes upon diagnosis**
 - 8.1. Limited impact of chemosensory changes compared to chemotherapy benefits
 - 8.2. Major impact of chemosensory changes compared to chemotherapy benefits
 9. **General side effects of chemotherapy**
 - 9.1. Food-related side effects
 - 9.2. Other side effects
 10. **Changes over time**
 - 10.1. Exacerbation of side effects with increased number of chemotherapy cycles
 - 10.2. Higher intensity of side effects at start of chemotherapy
-

Altered food preferences

A variety of altered food preferences were experienced by patients, which are expressed by a need for more or less intense flavours, changed food choices and food aversions.

To compensate for altered chemosensory perception, some patients described a need for more intense flavours, which was reflected by addition of condiments, like sugar, seasonings and salt or by choosing products with a distinctive flavour.

'I recognised, that during the period that I started tasting less, I used more salt and more products with strong flavours. I had also figured to eat herring: besides a lot of nutrients, it also has a strong flavour.' (Abraham)

Altered chemosensory perception did not always result in a preference for more intense stimuli, in contrast, some patients described a need for less intense flavours, specifically for spicy products.

'I need to be a bit careful not to eat spicy foods. Last Wednesday for instance, I made beans with a spicy curry paste and I had to pay the bill all night. That was too spicy, so I need to take into account not to use too much spicy herbs.' (Nicole)

Besides preferences for more or less intense flavours, patients sometimes needed to choose other types of food. Chemotherapy induced an enhanced sensitivity to cold, particularly a few days after oxaliplatin infusion, which resulted in a preference for warm

foods, the need to wear gloves to get food out of the refrigerator or an urge to put all foods in the microwave before consumption.

Many patients talked about eating food that could easily pass the oesophagus. Some patients needed to switch to liquid foods, in order to combat weight loss and maintain sufficient energy intake. Some specific dry foods, like bread and meat were avoided, because it could not easily pass the oesophagus.

'It should easily slide through, it should not be too dry and it has to be tasteful.' (Sam)

Another way to swallow dry foods, was to drink along with food. For Wilford this was a way to force the food to go down.

'If I do not manage to get the food down, I take a glass of apple juice, and swallow the food along with the apple juice just to get it inside. I just have to get it inside.' (Wilford)

Patients often complained about food aversions, which were frequently related to aversive cooking aromas. These aversions could be directed at specific foods, like meat, or more general towards reduced enjoyment of eating.

'If you cook vegetarian, or just normal, it has a certain smell. (...) It gives a smell which I find really annoying now. It causes me to lose my appetite before eating it' (Wilford)

Changed food preferences were a challenge for partners and relatives, who had to take the altered food preferences into account during shopping and cooking.

'You make sure that when you cook a meal you know that he likes it (...) I used to make him some oven baked fish, ... but as soon as it was time to eat he looked at his plate, took two bites and said "That's enough, well you don't have to cook that for me anymore."' (Charles's wife)

Practical constraints in daily life

Patients encountered many practical constraints in daily life, mostly because of obstruction of the oesophagus. These pertained to not being able to eat, drink or swallow, consequences for the planning of meals and dinners, and adapting to what was still possible to eat.

For some patients the daily routine was changed, meals and dinners were planned at different times of the day. For instance for Chadd, the daily pattern was changed in order not to get any gastric refluxes during the night.

'I'll eat as much as possible preferably in the early afternoon, around 2 pm or so. Not in the evening around 5 or 6 pm. Because I've had some of these refluxes at night, it was complete panic.' (Chadd)

Not being able to swallow the foods made patients slow down and take their time while consuming a meal, and therefore taking much more time.

'It seems as if the food does not pass that fast, as if it gets stuck. You have to slow down your eating, take pauses between bites.' (Nicole)

Patients had to adapt to what was still possible to eat, not only by choosing or avoiding specific types of food as previously described, but also by changing their food pattern into eating smaller portions, eating less frequently, or more frequently but in smaller portions.

'I rather eat more frequent during the day and smaller portions than once or twice a large meal.' (Sam)

Social functioning in daily life

Changes in social functioning were presented in several ways; patients felt restricted because eating was less sociable, needed to be planned, and was less pleasurable. Furthermore, partners and family members played a role in social functioning by adjusting themselves to the altered food preferences which sometimes resulted in a change of roles within the family.

Eating with family and friends was less sociable because it was less spontaneous and needed to be planned. Furthermore, patients sometimes avoided going out for dinner from a fear of not having the appropriate choices on a menu, or a fear for complaints during eating.

'But if you would say: 'let's go out for dinner this week with the four of us', I would say: rather not, I'm not that good accompany.' (Nixon)

Partners played an important role in the social aspect of eating. Relatives often tried to stimulate patients to eat, by taking into account patients food preferences and ensuring sufficient nutritional intake, which made mealtime less spontaneous.

'We try to do that [making decisions about dinner] together. Beforehand we think about meals for today or for the rest of the week. And by doing so, she [wife] takes care that it is not too dry and so on.' (Sam)

Patients sometimes tried to force themselves to eat from a feeling of guilt towards their partners because of their efforts into making food tasty.

'You are eating and think: I'll stuff it inside, but for my wife it's not pleasant at all because she is trying to make something out of it. I'll stuff it inside, but actually for me it didn't have to, because it just doesn't taste right.' (Jacob)

The social aspect of cooking and eating was also changed by a switch of roles for patients and partners in the household. A partner may take over grocery shopping and cooking, because a patient was not able to do it anymore, or to keep a patient from losing appetite from cooking smells by cooking him/herself.

Chemosensory changes influenced social aspects of eating resulting in a decreased pleasure in eating, where the role of a meal changed from something pleasurable into a compulsory way to ingest enough nutrients.

'Nowadays eating is a 'necessary evil'. So I do think the social aspect is noticeable. You are counting the protein and nutrients and it feels like a mathematical exercise. My wife is thinking about the meals we shall try this time. It is a quest to find what is possible and what tastes good and so on. Nutrition and taste have a whole new impact in that way, it's noticeable and not for the better.' (Sam)

Discussion

This study provides insight on the impact of chemosensory and food-related changes on the life's of oesophagogastric cancer patients undergoing palliative chemotherapy. We found a large individual variation in the intensity and impact of changes in taste or smell perception among patients. When patients experienced chemosensory and/or food-related changes, this did not only result in altered food preferences, but also had practical implications and meaningfully influenced social life.

In the current study, a relatively homogeneous group was interviewed, undergoing the same cytotoxic treatment, while other studies that examined chemosensory changes mainly used heterogeneous groups with respect to type of cancer and/or treatment.² We found that, also in a specific, rather homogeneous group, the impact and meaning of chemosensory changes greatly vary. The experiences of chemosensory changes found in the current study, generally support existing literature on this topic with respect to altered food preferences and changed social aspects of eating. More specific for this particular group of patients with OGC are the preferences and practical constraints regarding eating food that would easily pass the oesophagus.

Food preferences were influenced by chemosensory changes during chemotherapy in several ways. These are in concordance with previous studies where a need for both more and less intense flavours and food aversions to cooking aromas were described.^{1, 2, 21} Typical for oxaliplatin treatment was the increased sensitivity to cold food, which resulted in a preference for warm food.²²

Although it seems an obvious observation that the obstruction of the oesophagus has consequences for food preferences and dietary patterns, there is actually little literature available on the experiences of this phenomenon in this patient group. Studies in OGC patients have mainly focussed on experiences after surgery rather than during or after chemotherapy.^{23, 24} To our knowledge, this is the first study specifically focussing on the experience with regard to eating in this patient group.

