



Relationship between food behavior and taste and smell alterations in cancer patients undergoing chemotherapy: A structured review

K. Drareni, A. Dougkas, A. Giboreau, M. Laville, P. J. Souquet, M. Bensafi

► To cite this version:

K. Drareni, A. Dougkas, A. Giboreau, M. Laville, P. J. Souquet, et al.. Relationship between food behavior and taste and smell alterations in cancer patients undergoing chemotherapy: A structured review. *Seminars in Oncology*, 2019, 46 (2), pp.160-172. 10.1053/j.seminoncol.2019.05.002 . hal-02195266

HAL Id: hal-02195266

<https://hal.science/hal-02195266>

Submitted on 25 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Relationship between food behavior and taste and smell alterations in cancer patients undergoing chemotherapy: a structured review

**K. Drareni ^{a,b}, A. Dougkas ^a, A. Giboreau ^a, M. Laville ^c,
P.J. Souquet ^d, M. Bensafi ^{b*}**

^a Institut Paul Bocuse Research Centre, Château du Vivier, BP25, 69131 Ecully Cedex, France.

^b CNRS, UMR5292, INSERM U1028, Lyon Neuroscience Research Center, University Lyon, F-69000, France

^c Centre de Recherche en Nutrition Humaine Rhone-Alpes and CENS, University of Lyon 1, CH Lyon Sud, Hospices Civils de Lyon, 69310 Pierre Bénite, France.

^d CH Lyon Sud, Hospices Civils de Lyon, 69310 Pierre Bénite, France.

*Corresponding author:

Dr. Moustafa Bensafi,

Centre de Recherche en Neurosciences de Lyon

Inserm U1028 - CNRS UMR5292 - UCBL

Centre Hospitalier Le Vinatier - Bâtiment 462 - Neurocampus

95 boulevard Pinel, 69675 Bron Cedex, France

moustafa.bensafi@cnrs.fr

Abstract

INTRODUCTION Taste and smell alteration is a frequent side effect of chemotherapy. However, little is known about their influence on patients' food behavior and the mechanisms underpinning their occurrence. This lack of clarity is likely due to a series of factors among which heterogeneity in chemotherapy-induced taste and smell modifications may play a prominent role. The present review provides a critical overview of the evidence on the association between taste and smell alterations and food behavior modifications in cancer patients undergoing chemotherapy.

DESIGN The literature search was performed using PubMed and Google Scholar databases and restricted to literature for English-language articles published between 1990 and June 2018. Sensory related terms were combined with food behavior related terms to identify the studies that examined the association between these two terms. The retrieved studies were grouped based on the taste and smell assessment outcomes.

RESULTS Thirteen eligible articles were included in the review. The studies varied in design, length, methodology of assessment, and studied population. The categorization of studies depending on taste and smell assessment outcomes allowed the definition of three patient profiles: unaltered, hypo- and hyper-chemosensation (taste and/or smell). Alterations were significantly correlated with patients' energy intake and macronutrient preferences suggesting that sensitivity of each patient to olfactory and gustatory stimuli is likely to play a role in food behavior modulation during cancer and chemotherapy.

CONCLUSION The review summarizes and provides relevant associations between taste/smell alterations and food behavior while receiving chemotherapy considering existing individual variations. Given the sensory influence on food behavior modulation, a better characterization of smell and taste alterations before the launch of chemotherapy seems important for a better understanding and management of patients' food behavior trajectory over the treatment.

Key words: *Cancer, Chemotherapy, Taste, Smell, Food intake, Food behavior*

1. Introduction

Cancer patients treated with chemotherapy have reported adverse taste [1–4], and smell modifications [5,6], associated with deterioration of some quality of life aspects such as loss of appetite, fatigue [7,8], nausea [9] and decrease in energy intake [10]. Systemic chemotherapy for cancer often lacks specificity [11] and can cause distressing side effects such as alopecia [12], anemia [13], and sensory impairments, especially to chemosensory systems, that rely on the perception of molecular properties of stimulus [14]. During the administration of cytotoxic chemotherapy the chemosensory systems is exposed to more changes than other sensory systems [9,15,16]. This is possibly due to the short life span of gustatory and olfactory receptor cells and their frequent renewal [17], making them more vulnerable to cytotoxic chemotherapy drugs.

