Taste alterations and cancer treatment

Sophie van Oort[a], Ellen Kramer[a], Jan-Willem de Groot[b], and Otto Visser[c]

Purpose of review
In this review, we explore issues on the physiology of taste and smell and we critically review recent literature of taste and smell changes and the impact on food preferences throughout the cancer treatment trajectory.

Recent findings
Subjective measurements such as validated questionnaires can be valuable for the clinical setting and many studies describe taste and smell changes by self-report. Because both smell and taste are interrelated, these subjective results are difficult to interpret. Recent studies have looked more specifically at one type of malignancy with a consistent and homogeneous treatment with chemotherapy using objective taste assessment such as electrogustometry, liquid tastants or filter paper strips.

Summary
Taste is a combination of different sensations: smell, texture, temperature and saliva play an important role in determining the overall flavor of food. The mechanism for taste and smell abnormalities in cancer patients treated with systemic therapies remains unclear.

Keywords
alterations, chemotherapy, smell, taste

INTRODUCTION

Since 1989, the 5-year survival after the diagnosis with cancer has increased by 15%, from 47 to 62% [1]. However, a large part of patients will never be cured and frequently palliative systemic therapy is initiated. This means that long-term side effects of chemotherapy and quality of life play an important role in the lives of these patients. There are several known side effects from systemic therapy such as fatigue, nausea, pain, hair loss and depression [2▪,3▪]. Another common, but underexposed side effect of systemic therapy is changes in taste and smell perception, with a prevalence of 45–85% for subjective taste changes and 5–60% for smell changes [4▪▪,5]. Moreover, taste change is mentioned in the top five of the most unpleasant side effects by patients.

Possibly, smell and taste changes can lead to altered food preferences, and can thereby contribute to loss of appetite, reduced food intake and weight changes. Food preferences are often not based on nutrients, such as protein, carbohydrates and fats, but on flavor: 'You eat what you like…' [6▪,7]. A good nutritional status is of great importance for cancer patients receiving chemotherapy, as they need to consume enough energy and nutrients to recover from chemotherapy treatment [6▪]. In addition, malnutrition has been associated with reduced quality of life, reduced treatment tolerance and increased treatment side effects, leading to an increase in mortality and prolonged hospital stay [3▪,7]. In this review, we will critically review recent literature of taste and smell changes and the impact on food preferences throughout the cancer treatment trajectory.

THE PHYSIOLOGY AND PSYCHOLOGY OF TASTE AND SMELL

Taste is actually a combination of different sensations: smell, texture, temperature and saliva play an important role in determining the overall flavor of food.

During mastication, food is mixed with saliva. Saliva dilutes taste substances and transports them to the taste buds on the tongue and soft palate. Five basic tastes have been established: sweet, sour,

[a]Clinical Laboratories, Isala Clinics, [b]Department of Oncology and [c]Department of Hematology, Isala Oncology Center, Zwolle, The Netherlands

Correspondence to Otto Visser, Department of Hematology, Isala Oncology Center, Isala Clinics, PO box 10400, 8000 GK Zwolle, The Netherlands. Tel: +00 31 38 4246040; e-mail: o.visser@isala.nl

Curr Opin Support Palliat Care 2018, 12:162–167
DOI:10.1097/SPC.0000000000000346

KEY POINTS

- Objective measurements of disturbances in smell and taste during and after chemotherapy are complex and difficult; preferably they have to be studied simultaneously.
- Systemic chemotherapy induces taste and odor changes due to cytotoxic damage to the rapidly dividing taste and smell receptor cells, also less quantity or quality of saliva interferes.
- Future research should ideally be performed in homogeneous treated patients groups with objective and validates tests.

bitter, salty and umami (the savouriness of protein-rich foods). Tastes are signaled when they activate taste receptors located on the tongue, soft palate, oropharynx and esophagus [8▪]. These taste receptors are clustered in taste buds. The lingual taste buds are located on structures called papillae. There are three types of papillae: The fungiform papillae are distributed in the anterior two-thirds of the tongue and vary in number from two hundred to several hundred. The foliate papillae are located on the posterior lateral sides of the tongue. The circumvallate papillae are located in the rear of the tongue. The fungiform papillae may contain as many as 20 taste buds each. The circumvallate and foliate papillae can have hundreds of taste buds [9]. The sense of taste comes from the binding of chemicals to the different types of taste receptors. The initial site of signal transduction is at the taste pore. Protein stimulus interaction induces a change in the cell membrane, opening ion channels and allowing stimulus ions to enter directly through the channels [9]. In general, salty and sour tastes are signaled through ion channels, while sweet, bitter and umami are signaled by G-protein-coupled receptors [8▪]. The taste receptors are innervated on the basal side by three separate cranial nerves: the facial nerve (n. VII), the glossopharyngeal nerves (n. XI) and the vagus nerve (n. X). When these nerves are activated, they transmit the taste information to the cerebral cortex for further interpretation [8▪,10].