Changes in social aspects of eating were reported as burdensome and entailed several aspects of social functioning. Similar to previous studies, mealtime acquired a new meaning by becoming a forced way to ingest nutrients, rather than an enjoyable part of the day.^{22, 23, 25, 26} Social consequences, like the inability to eat with family and friends and altered family roles, have been reported in previous studies among patients with various cancer sites undergoing chemotherapy.^{11, 22} However, changed social functioning may not

be solely due to chemosensory changes, as these social consequences have been reported in studies in oesophageal cancer patients that do not undergo chemotherapy, as well.^{23, 25}

Oesophagogastric cancer patients are susceptible to weight loss, which is associated with a reduced quality of life and a poor prognosis of the disease.¹⁷ The current study shows that OGC patients undergoing chemotherapy both have problems regarding chemosensory changes and difficulties with obstruction of the oesophagus, hence making nutritional advice more complex. Nutritional advice for this patient group therefore should be multidimensional and go beyond aiming for sufficient protein and energy intake, mainly taking into account the changed food preferences and practical constraints, and should aim towards enhancing the enjoyment of food. Furthermore, care strategies should not only be directed at the patient but should also take into account the role that the partner and family play in a household. Finally, health-care professionals should explicitly ask for chemosensory changes, as patients do not always mention these side effects spontaneously. Nevertheless, the results of our study show that these changes can have a substantial impact on daily life and therefore should not be disregarded in hospital practice.

Applying template analysis as a method to explore the experiences of patients with OGC resulted in a rich description of the impact of chemosensory changes and altered food preferences on the daily life of patients and their relatives. The inclusion of a small, homogenous sample of study participants allowed for in-depth exploration of the lived experience of having OGC and suffering from chemosensory changes. We did not specifically select patients with previously reported taste or smell alterations, which has been done mostly in previous qualitative studies investigating chemosensory changes during chemotherapy,^{11, 22, 27} but instead included also patients experiencing no or little changes in their taste and smell perception, to gain insight into a broad range of experiences. However, including only patients from the Netherlands, where standard cytotoxic treatment for oesophagogastric cancer patients only includes oxaliplatin and capecitabine, may limit the transferability of our results to other treatment regimens, contexts or countries. In other cultures, pre-existing food preferences may be different from those in the Netherlands, including the addition of other spices or the use of other ways to prepare food. Moreover, food-related behaviours and the social rituals around sharing food together may differ across cultures, resulting in different practical or social consequences of both the anatomical changes related to tumour growth and the

chemosensory changes following palliative chemotherapy. Future research thus should include patients from different cultural backgrounds in different contexts.

Conclusion

The present study shows that there was a large variation in the impact of chemosensory and food-related changes in OGC patients. These changes had a substantial impact on food preferences and had various practical and social consequences in the daily life of patients and their relatives. Specific nutritional care for these patients should be directed towards higher food enjoyment and take the specific complaints due to the location of the tumour into account.

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Chapter 7

Chemosensory determinants of quality of life after systemic therapy for breast cancer: the importance of trastuzumab

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Submitted

Abstract

Background: Altered taste and smell function are frequently observed during chemotherapy. However, little is known about the relationship between taste and smell changes and quality of life (QoL), especially after chemotherapy has ended.

Aim: To assess self-reported taste and smell perception after chemotherapy in breast cancer patients, compared to women without cancer, and to determine the association between taste and smell perception and QoL after the end of chemotherapy.

Methods: We included 135 newly diagnosed breast cancer patients that completed chemotherapy and 114 women without cancer. Questionnaires on taste, smell and QoL were completed shortly after and 6 months after chemotherapy (patients) or at two moments that were 6 months apart (controls).

Results: Self-reported taste and smell perception were significantly lower in patients shortly after chemotherapy compared to the control group. Most patients recovered 6 months after chemotherapy, but patients treated with trastuzumab reported a lower taste and smell perception compared to patients not receiving trastuzumab. A lower self-reported taste and smell was significantly associated with a worse QoL, social, emotional and role functioning shortly after chemotherapy. Six months after chemotherapy, taste and smell were still significantly associated with QoL, social and role functioning, but only in patients treated with trastuzumab.

Conclusions: Most taste and smell alterations recover within six months after the end of chemotherapy for breast cancer, except for patients receiving trastuzumab. These results highlight the importance of monitoring taste and smell alterations during treatment with chemotherapy and trastuzumab, as they have an impact on quality of life.

Introduction

Taste and smell alterations are amongst the most distressing side effects of chemotherapy treatment in cancer patients and may seriously impact everyday life of cancer patients.¹ Qualitative studies show that taste and smell alterations during chemotherapy have an impact on patient's lives in terms of household roles (e.g. partners that take over grocery shopping and cooking) and social interactions (e.g. not eating out or inviting friends for dinner).^{2,3} Quantitative studies have also shown that cancer patients with an altered taste and/or smell during chemotherapy, have a lower quality of life.⁴⁻⁷

Previous research has shown that taste and smell alterations are largely transient, and usually recover within the first three months after the end of chemotherapy.⁸⁻¹⁰ However, some studies suggest that taste and smell may be distorted well beyond the end of chemotherapy.¹¹⁻¹³ To date, there is not much known about clinical factors that influence taste and smell perception after the end of chemotherapy, but the subsequent treatment that patients receive, may be of potential interest. E.g breast cancer patients treated with neo-adjuvant chemotherapy may still undergo surgery and/or radiotherapy, about 60-75% of patients receive hormonal therapy¹⁴ and approximately 30% of patients receives trastuzumab.^{15,16} It is currently unknown however if, and to what extent, these factors relate to taste and smell perception, and whether it is related to quality of life after the end of chemotherapy.

To understand more about the nature and impact of taste and smell changes after chemotherapy treatment, the aim of the current study was twofold. First, we assessed reported taste and smell changes shortly after, and 6 months after chemotherapy in breast cancer patients compared to a group of women without breast cancer. Second, we aimed to determine the association between taste and smell perception and quality of life (QoL) shortly after and 6 months after chemotherapy.

Materials and methods

Participants

This study is part of the COBRA-study¹⁷, an observational multi-center study among breast cancer patients during chemotherapy and a control group of women without cancer of similar age. Women with newly diagnosed, stage I-IIIb, operable breast cancer, who were scheduled for 2nd or 3rd generation chemotherapy were compared to women without cancer of similar age. Eligible participants were at least 18 years old and able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, pregnancy or the intention to get pregnant during the study period, dementia or other mental conditions that made it impossible to comply with study procedures. The protocol was approved by the Medical Ethical Committee of Wageningen University (ABR NL40666.081.12). All participants provided written informed consent before enrolment.

Study design

We assessed self-reported taste and smell perception and quality of life at two moments. For breast cancer patients this was within one month after the last chemotherapy cycle (T1) and approximately 6 months after the last chemotherapy cycle (T2). In the control group this was at two moments that were approximately 6 months apart. In total 135 patients and 114 controls were included in the analyses. Patients that did not fill in the questionnaires within one month after the last chemotherapy cycle (T1), or did not fill in the questionnaires within 5-8 months after the last chemotherapy cycle (T2) were excluded from the analyses (n=7). On average, the time between the first and second measurement was 207±18 days (patients) and 194±17 days (controls).

Measurements

Self-reported taste and smell

The Appetite, Hunger feelings and Sensory Perception (AHSP) questionnaire was used to assess self-judgement of taste and smell perception.¹⁸ The questionnaire consists of questions answered on a 5 point Likert scale. For this study, we used the taste (8 items, score range 8-40) and smell (6 items, range 6-30) scale. A higher score corresponds to a more positive judgement about current taste and smell perception.