In addition to these physiological changes, cognition is also altered with patients exhibiting difficulties in gustatory and olfactory recognition [18] or overall hedonic appreciation [19,20]. However, at higher levels of integration, gustation and olfaction do not result in independent percepts; but instead, in combination with somatosensory inputs [21,22] including trigeminal nerve endings located in the oral and nasal cavities [23], they lead to a unitary perception called flavor. This multisensory percept is considered to be a major determinant of food acceptance or rejection [24]. A recurrent hypothesis in the fields of oncology and nutrition is that any alteration of taste and/or smell (during chemotherapy for instance) may have significant consequence on flavor perception and on the hedonic judgment of food. In cancer patients undergoing chemotherapy, that may be reflected in changes in food preferences [25,26], development of aversions [27,28], decrease in food enjoyment [29], changes in dietary habits and loss of appetite [26,30]. Although this assumption has been mentioned in various articles in the field [20,31,32], there is no structured review that

summarizes how taste and smell alterations are specifically related to modifications in food behavior in cancer patients receiving chemotherapy.

In particular, whereas some reviews have examined taste and smell modifications during cancer and/or chemotherapy [29,33–44] and others explored the effect of cancer and/or chemotherapy on food behavior and nutrition, none explored potential associations between the taste/smell modifications and food behavior. Understanding the relationship between chemosensory alterations during chemotherapy (mainly taste and smell) and modification of food behavior is important at two levels: 1/ at a fundamental level, it allows a better understanding of the sensory and cognitive mechanisms that connect the sensory systems to neural network involved in the process of food intake; 2/ at a clinical level, this may contribute to the improvement in the care of patients, considering the impact of taste and smell alterations throughout the treatment on food intake and eating enjoyment.

The main aim of the present review is to discuss scientific and clinical findings from studies investigating the link between taste and smell alterations and food behavior modifications in cancer patients undergoing chemotherapy. For a better understanding of the chemosensory perception and its importance in daily life, this review first introduces the sensory systems involved in flavor perception (i.e. gustation, olfaction, trigeminal sensitivity). Secondly, we define the concept of food behavior and its determinants. Thirdly, we review the existing literature exploring both taste and smell alterations and food behavior changes during chemotherapy. We further examine whether a homogeneous profile of chemosensory alterations exists or whether chemotherapy and/or cancer have differential impact on patients' chemosensory capabilities (i.e. hyposensitivity, hypersensitivity, mixed profiles, no change, etc.). In addition, the relationship between these sensory change profiles and food behavior alterations in this population is discussed. The review concludes by opening future

perspectives that consider early evaluation of alterations in taste and smell (at the individual level) for better management of the future food behavior alterations of the patient.

1.1. Chemo-sensation: definition and underlying sensory systems

The chemosensory processes involve the olfactory, gustatory and trigeminal systems and enable the detection and recognition of external chemical signals. These fundamental sensory modalities are shared by most multicellular organisms and significantly impact their behavior [45]. For instance, environmental chemical signals allow the detection of food, reproductive partners, prey and predators. In the following section, we present an overview of the functioning of each chemosensory system.

1.1.1. The gustatory system

At the periphery, the gustatory system includes an array of taste buds in the oral and pharyngeal cavities. Taste buds are located around small structures known as papillae, which are found mainly on the upper surface of the tongue (but also on the soft palate, upper esophagus, cheek and epiglottis). There are four known types of papillae: foliate, circumvallate, fungiform and filiform, distributed on different zones of the surface of the tongue (*Figure 1*) [46]. Taste perception is the result of an interaction between sapid molecules and taste receptors in specialized epithelial gustatory cells present in taste buds [47]. Taste buds are located on the tongue and have a lifespan of 5-20 days [17].