The sense of smell, or olfaction, is much more complex than the sense of taste. People can distinguish more than one trillion of different smells [11]. Smelling is caused by one or more volatilized chemical compounds, generally at a very low concentration, that humans perceive by the sense of olfaction. There are two different routes by which odors can reach the olfactory epithelium. The ortho-nasal route is already being used before eating, it basically determines whether something is edible or not. Vaporized molecules from the environment enter through the nose and then bind to receptors in the olfactory epithelial mucosa that are located along the superior and middle turbinates and on the upper part of the nasal septum [12,13]. The surface of the epithelium has a mucous layer secreted by submucosal Bowman's glands. Within its secretions are 'odorant binding proteins' that facilitate the transport of odorants to receptors and are thought to remove odorants from the receptor area once activation has occurred [14,15]. Then, an electric signal is passed through the olfactory nerve to the olfactory bulb, part of the limbic system, and to olfactory and other areas in the brain. An odorant stimulus is typically recognized by multiple receptors, and different odorants are recognized by combinations of receptors. The olfactory system does not interpret a single compound, but instead the whole odorous mix, the patterns of neuron signals helping to identify the smell [16]. The second route is the retronasal route. During mastication of food, odor molecules are released. Through the back of the oral cavity, these odor molecules can reach the olfactory epithelium [12].

Interpretation of the taste begins, relating smell and taste to past experiences and in relation to the substance(s) ingested. Olfactory and taste information is further processed and projected through different pathways to the central nervous system, which controls emotions and behavior as well as basic thought processes. When food is eaten, smell, taste and somatosensory (irritation, texture and temperature) signals as well as psychological elements including emotions and behavior determine the overall flavor of food [12,16].

POTENTIAL CAUSES OF TASTE AND SMELL CHANGES IN CANCER PATIENTS

The mechanism for smell and taste abnormalities in cancer patients remains unclear. The most generally accepted hypothesis is that systemic therapy induces taste and odor changes due to cytotoxic damage to the rapidly dividing taste and smell receptor cells. Taste and smell receptor cells have a relatively short life span: 10 days for taste receptor cells and 30 days for smell receptor cells and therefore there is a high turnover of these cells [2▪,3▪,8▪]. Damage to these receptors may lead to a reduced number of taste and smell receptor cells, altered receptor surface or interrupted neural coding. However, there are various other mechanisms of smell and taste alterations including reduced sensitivity to smell and taste, disturbed perception of smell or taste and phantom tastes or smells, such as a metallic taste in the mouth [3▪]. Some chemotherapy is already known to

directly induce taste and odor changes, such as platinum-based chemotherapy, cyclophosphamide, doxorubicin and 5-FU and taste-alterations are a commonly reported side effect of tyrosine kinase inhibitors [5]. Furthermore, cancer patients often receive supportive medications such as antibiotics, which also can affect the taste and smell [3▪]. A dry mouth due to less quantity or quality of the saliva is also often seen as a side effect of chemotherapy and can therefore affect taste perception. Chemotherapy and radiotherapy (especially in the head/neck area) are known to affect salivary glands and saliva production, which can cause oral mucositis. Too little saliva can therefore cause a dry mouth, but it can also disrupt taste perception because saliva plays a major role in the taste transfer [17].

ASSESSMENT OF TASTE AND SMELL CHANGES

Because smell, taste and food intake are intertwined, it is preferable to evaluate it together. Taste and smell changes can be assessed both objectively and subjectively. Objective measurements can give more insight in the physiology and the course of taste and smell changes. Subjective measurements in the form of validated questionnaires can be valuable for a clinical setting. Many studies describe taste and smell changes by self-report. However, it is difficult for a patient to accurately judge their own sense of smell and taste, because both are interrelated [2▪,6▪]. Therefore, it is important to measure both taste and smell function objectively.

Objective taste assessment includes electrogustometry, liquid tastants and filter paper discs/strips. The filter-paper taste strips (Burghart, Wedel, Germany) is frequently chosen and can be used to determine sweet, sour, salty and bitter taste thresholds (THR). 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. Scores for each taste range from 0 to 4. A total taste score can be derived by summing the scores of each taste and ranged from 0 to 16 [18].

Objective methods to assess smell include 'Sniffin Sticks', the Cross-Cultural Smell Identification Test, the University of Pennsylvania Smell Identification Test and the Connecticut Chemosensory Clinical Research Center test [2▪,3▪]. To assess smell function, the 'Sniffin Sticks' (Burghart) are commonly used. The test consists of three parts: a detection THR, discrimination (DIS) test and odor identification test. For the THR, scores range from 1 to 16, for the identification 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 identification. Higher scores indicate a better olfactory function [19,20]. There is a newly developed food preference task available, 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 can be used to examine the influence of different factors on changes in food preferences [21▪▪].