To assess the prevalence of taste and smell changes in patients, two questions were added from the 16-item taste and smell questionnaire.¹⁹ 1. "Have you noticed any changes in your sense of taste compared to before chemotherapy?" and 2. "Have you noticed any changes in your sense of smell compared to before chemotherapy?" Answer possibilities: no, it is the same; yes, it is better; yes, it is worse.

Quality of life

The EORTC QLQ-C30 was used to assess health related quality of life (QoL).²⁰ For this study we used the scales for global QoL, and the functional scales for social, role and emotional functioning. Questions were asked on a 4-point Likert scale, and were transformed to scales from 0-100 according to the questionnaire guidelines.²¹ For all QoL scales, a higher score corresponds to a better QoL or level of functioning.

Demographic and clinical characteristics

All participants filled out a general questionnaire for demographic information which included age, smoking status (current, former, never), educational level (low, middle, high) and living situation (alone, with partner and/or children). Information on the stage of disease at diagnosis (stage I, II or III) and treatment (neo- or adjuvant chemotherapy, type of chemotherapy, hormone treatment yes/no, trastuzumab yes/no) was obtained from the patients' medical records. Chemotherapy regimens were categorized to combined and sequential regimes. Combined regimes included schemes where all different components were administered together during all cycles, such as TAC (6x docetaxel, doxorubicine and cyclofosfamide every 3 weeks). Sequential regimes included schemes where different components were administered in different cycles such as ACP (ACP: 4 x adriamycine and cyclofosfamide every 3 weeks followed by 12 x paclitaxel weekly).

Data analysis

Demographic, clinical variables and prevalence of taste and smell changes are presented as mean \pm SD or n (%). We used a linear mixed model analysis to assess differences in the AHSP subscales for taste and smell and quality of life outcomes over time and between groups. Time (T1 and T2) and group (patient and controls) were included in the model as fixed factors and participants as random factor.

Analysis of covariance was used to assess associations between demographic, clinical variables (stage of disease, adjuvant/neo-adjuvant treatment, type of chemotherapy,

hormone treatment and trastuzumab) and taste and smell, on both time points separately. Analysis of covariance was also used to assess the association between taste, smell and quality of life. Relevant covariates were included in the models based on literature and change of the regression coefficient. Variables changing the regression coefficient $\geq 10\%$ in the adjusted model compared to the crude model were included in the final model. Final models were adjusted for age. Possible effect modifiers were assessed by including interactions in the model. Variables assessed as effect modifiers were: adjuvant/neo-adjuvant treatment, type of chemotherapy (combined vs sequential), hormone treatment (yes vs no) and trastuzumab (yes vs no). Statistical analyses were performed using SPSS statistics version 23 (IBM Corporation, Armonk, New York, USA). A p-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the patient and the control group are shown in table 7.1. The breast cancer patients had a slightly lower age and higher BMI than the women without breast cancer. Furthermore, the patient group had more current smokers and fewer former smokers than the control group. The groups were similar in education level and living situation. Most patients had a stage II tumor and were treated with adjuvant chemotherapy.

Taste and smell perception over time

At T1 (shortly after chemotherapy), 65% of patients reported their taste perception as worse compared to before chemotherapy, 3% reported a better taste perception and 32% reported their taste perception as unchanged. Six months later (T2), 16% of patients reported a worse taste perception, 8% a better taste perception and 76% reported their taste to be the same as before chemotherapy.

For smell at T1, 19% of patients reported their smell perception to be worse, 16% reported a better smell perception and 65% reported their smell to be the same as before chemotherapy. Six months later (T2), only 3% reported a worse smell perception, 12% better, and 85% reported their smell perception to be the same as before chemotherapy.

Table 7.1. Demographic and clinical characteristics of the participants in the study presented as mean (SD) or n (%).

	Control n= 114	Patients n= 135
Demographic characteristics		
Age (years)	55.4 (10.2)	52.5 (9.1)
BMI (kg/m ²)	24.9 (3.5)	26.0 (4.0)
Smoking*		
Current	10 (9)	21 (15)
Former	62 (54)	56 (42)
Never	42 (37)	57 (43)
Education*		
Lower	9 (8)	12 (9)
Middle	32 (28)	42 (31)
Higher	73 (64)	80 (60)
Living situation*		
Alone	15 (13)	16 (12)
With partner and/or children	99 (87)	118 (88)
Clinical characteristics		
Adjuvant chemotherapy		83 (61)
Neo-adjuvant chemotherapy		52 (39)
Stage		
I		36 (27)
II		79 (59)
III		19 (14)
Chemotherapy		
Combined treatment		62 (46)
Split treatment		73 (54)
Hormone treatment*		
Yes		104 (78)
No		30 (22)
Trastuzumab		
Yes		31 (23)
No		104 (77)

* 1 missing for patient group

Both shortly after chemotherapy (T1) and half a year after chemotherapy (T2), breast cancer patients reported a lower taste perception compared to the control group (figure 7.1a). However, in the patient group, self-reported taste perception improved over time, while the control group remained stable. Results were similar for self-reported smell perception (figure 7.1b), although there was no significant difference between patient and control group for smell perception at T2.

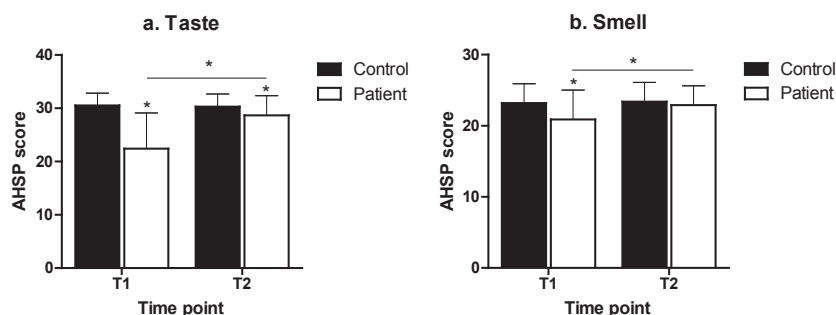


Figure 7.1. Taste and smell scores (mean ± SD) of the AHSP questionnaire over time for the patient and control group. T1 represents the first measurement (control) and shortly after chemotherapy (patients), T2 represents 6 months after the first measurement (control) or after chemotherapy (patients). * indicates a significant difference at $p < 0.05$.

Determinants of self-reported taste and smell in breast cancer patients

Both shortly after (T1) and half a year after chemotherapy (T2), the following parameters were not significantly associated with self-reported taste or smell; age, BMI, smoking status, living situation, education level, stage of disease, receiving adjuvant or neo-adjuvant treatment, type of chemotherapy and receiving hormone treatment. Only trastuzumab showed an association with self-reported taste and smell half a year after chemotherapy (T2), but not shortly after chemotherapy (T1). At T2, breast cancer patients that received trastuzumab scored 2.6 points lower on the taste scale ($\beta = -2.6$, 95%CI: -4.17 ; -1.08, $p = 0.001$) and 2.0 points lower on the smell scale ($\beta = -2.0$, 95%CI: -3.12 ; -0.87, $p = 0.001$) compared to patients that were not treated with trastuzumab.

Quality of Life over time

Global QoL was significantly lower in the patient group compared to the control group at both time points (figure 7.2a), but significantly improved half a year after chemotherapy. These patterns between groups and over time were similar for role functioning and social functioning (figure 7.2b-c). For emotional functioning, patients scored lower compared to the control group at T1 and T2, and this did not improve half a year after chemotherapy (figure 7.2d).

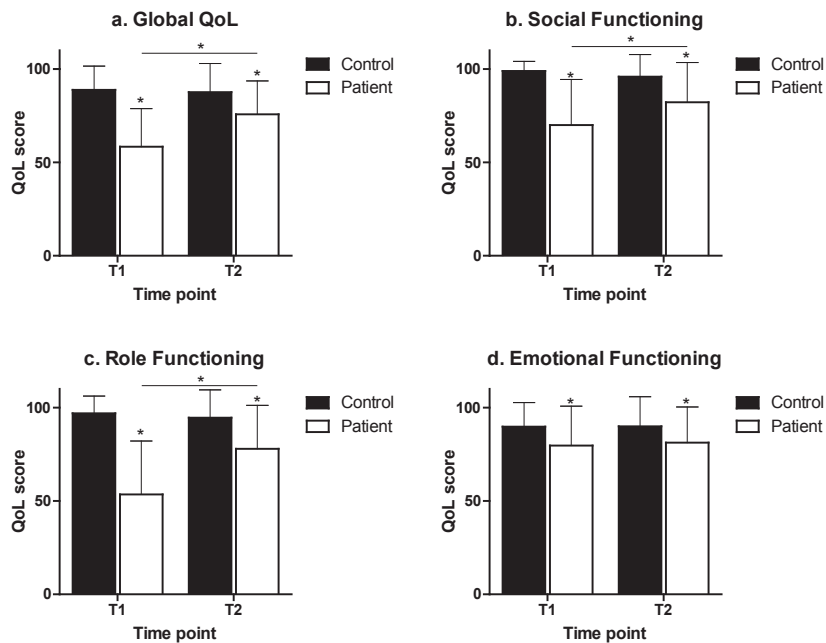


Figure 7.2. Global Quality of Life (a) and Function scales (b. social, c. role and d. emotional functioning) of the EORTC-QLQ-C30 (mean \pm SD) over time for the patient and control group. T1 represents the first measurement (control) and shortly after chemotherapy (patients), T2 represents 6 months after the first measurement (control) or after chemotherapy (patients). * indicates a significant difference at $p < 0.05$.

Associations between taste, smell and quality of life shortly and half a year after chemotherapy

In patients, shortly after chemotherapy, a better reported taste and smell was significantly associated with better global quality of life, role functioning, social functioning and emotional functioning (table 7.2).

Table 7.2. The association between taste, smell and quality of life outcomes in breast cancer patients shortly after chemotherapy (T1), adjusted for age. β represents the difference in QoL outcome per 1 unit higher score within the AHSP category.

Taste	β	SE	p-value	95% CI
Global QoL	0.99	0.26	<0.001	0.47 ; 1.51
Role functioning	1.74	0.36	<0.001	1.03 ; 2.44
Social functioning	1.14	0.32	<0.001	0.51 ; 1.77
Emotional functioning	0.79	0.28	<0.005	0.24 ; 1.35
Smell	β	SE	p-value	95% CI
Global QoL	1.09	0.44	0.02	0.21 ; 1.96
Role functioning	1.50	0.62	0.02	0.27 ; 2.74
Social functioning	1.69	0.52	<0.01	0.65 ; 2.72
Emotional functioning	1.23	0.46	<0.01	0.32 ; 2.14

The association between taste, smell and global quality of life, role functioning and social functioning, was different for patients receiving trastuzumab compared to patients not receiving trastuzumab (table 7.3). Only in patients that received trastuzumab, both a better reported taste and smell perception were significantly associated with a better global QoL, role functioning and social functioning.

Self-reported taste and smell perception were not significantly associated with emotional functioning half a year after chemotherapy (Taste: $\beta=0.82$, 95%CI: -0.15 ; 1.78, $p=0.10$, Smell: $\beta=0.91$, 95%CI: -0.42 ; 2.24, $p=0.18$).

Table 7.3. The association between taste, smell and quality of life outcomes in breast cancer patients half a year after chemotherapy, (T2) stratified for trastuzumab, adjusted for age. β represent the difference in QoL outcome per 1 unit higher score within the AHSP category.

Taste	Patients receiving trastuzumab				Patients not receiving trastuzumab			
	β	SE	p-value	95% CI	β	SE	p-value	95% CI
Global QoL	2.52	0.77	<0.01	0.92 ; 4.12	0.76	0.53	0.15	-0.29 ; 1.81
Role functioning	3.01	0.88	<0.01	1.19 ; 4.82	0.24	0.77	0.76	-1.29 ; 1.76
Social functioning	3.47	0.93	<0.001	1.56 ; 5.38	0.78	0.62	0.21	-0.46 ; 2.01
Smell	β	SE	p-value	95% CI	β	SE	p-value	95% CI
	β	SE	p-value	95% CI	β	SE	p-value	95% CI
Global QoL	3.11	1.16	0.013	0.72 ; 5.49	0.37	0.72	0.60	-1.06 ; 1.81
Role functioning	3.05	1.39	0.04	0.18 ; 5.92	-0.29	1.04	0.78	-2.36 ; 1.77
Social functioning	4.18	1.42	<0.01	1.25 ; 7.10	0.52	0.84	0.54	-1.16 ; 2.20

Discussion

In this study we aimed to assess reported taste and smell changes shortly after, and 6 months after chemotherapy in breast cancer patients compared to a group of women without breast cancer. Furthermore, we aimed to determine the association between taste and smell perception and quality of life (QoL) shortly after, and 6 months after chemotherapy.

In line with previous studies in breast cancer patients, we show that taste and smell perception are altered shortly after the end of chemotherapy, but mostly recover within six months after the end of treatment.^{8,9} The prevalence of taste (68%) and smell (35%) alterations shortly after chemotherapy are also within the range described in previous literature for taste (45-84%) and smell (5-60%).²² Interestingly, half a year after chemotherapy self-reported taste and smell perception were lower in patients receiving trastuzumab compared to patients not treated with trastuzumab. This finding is especially relevant, because half a year after chemotherapy, these patients also had a lower quality of life, social functioning and role functioning.

We found that a lower taste and smell perception was associated with a lower quality of life, which is in line with previous studies in cancer patients during chemotherapy.^{4,5,23} In addition, role and social functioning were affected by a worsened taste and smell perception. In daily life, the sense of taste and smell play an important role in eating, but also for social communication, personal hygiene and detection of environmental hazards.²⁴ For instance, women with good smell function tend to have more active social lives than those with diminished smell function.²⁵ In addition, problems with cooking are commonly reported in patients with olfactory dysfunction, as they have difficulties with smelling whether food is spoiled.^{24,26} Furthermore, in cancer patients, role functioning may be affected because a partner needs to take over cooking tasks, because cooking smells are offensive or nauseating.^{2,23}

To our knowledge, this is the first study that assessed taste or smell changes as a primary outcome measure in combination with trastuzumab as a factor. Patients treated with trastuzumab had a lower taste and smell perception half a year after chemotherapy compared to patients not treated with trastuzumab. However, more research is needed to confirm our findings. Furthermore, there are several factors that require further investigation in the future. Firstly, it is necessary to assess the nature and prevalence of taste and smell alterations over the whole treatment trajectory of trastuzumab. For

chemotherapy, alterations are the worst early in the chemotherapy cycle, and generally recover after chemotherapy has ended. Therefore, assessments of taste and smell perception are necessary before, at several moments during, and after the end of treatment with trastuzumab. This will give insight as to whether these alterations might diminish or worsen over the trajectory, and whether these alterations recover after the end of treatment with trastuzumab. Secondly, the possible mechanism how trastuzumab can impact taste and smell perception needs investigation. For chemotherapy, the general hypothesis is that it acts on rapidly dividing cells, and therapy may therefore also impact the taste and smell receptor cells that have a turnover rate of 1 week to a month.^{27, 28} Objective measurements of taste and smell function could help to elucidate whether these alterations are due to actual dysfunction of the sense of taste and/or smell. However, the mechanism of trastuzumab on chemosensory perception is yet unclear. Thirdly, research has shown that a lower taste perception during chemotherapy in breast cancer patients is associated with a lower energy intake, specifically for protein and fat intake.¹⁷ Potentially, patients that are treated with trastuzumab and report a lower taste perception, have a lower energy intake as well, which might have an impact on their nutritional status.