SMELL AND TASTE ALTERATIONS IN CANCER PATIENTS

To date, research has mainly focused on nausea, food aversions and metallic taste caused by chemotherapy. However, less research has been performed on smell and taste changes in patients with cancer and its influence on food preference. A few articles have attempted to map out taste and odor changes in chemotherapy [2▪,3▪,6▪,7,8▪]. So far, both increased and lowered taste THRs have been found for the five basic primary flavors (sweet, sour, salty, bitter and umami) but results are inconsistent. This may be because most studies have been conducted in heterogeneous cancer populations with different malignancies, treatments and stages of the disease. There are also studies that have only looked at *subjective* taste and smell changes in chemotherapy.

SYSTEMIC CHEMOTHERAPY

There are only a few studies that have looked specifically at one type of malignancy with a consistent and homogeneous treatment with chemotherapy. These studies are summarized in Table 1.

De Vries *et al.* [4▪▪] showed that chemotherapy (containing anthracyclines and taxanes) induced both objective and subjective taste changes in women with breast cancer and in patients with advanced esophageal and gastric cancer (treated with capecitabine and oxaliplatin) [22▪▪]. Patients with testicular cancer treated with cisplatin-based chemotherapy also temporarily suffered from subjective taste changes [23▪▪]. In this group, the objective taste remained reasonably stable over time and only showed a higher THR for salt at the end of therapy. In the patients treated for breast cancer the taste changes were temporary, and recovered approximately 6 months after chemotherapy. Changes found in the sense of smell were small and NS. The smell THR value went down slightly and the discriminating and identifying capacity of different smells remained similar [4▪▪]. These nonsignificant results

Table 1. Selected studies

Reference	Type of cancer	Chemotherapy	Measurement		Outcome
			Measurement		
			Subjective	Objective	
De Vries *et al.* [4▪▪]	Breast	Taxanes Anthracyclines/taxanes Platinum containing	Food preference: MTPRT Taste & smell: self-reported taste and smell (VAS scale)	Smell: 'Sniffin Sticks' Taste: taste strips and fruit-flavored beverages	Decreased liking of high-protein, high-fat products Decreased objective and subjective taste and smell function Lower sensitivity for sweet and salt
De Vries *et al.* [22▪▪]	Oesophagogastric	Capecitabine/ oxaliplatin	The AHSP Questionnaire	Smell: 'Sniffin Sticks' Taste: taste strips	Decreased objective taste function Lower preference for high-protein products
Ijpma *et al.* [23▪▪]	Testicular	Cisplatin-based	AHSP questionnaire MTPRT FFQ	Smell: 'Sniffin Sticks' Taste: taste strips Body composition: scale/ DEXA scan	Lower smell threshold Increased salt taste threshold Tansient decrease of subjective taste, appetite and hunger feelings
Boltong *et al.* [24]	Breast	Taxane-based Docetaxel Paclitaxel	Food liking: 9-point hedonic scale Appetite: 10-point scale Dietary intake data according to the USDA	Taste: whole mouth method using solutions (sweet, sour, salty, bitter and umami)	Taste function significantly reduced early in cycle Appetite and liking of sweet food decreased early in the cycle Lower protein and kJ intake and a decline in BMI
Mirlohi *et al.* [25▪]	Brain tumors	Radiation and temozolomide	Taste and Smell Questionnaire	Saliva analysis (proteins, electrolytes and metals)	
Walliczek-Dworschak *et al.* [26▪]	Testicular	BEP (cisplatin, etoposid, bleomycin) or VIP (etoposide, ifosfamide, cisplatin	Smell: 5-point Likert scale Quality of life: BDI test	Smell: 'Sniffin Sticks'	Significant lower smell threshold on day 90 which recovered on day 180
Turcott *et al.* [27▪▪]	Lung	Cisplatin/Paclitaxel	QOL: HRQL Nutritional Assessment System Habits and Nutrient Intake (SNUT) PG-SGA AC/S-12	Taste: whole mouth method using solutions (sweet, bitter and umami) Body composition: Bodystat QuadScan	Lower detection and recognition thresholds for umami and bitter Decreased health-related quality of life and appetite loss Lower intake of protien
Belqaid *et al.* [28▪]	Lung	Systemic therapy (targeted therapy or chemotherapy) Or Localized therapy (surgery or stereotactic radiotherapy)	Taste and Smell Survey ESAS FAACT PG-SGA		Patients have individual experiences of TSAs TSA change over time, e.g. different TSA intensity category TSA may be influenced by contextual factors, e.g. other symptoms and life situation