Unfortunately, there are currently no effective interventions for taste and smell alterations in cancer patients. Still, it is important to monitor these alterations over the treatment trajectory in breast cancer patients, in particular given the impact on quality of life and the potential nutritional consequences. After chemotherapy has ended, specifically patients that are treated with trastuzumab are a group of interest that warrant the attention of clinicians.

In conclusion, this study shows that most taste and smell alterations recover after chemotherapy for breast cancer, but importantly, not for patients that receive trastuzumab. These results highlight the importance of monitoring taste and smell alterations during treatment with chemotherapy and trastuzumab, as they have an impact on quality of life.

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Chapter 8

General discussion



General discussion

Where did we start?

The starting point of this thesis was the observation that breast cancer patients seem to gain weight during and after chemotherapy^{1,2}, which is characterized by a change in body composition, with an increase in fat mass, and a decrease, or no change in lean mass.^{3,4} Potentially, taste and smell changes during chemotherapy could play a role in this change in weight and body composition in breast cancer patients, by changing food preferences and food intake (figure 8.1).

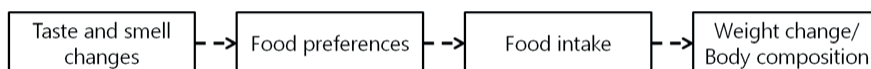


Figure 8.1 Hypothetical chain of events for how taste and smell changes could contribute to weight change and body composition.

Furthermore, changed taste and smell perception may not only impact patients through changed food preferences and food intake, but can also play an important role in everyday functioning and quality of life. This thesis assessed the influence of chemosensory changes on food preferences, food intake and quality of life in breast cancer patients. To get insight in whether chemosensory changes and their consequences during chemotherapy are similar or different in specific cancer populations, this thesis also focussed on advanced oesophagogastric cancer patients, as these patients probably have a poorer nutritional status upon start with chemotherapy compared to breast cancer patients.

The following research questions were addressed in this thesis:

1. How can we systematically measure food preferences in terms of macronutrients and tastes?
2. How do (objective and subjective) taste and smell perception change over the course of chemotherapy?
3. How do food preferences and food intake change over the course of chemotherapy, and are they related to taste and smell perception?
4. What are the consequences of chemosensory changes during chemotherapy for daily life and quality of life?

This final chapter starts with answers to these research questions based on the work presented in this thesis, after which methodological considerations are discussed. Subsequently the potential role for chemosensory changes in weight change during chemotherapy will be discussed, as well as the impact and relevance of these findings for clinical practice, and suggestions for future research. This discussion will end with an overall conclusion.

How can we systematically measure food preferences in terms of macronutrients and tastes?

In **chapter 2**, the development and validation of the Macronutrient and Taste Preference Ranking Task (MTPRT) was described.⁵ The study showed that the MTPRT can detect shifts in preferences for both tastes (sweet, savoury) and macronutrients (high-fat, high-carbohydrate, high-protein and low-energy) upon sensory specific satiety induced by a standardized sweet or savoury meal. Furthermore, these results were reproducible under similar conditions, demonstrating that the MTPRT is a reliable method to measure changes in preferences for macronutrients and tastes.

How do (objective and subjective) taste and smell perception change over the course of chemotherapy?

We assessed changes in taste and smell breast cancer patients (**chapter 4**) and oesophagogastric cancer patients (**chapter 3**) undergoing chemotherapy. In both patient groups, objectively measured taste function was decreased during chemotherapy. Results in breast cancer patients also indicated that this deteriorated taste function was recovered half a year after chemotherapy. For objectively measured olfactory function, there was a small decrease during chemotherapy in breast cancer patients, but no change in oesophagogastric cancer patients.

Considering subjective measures of taste and smell perception, breast cancer patients reported a worsened taste and smell perception during (**chapter 4, 5**) and shortly after chemotherapy (**chapter 4, 7**), which mostly recovered half a year after chemotherapy (**chapter 4, 7**). However, breast cancer patients receiving trastuzumab, reported a poorer taste and smell perception half a year after the end of chemotherapy. In oesophagogastric cancer patients, the quantitative study (**chapter 3**) showed no changes in subjective taste and smell perception, while the qualitative study (**chapter 6**) did show

that oesophagogastric cancer patients experience taste and smell changes during chemotherapy.

Overall, the studies in this thesis show that chemotherapy induces a transient decrease in taste and smell perception, which is most pronounced for taste. However, both in breast and oesophagogastric cancer patients, subjective taste measures were not associated with objective taste measures, indicating that these measures encompass different aspects of taste perception.

How do food preferences and food intake change over the course of chemotherapy, and are they related to taste and smell perception?

Breast cancer patients liked high-protein, high-fat, sweet and savoury products less during chemotherapy, as measured with the MTPRT (**chapter 4**). In contrast, the relative preferences (ranking scores) for macronutrients did not shift during chemotherapy. Relative preference for savoury products over sweet products was higher during chemotherapy in breast cancer patients, but these results could not completely be attributed to chemotherapy, as the control group also shifted their taste preferences similarly over the study period. The dietary intake during chemotherapy (**chapter 5**) was in line with the changed macronutrient preferences (**chapter 4**), as breast cancer patients had a lower total energy intake, expressed in a lower protein, fat and alcohol intake during chemotherapy compared to a control group of women without cancer.

In oesophagogastric cancer patients, the quantitative study did not show changes in food preferences as measured with the MTPRT. However, in the qualitative study patients do report to have altered preferences, for instance to prefer more or less intense flavours, specific aversions, avoiding cold food and to prefer food that could easily pass the oesophagus.

In both breast and oesophagogastric cancer patients, objective measures of taste and smell were not correlated with food preferences, but self-reported measures were. A lower self-reported taste perception was associated with a lower preference or liking for high-protein (both patient groups), low-energy, savoury and sweet products (only breast cancer patients). Furthermore, a lower self-reported taste perception was associated with a lower dietary intake in breast cancer patients (**chapter 5**).

Overall, the results show that changed food preferences during chemotherapy are macronutrient specific but not taste specific in breast cancer patients, but do not change

for macronutrient or tastes in oesophagogastric cancer patients. Only subjective measures of taste and smell were associated with food preferences and food intake.

What are the consequences of chemosensory changes during chemotherapy for daily life and quality of life?

In both oesophagogastric cancer patients (**chapter 6**) and breast cancer patients (**chapter 7**), we showed that taste and smell changes had a negative impact on social and role functioning in daily life and quality of life. In the qualitative study oesophagogastric cancer patients described a substantial impact of chemosensory and food-related changes on daily life (by changing daily routines), social life (eating being less sociable) and roles in the household (changing roles in cooking and grocery shopping). The quantitative study in breast cancer patients showed similar results, with a worse taste and smell perception being related to a worse global quality of life, role, social and emotional functioning shortly after chemotherapy. In patients treated with trastuzumab, a worse taste and smell perception was still associated with quality of life, social and role functioning half a year after chemotherapy had ended.

Overall, our studies showed that in both patient groups, taste and smell changes have a significant impact on quality of life and daily life through changed social and role functioning.

Methodological considerations

Objective versus subjective taste and smell perception

In this thesis, chemosensory perception was assessed both objectively and subjectively, in breast cancer patients and oesophagogastric cancer patients. Although in both patient groups objective taste function declined, this did not correlate with subjective experience of taste perception, thereby confirming that humans are not well able to rate their actual taste or smell function.⁶⁻⁸ However, the factors that influence subjective taste and smell perception in cancer patients are not quite clear. Subjective taste perception is likely to be related to overall flavour perception, which is influenced by olfactory, gustatory, and somatosensory signals.⁹ Furthermore, it has also been suggested that reported taste changes are more hedonic in nature, meaning one refers to food not tasting good anymore, which is interpreted as a changed taste perception.^{10, 11} However, what makes food not taste good anymore should be investigated in further research. It has been reported in qualitative studies that cancer patients undergoing chemotherapy report to

be more sensitive to specific odours, or to prefer more or less intense flavours.^{12, 13} This could be further investigated by studying both supra-threshold tastes and odours with varying intensities, and assessing these on both perceived intensity and liking. This will give insight in whether patients perceive tastes and/or smells as more or less intense, and whether that is related to preferences of these tastes and smells. For odours, stimuli should be chosen to represent different food categories like in the MTPRT, based on macronutrients and tastes, to assess whether the decreased liking we found in breast cancer patients is related to the olfactory perception of these food categories.

Food preferences

To assess food preferences for macronutrients and tastes, we developed the MTPRT, which was described in chapter 2. It was shown that this is a reliable tool when using it in an experimental setting by inducing sensory specific satiety. In our studies in cancer patients, we used the MTPRT in an observational setting, which clearly has consequences for standardization of the testing procedures within and between patients. Ideally, all test sessions for all participants would have been at the same time of day, but in practice it was only possible to schedule sessions generally at the same part of day (morning or afternoon). The rankings of the MTPRT might be more susceptible for daily fluctuations, while rating of liking might be less prone to this. This is supported by a series of studies of Kramer et al¹⁴, who showed that the appropriateness of foods in an eating context did not affect liking ratings, but they concluded that including choice in their studies would have reflected appropriateness. Possibly, because of the variety in test contexts in the observational studies described in this thesis (e.g. different times of day), it was not possible to detect systematic shifts in macronutrient or taste preferences in the rankings of the MTPRT. Future studies should investigate how factors like time of day, meal context, hunger feelings and personal characteristics in a large group of healthy participants are of influence on the MTPRT liking and ranking outcomes to substantiate this hypothesis.

Qualitative versus quantitative research

In chapter 6 we used a qualitative approach to explore the experiences of chemosensory and food-related changes in oesophagogastric cancer patients undergoing chemotherapy, and its impact on daily life. Qualitative research allows to gain insight in the variety of experiences that patients have, but is not designed to quantify the frequency of observed experiences. By using qualitative research, is it possible to grasp

experiences and nuances that quantitative measures might not capture.¹⁵ The qualitative study did show that oesophagogastric cancer patients experienced changes in taste, smell and food preferences, while self-reported taste and smell and food preferences did not seem to change in the quantitative study. Possibly, the quantitative methods were not sensitive enough to detect these changes, but it is also possible that some these changes were already experienced before the start of chemotherapy. However, the MTPRT was designed to measure food preferences for macronutrients and tastes, and it is therefore not surprising that the MTPRT did not detect preferences for more or less intense flavours and foods that could easily pass the oesophagus.

A potential role for chemosensory perception, food preferences and food intake in weight change during chemotherapy?

It was hypothesized that chemosensory changes could have a role in weight gain and changing body composition of breast cancer patients, through a shift in food preferences from savoury, protein-rich products towards a preference for sweet, carbohydrate and fat-rich products. This could subsequently influence dietary intake in terms of lower protein intake, higher carbohydrate and fat intake and thereby potentially influence body weight and body composition. However, our findings could not confirm this proposed sequence of events in breast cancer patients (as summarized in figure 8.2).

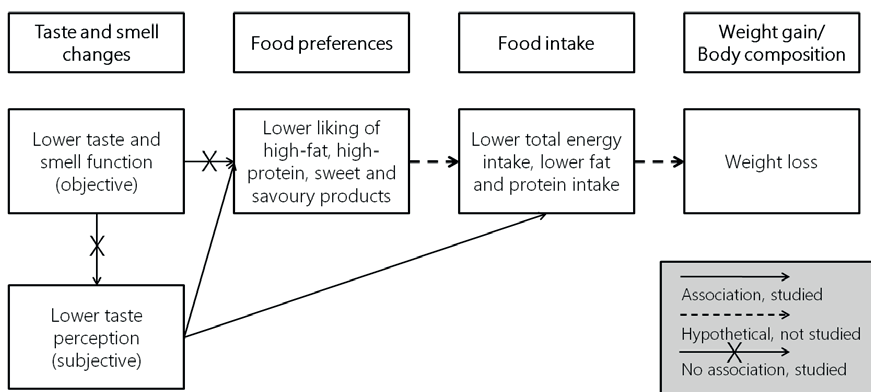


Figure 8.2. Findings and (hypothetical) associations based on results in breast cancer patients in this thesis

The results of the breast cancer studies in this thesis suggest that if patients experience taste changes, it is more likely that they like high-fat and high-protein products less, resulting in a lower total energy, fat and protein intake. Thus, the results do not suggest a role for chemosensory changes and diet in weight gain, but more likely in weight loss. That is, when other factors that affect energy balance, such as physical activity, would stay the same, but that is probably not the case. Physical activity has been found to be lower during chemotherapy in breast cancer.^{3, 16} However, there is currently an increasing focus on staying physically active during treatment, as it has been shown to be beneficial for physical functioning, fatigue and side effects like nausea, vomiting and pain.^{17, 18} Therefore it is essential to study factors, besides nutritional intake, that could have an impact on weight change during chemotherapy. A recent meta-analysis concluded that weight gain in breast cancer patients undergoing chemotherapy actually has decreased over time¹⁹; weight gain was most pronounced in patients treated with CMF regimes, which is seldom used in breast cancer patients currently.²⁰ Part of this thesis was performed within the COBRA-study, which currently investigates to what extent weight gain and changes in body composition during chemotherapy are still occurring with current chemotherapeutic regimes in the Netherlands. Our results in breast cancer patients may show, that patients who experience no, or mild chemosensory changes, might be the patients who stay stable in weight, or gain weight, as suggested by a recent qualitative study.²¹ However, this association has shown mixed results in previous studies, by both showing an association between taste and smell changes and weight loss¹³, but also no associations.^{22, 23} Therefore this should be further investigated in future analyses in the COBRA-study, in combination with other factors that may have an influence on weight change.

The results in oesophagogastric cancer patients were in line with findings in breast cancer patients, as worse self-reported taste perception was associated with lower preference for high-protein products. However, the oesophagogastric cancer patients did not have changed subjective taste and or smell perception, or changed food preferences during chemotherapy as measured chapter 3. This suggest that the relation between taste perception and food preferences might not depend on changes during chemotherapy. However, this should be further investigated with studies that also include patients that do not undergo chemotherapy.

Taste and smell changes during chemotherapy: (why) should we care?