AC/S-12, anorexia/cachexia scale; AHSP, the appetite, hunger and sensory perception questionnaire; BDI, beck depression inventory; BEP, cisplatin, etoposide, bleomycin; DEXA, dual energy x-ray absorptiometry; ESAS, edmonton symptom assessment system; FAACT, functional assessment of anorexia-cachexia therapy; FFQ, food frequency questionnaire; HRQL, health-related quality of life; MTPRT, macronutrient and taste preference task; PG-SGA, patient generated subjective global assessment; QOL: quality of life; SNUT, nutritional assessment system habits and nutrient intake; TSA, taste and smell alteration; USDA, United States department of agriculture; VAS, visual analog scale; VIP, etoposide, ifosfamide, cisplatin.

may be due to the moment of measurement, which was at the end of the treatment. Taste and odor changes could be already (partially) restored at that moment.

Indeed, temporary taste changes were observed in patients with breast cancer who were treated with adjuvant chemotherapy [24]. These taste changes appear to have a cyclical course and are experienced in the first 4–6 days after chemotherapy. These changes are usually resolved at the end of the chemotherapy cycle; this process repeats itself with each cycle. In most patients, taste changes have completely disappeared 2 months after the last chemotherapy cycle.

Chemotherapy often causes patients to have food aversions against meat, which has a high-fat and high-protein content [4▪▪,22▪▪]. The taste changes are associated with reduced caloric intake, lower protein intake and reduced appetite [24] and the body composition of the patients already changes within 12 weeks after the start of chemotherapy. The percentage of fat mass increased during chemotherapy, while the lean mass and bone density decreased [23▪▪]. Advice on taste and nutrition can, therefore, best be given in the first week of chemotherapy.

The impact of cancer therapy on taste and smell functions and salivary constituents was examined by Mirlohi *et al.* [25▪]. In 22 newly diagnosed patients with primary malignant gliomas who were treated with radiation and temozolomide followed by 6 monthly cycles of temozolomide, chemosensory functions were assessed at 0, 3, 6, 10, 18 and 30 weeks and paired samples of saliva were collected. Salivary analyses were performed in parallel on 22 healthy volunteers. Chemosensory complaints of cancer patients increased significantly during treatment ($P = 0.04$) except at 30 weeks. Neither time nor treatment had a significant impact on salivary parameters in cancer patients. The authors concluded that the impact of intensive treatment on chemosensory functions can range from minimal to moderate impairment. Extensive analysis of salivary lipid oxidation [which measured iron (Fe)-induced oxidative stress], metals and total protein did not provide reliable measures of chemosensory dysfunctions over time.

TARGETED THERAPY

Little is known about targeted therapy and its impact on taste and smell. Patient-reported taste alterations are a commonly reported side-effect of protein kinase inhibitors. van der Werf *et al.* [5] reviewed possible mechanisms such as oral toxicity and altered taste or smell perception, but further research is necessary.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

In patients with hematological malignancies, hematopoietic stem cell transplantation (HSCT) is widely used as a potentially curative treatment. The prevalence of oral complications in both autologous and allogeneic HSCT recipients is high [17]. Frequently encountered oral complications include mucositis, infections, oral dryness, taste changes and graft versus host disease in allogeneic HSCT.

The taste perception of transplant patients was evaluated by Boer *et al.* [29]. Salivary flow rate and oral pathologies were studied in three different groups of patients ($n = 61$) undergoing HSCT at different time points after transplantation. Taste acuity was measured, unstimulated saliva was collected and salivary flow rates (ml/min) were determined. Saliva flow rate was diminished in 10 of 61 (16%) patients. With respect to taste, only sweet and salty taste remained altered. Significantly, there was no correlation between taste dysfunction, hyposalivation or oral chronic graft versus host disease.

CONCLUSION

Smell and taste alterations after systemic chemotherapy depend on many individual factors such as the type of malignancy and type of systemic chemotherapy. The physiology of smell and taste is complex and objective measurements of disturbances in smell and taste is difficult. So far, studies indicate that smell and taste changes are worst early in the chemotherapy cycle. There are few data on new treatment modalities such as targeted therapy affecting taste and smell. Future research should be focused on homogeneous study populations with objective, validated techniques at specific time points during treatment.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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The review evaluates objective and subjective assessment of taste and smell and discusses the prevalence of TSCs in cancer. Routine evaluation of taste and smell changes should be part of all nutritional assessment in cancer patients.

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The review summarizes the prevalence of taste and smell dysfunction, using a variety of gustatory and olfactory tests, in both patients on treatment and cancer survivors. Future research should aim to increase consistency in the choice of assessment methodology used to assess taste and smell alterations.

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This is the first study that longitudinally assessed food preferences 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.

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The Macronutrient and Taste Preference Ranking Task (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 can be used for both hypothesis-driven and exploratory studies to examine the influence of different factors on changes in food preferences.

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