As mentioned in the previous section, possibly patients who experience no, or mild chemosensory changes, might be the patients who stay stable in weight, or gain weight. Thus, patients who do experience chemosensory changes, may have a decreased dietary intake and are potentially at risk for malnutrition. This already highlights the importance of attention for these complaints from a nutritional point of view. Moreover, our results show that the impact of chemosensory changes goes beyond nutrition, by having a negative impact on daily life and quality of life. Patients are not always specifically informed about chemosensory changes and their consequences prior to commencement of chemotherapy.²² Being well informed about these alterations may prepare patients about this issue and thereby also lead to less discomfort during treatment.²⁴

It can be beneficial to monitor chemosensory changes during chemotherapy, especially in patients who are at risk for malnutrition, like elderly patients and patients with cancer in the gastrointestinal tract.^{25, 26} Malnutrition in cancer patients can in turn lead to poorer response to chemotherapy, a longer hospital stay and survival.^{26, 27} Monitoring taste and smell changes may help to signal potential malnutrition in an early stage and may help to tailor dietary advice, according to the needs and complaints of cancer patients. Moreover, it is important to explicitly ask for these changes, as we found in oesophagogastric cancer patients that they do not spontaneously talk about these changes. The studies presented in this thesis do not suggest an added value of objective measurement of taste and smell perception over subjective taste and smell perception.

Although currently there are no evidence based interventions or treatments to alleviate chemosensory alterations during treatment, in the future these could be designed. These interventions should aim to enhance enjoyment of eating, which could possibly be designed based on the management strategies that patients report. Furthermore, it is important to involve patients' family and carers in these interventions, as they often take over roles within the households.

Taste and smell changes during chemotherapy: now what?

Several suggestions for future research were made in the chapters of this thesis and throughout this discussion. Here some additional suggestions are discussed.

First, there is need for further insight in the mechanisms of taste and smell alterations during chemotherapy. Mechanistic work in animal models, investigating the influence of

chemotherapy on the gustatory and olfactory epithelium can provide more understanding why and how chemotherapy affects chemosensory function. Recently, it was shown that a specific signalling pathway (Hedgehog signalling pathway) is essential for taste organ maintenance and function.^{28, 29} This same pathway is inhibited by specific chemotherapeutic agents used in basal cell carcinoma³⁰, which explains why patients treated with these agents can experience taste disturbances. In addition, animal studies suggest that cyclophosphamide induces disruption of umami and salt taste and the taste and olfactory epithelium.³¹⁻³³ Moreover, these studies also showed the temporality of taste and which may explain why these changes are cyclic and temporal in humans.^{22, 34} Animal studies thus far are mostly addressing one cytotoxic agent and one specific taste, while often cytotoxic agents are used in combinations. Therefore, similar studies using combinations of agents with several tastes are needed to provide a better insight how it works in humans.

Furthermore, studies in humans can also give more insight in mechanisms of chemosensory changes during chemotherapy in cancer patients. For instance by quantification of taste buds, taking papillae biopsies and assessing taste gene expression.^{35, 36} Neuroimaging techniques could also be used during chemotherapy, to get insight whether gustatory and olfactory processing in the brain is different. Doing this with different types of stimuli that represent different macronutrients and tastes, as proposed under methodological considerations, this can give understanding why certain products are more or less liked upon chemotherapy. Furthermore, the role of salivary flow on chemosensory perception would be of interest to explore. Saliva acts as a carrier to transport taste substances to taste receptors and plays a role in the aroma release in the mouth, and thereby contributes to flavour perception.³⁷ A dry mouth and less saliva are often reported as a side effect of chemotherapy³⁸, which we also observed in chapter 5 in breast cancer patients.³⁹ Potentially, a reduced salivary flow during chemotherapy can result in a decreased taste function.⁴⁰ Finally, it would be of interest to assess the similarities and differences between chemosensory changes and food preferences during chemotherapy with women during pregnancy. Just like cancer patients during chemotherapy, pregnant women frequently report chemosensory changes and food aversions.^{41, 42} Insight in whether the experiences are of similar, or different nature, may give information whether these changes have similar aetiologies.

Conclusions

From this thesis we can conclude that chemotherapy affects mainly taste perception, which is associated with a lower preference for food products and lower dietary intake. Furthermore, chemosensory changes can have a substantial impact on cancer patients' lives, in a practical way by changing daily patterns of eating, but also socially and in roles in the household. Our results indicate that it is not necessarily an actual change in the sense of taste or smell that has an impact on patients, but flavour perception as a whole and possibly a lower enjoyment of food. Worsened chemosensory perception during chemotherapy could lead to a worsened nutritional status, and could thereby negatively impact the response to chemotherapy. Therefore chemosensory perception should be monitored during chemotherapy. Future studies should investigate the mechanisms behind chemosensory changes during chemotherapy in more detail, which factors contribute to the subjective perception of taste and smell, and possible interventions to alleviate chemosensory disturbances during chemotherapy.

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Summary

Dankwoord

About the author

List of publications

**Overview of completed
training activities**

Summary

Taste and smell changes are common side effects during chemotherapy in cancer patient and may have an impact on food preferences, food intake and quality of life. However, these relations have hardly been studied systematically in specific cancer populations. The overall aim of this thesis was to assess how the sense of taste and smell change upon treatment with chemotherapy in breast cancer and oesophagogastric cancer patients, and to investigate their consequences in terms of food preferences, food intake and quality of life.

To measure food preferences for both macronutrients and tastes, the Macronutrient and Taste Preference Ranking Task (MTPRT) was developed. in **chapter 2**, it was shown that by inducing sensory specific satiety for a standardized sweet and savoury meal, it is possible to detect shifts in preferences for both tastes and macronutrients with the MTPRT, and that these results are reproducible.

In **chapter 3** we studied objective and subjective taste and smell perception and food preferences in advanced oesophagogastric cancer patients undergoing palliative chemotherapy. The result showed that only objective taste function decreases during chemotherapy, but other chemosensory measures were unchanged. A lower subjective taste perception was related to a lower preference for high-protein products. Therefore it is important to consider patients' taste perception, when providing dietary advice to OGC patients

Chapter 4 describes a study with similar outcome measures as chapter 3, but in breast cancer patients at several time points during and after chemotherapy, and compared to a healthy control group. The study showed that breast cancer patients like high-protein, high-fat, sweet and savoury products less during chemotherapy, thus showing altered preferences for macronutrients, but not for tastes. Furthermore, results showed a temporary decrease in taste and smell perception during chemotherapy. These findings show that patients should be informed prior to treatment on chemosensory changes, and that these changes should be monitored during treatment due to the consequences for nutritional intake and quality of life

In **chapter 5** we assessed the dietary intake of breast cancer patients before and during chemotherapy compared to a healthy control group, and associations with experienced symptoms during chemotherapy. It was shown that symptoms induced by chemotherapy

were associated with lower total energy, protein and fat intake, which was manifested by a lower intake of specific food groups. Therefore, to ensure an optimal dietary intake during chemotherapy, it is important to monitor nutritional status and symptom burden during chemotherapy in breast cancer patients.

To better understand the impact of chemosensory changes during chemotherapy on daily life, 13 advanced oesophagogastric cancer patients were interviewed (see **chapter 6**). Patients described a substantial impact of chemosensory and food-related changes on daily life (by changing daily routines), social life (eating being less sociable) and roles in the household (changing roles in cooking and grocery shopping).

Finally, in **chapter 7**, we assessed the association between self-reported taste and smell perception and quality of life in breast cancer patients. A worse taste and smell perception was associated with a worse global quality of life, role, social and emotional functioning shortly after chemotherapy. In patients treated with trastuzumab, a worse taste and smell perception was still associated with quality of life, social and role functioning half a year after chemotherapy had ended.

From the studies in this thesis we can conclude that chemotherapy mainly affects the sense of taste. The subjective perception of taste was associated with a lower preference for food products and lower energy intake. This indicates that it is not necessarily an actual change in the sense of taste or smell that has an impact on patients, but flavour perception as a whole and potentially a lower enjoyment of food. Moreover, these perceived changes in taste and smell can have a substantial impact on cancer patients' lives, in a practical way by changing daily patterns of eating, but also socially and in roles in the household. A changed chemosensory perception during chemotherapy may lead to a worsened nutritional status, and could thereby negatively impact the response to chemotherapy. Therefore chemosensory perception should be monitored during chemotherapy. Future studies should further investigate the mechanisms behind chemosensory changes, factors that contribute to subjective taste perception and possible interventions to alleviate chemosensory changes during chemotherapy.

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Doei, tabée en de groeten,

Yfke

About the author



Yfke Carlijn de Vries was born on May 16th, 1990 in Noordbergum, the Netherlands. After completing secondary school at Dockinga College in Dokkum, she moved to Wageningen to start her Bachelor's programme in Nutrition and Health at Wageningen University. After her BSc she enrolled in the MSc specialisation on Sensory Science, a double degree programme of Wageningen University and Copenhagen University. As part of the MSc programme, she studied five months in

Copenhagen to attend several courses. After her MSc thesis on fat-odour detection at Monell Chemical Senses Center and Wageningen University, she completed her internship at the German Institute for Human Nutrition, where she studied the effects of glucose and caffeine on cognitive function. After finishing her MSc, Yfke was appointed as PhD candidate at Wageningen University in the chair group of Sensory Science and Eating Behavior. Her research focussed on the impact of changes in chemosensory perception on food preferences, food intake and quality of life during chemotherapy in cancer patients. Yfke's research was part of the Top Institute Food and Nutrition project on 'Sensory & Liking'. During her PhD, Yfke joined the educational programme of the graduate school VLAG. She attended several (inter)national conferences and courses and was involved in teaching and supervising BSc and MSc students during their thesis projects. Furthermore, Yfke was a member of the organizing committee of the PhD study tour to the East Coast of the USA in 2015. In 2017, she was selected for the 23rd Essentials programme of the European Nutrition Leadership Platform (ENLP).

List of publications

Publications in peer-reviewed journals

Berg, M. M. G. A., Winkels, R. M., Kruif, J. T. C. M., Laarhoven, H. W. M., Visser, M., Vries, J. H. M., **de Vries, Y. C.**, Kampman, E. (2017). Weight change during chemotherapy in breast cancer patients: A meta-analysis. *BMC Cancer*, 17(1). doi: 10.1186/s12885-017-3242-4

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de Vries, Y. C., van den Berg, M. M. G. A., de Vries, J. H. M., Boesveldt, S., de Kruif, J. T. C. M., Buist, N., Haringhuizen, A., Los, M., Sommeijer, D. W., Timmer-Bonte, J. H. N., van Laarhoven, H. W. M., Visser, M., Kampman, E., Winkels, R. M. (2017). Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. *Supportive Care in Cancer*, 25(8), 2581-2591. doi: 10.1007/s00520-017-3668-x

Postma, E. M., **de Vries, Y. C.**, & Boesveldt, S. (2017). Smakelijk eten voor patiënten met kanker: de invloed van reuk- en smaakver storing op eetgedrag. *Nederlands Tijdschrift voor Geneeskunde*, 161(9).

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Submitted publications

de Vries, Y. C., Boesveldt, S., Kampman, E., de Graaf, C., Winkels, R. M., & van Laarhoven, H. W. M. Low reported taste function is associated with low preference for high protein products in advanced oesophagogastric cancer patients undergoing palliative chemotherapy.

de Vries, Y. C., Kelfkens, C. S., Posthuma, E. E., Boesveldt, S., van den Berg, M. M. G. A., de Kruif, J. T. C. M., Haringhuizen, A., Sommeijer, D. W., Buist, N., Grosfeld, S., de Graaf, C., van Laarhoven, H.W.M., Kampman, E., Winkels, R. M. Chemosensory determinants of quality of life after systemic therapy for breast cancer: the importance of trastuzumab.

de Vries, Y. C., Winkels, R. M., van den Berg, M. M. G. A., de Graaf, C., Kelfkens, C. S., de Kruif, J. T. C. M., Göker, E., Sommeijer, D.W., Grosfeld, S., van Laarhoven, H.W.M., Kampman, E., Boesveldt, S. Altered food preferences and chemosensory perception during chemotherapy in breast cancer patients: a longitudinal comparison with healthy controls.

Abstracts and presentations

de Vries, Y. C., Boesveldt, S., Winkels, R. M., van Laarhoven, H. W. M., Kampman, E., & de Graaf, C. (2016). Sensory changes and dietary intake during chemotherapy in breast cancer patients. Top Institute Food and Nutrition Symposium 'Inspiration for Application', Groningen, NL. (oral presentation)

de Vries, Y. C., Boesveldt, S., Winkels, R. M., van Laarhoven, H. W. M., Kampman, E., & de Graaf, C. (2016). Subjective and objective gustatory and olfactory functioning during chemotherapy in breast cancer patients and women without breast cancer. Association for Chemoreception Sciences Annual Meeting, Bonita Springs, USA. (poster presentation)

de Vries, Y. C., Winkels, R. M., Boesveldt, S., van den Berg, M. M. G. A., de Kruif, J. T. C. M., van Laarhoven, H. W. M., Kampman, E., & de Graaf, C. (2016). Taste, smell and food preferences during chemotherapy in breast cancer patients. European Breast Cancer Conference, Amsterdam, NL. (poster presentation)

de Vries, Y. C., Winkels, R. M., Boesveldt, S., Laarhoven, H. W. M., Kampman, E., & de Graaf, C. (2015). Reported changes in sensory perception, appetite and hunger feelings during chemotherapy in breast cancer patients. British Feeding and Drinking Group Annual Meeting, Wageningen, NL. (poster presentation)

de Vries, Y. C., Winkels, R. M., Boesveldt, S., Laarhoven, H. W. M., Kampman, E., & de Graaf, C. (2014). Reported changes in sensory perception, appetite and hunger feelings during chemotherapy in breast cancer patients. Paper presented at the Nutritional Science Days, Deurne, NL. (oral presentation)

Overview of completed training activities

Discipline specific courses and activities		
Course 'Basic oncology'	Ellecom, NL	2013
Course 'NutriScience, a multifaceted approach to nutrition research'	Wageningen, NL	2013
Course 'Smell and Taste, a practical introduction to the physiology and pathophysiology of the chemical senses'	Dresden, DE	2013
Evening symposium oncology days	Ede, NL	2013
Course 'Sensory evaluation and food preferences'	Copenhagen, DK	2014
Masterclass Diet & Cancer	Wageningen, NL	2014
Nutritional Science Days	Deurne, NL	2014
Annual meeting of the British Feeding and Drinking Group	Wageningen, NL	2015
Top Institute Food and Nutrition annual meeting	TIFN	2014 2016
European Breast Cancer Conference	Amsterdam, NL	2016
Annual meeting of the Association for Chemoreception Sciences	Bonita Springs, USA	2016
TIFN symposium 'Inspiration for application'	Groningen, NL	2016
General courses and activities		
VLAG PhD week	Wageningen, NL	2013
Minisymposium 'How to write a world class paper'	Wageningen, NL	2013
TIFN PhD Workshops	Wageningen, NL	2015
Scientific Writing	Wageningen, NL	2016
Mixed Models	Amsterdam, NL	2016
Career perspectives	Wageningen, NL	2016
European Nutrition Leadership Platform - Essentials seminar	Luxembourg, LU	2017
Optional courses and activities		
Preparation of research proposal	Wageningen, NL	2013
Organizing and participating in PhD study tour to the East Coast USA	USA	2015
Staff seminars & Chair group meetings	Wageningen, NL	2013-2017

Colophon

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