On a functional level, the gustatory system works as a nutrient sensing system. It enables the detection, recognition and discrimination of the five basic tastes - sweet, bitter, umami, sour and salty, which can be combined to form more elaborate taste sensations [48]. Salty and sour tastes are detected through ion channels (Na^+ for salt and intracellular proton concentration for sour) [49,50]. Sweet, bitter and umami tastes are mediated by G protein

coupled receptors (GPCRs) [47]. The proteins called T1R1, T1R2 and T1R3 detect sweet and umami tastants, while T2Rs is specific to bitter. The combination of these receptors with their specific ligand (contained in the sapid molecule) triggers a series of intracellular reactions [36,51]. The sensory information is transmitted to the primary taste cortex via three cranial nerves that carry taste sensations from different areas: the facial nerve (VII) from the anterior two thirds of the tongue; the glossopharyngeal nerve (IX), from the posterior one third of the tongue; and the vagus nerve (X) from the back of the oral cavity. These sensations are then transmitted to secondary or associative cortical areas common to olfactory and gustatory sensations (*Figure 1*) [14,46].

An important factor that plays a fundamental role in gustatory perception is saliva. Saliva is the first digestive fluid in the food canal. It is secreted by the salivary glands and poured directly into the oral cavity [52]. Saliva helps in chewing food, forming and swallowing the food bolus, and digesting starch (amylase) [53]. Saliva also serves as the solvent of sapid molecules, which need to be dissolved in order to be detected by the taste receptor cells. By detecting these molecules, the gustatory system provides qualitative information of the ingested food. It is estimated that about 2 ml of saliva are secreted every 15 to 20 minutes. A decrease in salivary flow leads to xerostomia (mouth dryness), which makes the detection of sapid molecules more difficult, complicates the action of mastication and swallowing and may cause oral problems such as mucositis or candidiasis [54].

1.1.2. The olfactory system

At the periphery, the human olfactory system is characterized by the large number and the diversity of its sensory receptors (between 350 and 400), which are G-protein coupled receptors that enable the detection and discrimination of a very large number of odorants [55]. The neurons of the olfactory receptors are in direct contact with the environment, which

facilitates the detection of environmental chemical molecules [56]. These neurons are located in the olfactory epithelium, a specialized tissue of about 2.5 to 10 cm² in surface area located on the roof of the nasal cavity. The neurons are bipolar cells with several cilia, which contain the olfactory receptors on their surface projecting into the nasal mucosa. The mucus moistens the nasal cavity but also plays an important role in olfactory perception, as it is involved in the dissolution of some hydrophobic odorant molecules, their transport to receptor sites, and the degradation and the removal of the excess odorants [57].

There are two ways of transporting odorous molecules towards the nasal epithelium: (i) the *ortho-nasal pathway* ensures the detection of volatile odorous molecules by the olfactory receptors following their passage through the nasal cavity, (ii) the *retro-nasal pathway* enables the detection of aromas contained in the food. The later path is triggered by the action of chewing food, which induces the release of its flavors [58]. It is suggested that ortho-nasal and retro-nasal olfaction may be sustained by distinct neural processes [59]. Whether via the ortho-nasal or retro-nasal route, once the interaction between the odorous molecule and receptor is established, the sensory information is then transmitted via the olfactory nerve (I: olfactory) to a central structure called the olfactory bulb (**Figure 1**). The olfactory bulb is composed of excitatory and glutaminergic mitral cells and is located in the cranial chamber in both hemispheres. Thereafter, the olfactory tract connects the olfactory bulbs to the brain areas involved in the perception and identification of odors including (among others) the primary olfactory cortex (piriform cortex, part of the amygdala) and both the orbito-frontal cortex and insula, which play a role in hedonic and associative treatment with other sensory modalities (**Figure 1**) [60]. The sense of smell is therefore closely related to other senses, especially the gustatory and trigeminal systems, as well as to emotion and memory [61].

PLEASE BE SURE TO PROVIDE US THE MOST ORIGINAL VERSION OF THIS
FIGURE THAT YOU HAVE AND IF THIS IS FROM ANOTHER SOURCE PLEASE
CITE THAT SOURCE AND IMMEDIATELY OBTAIN PERMISSION FOR ITS USE

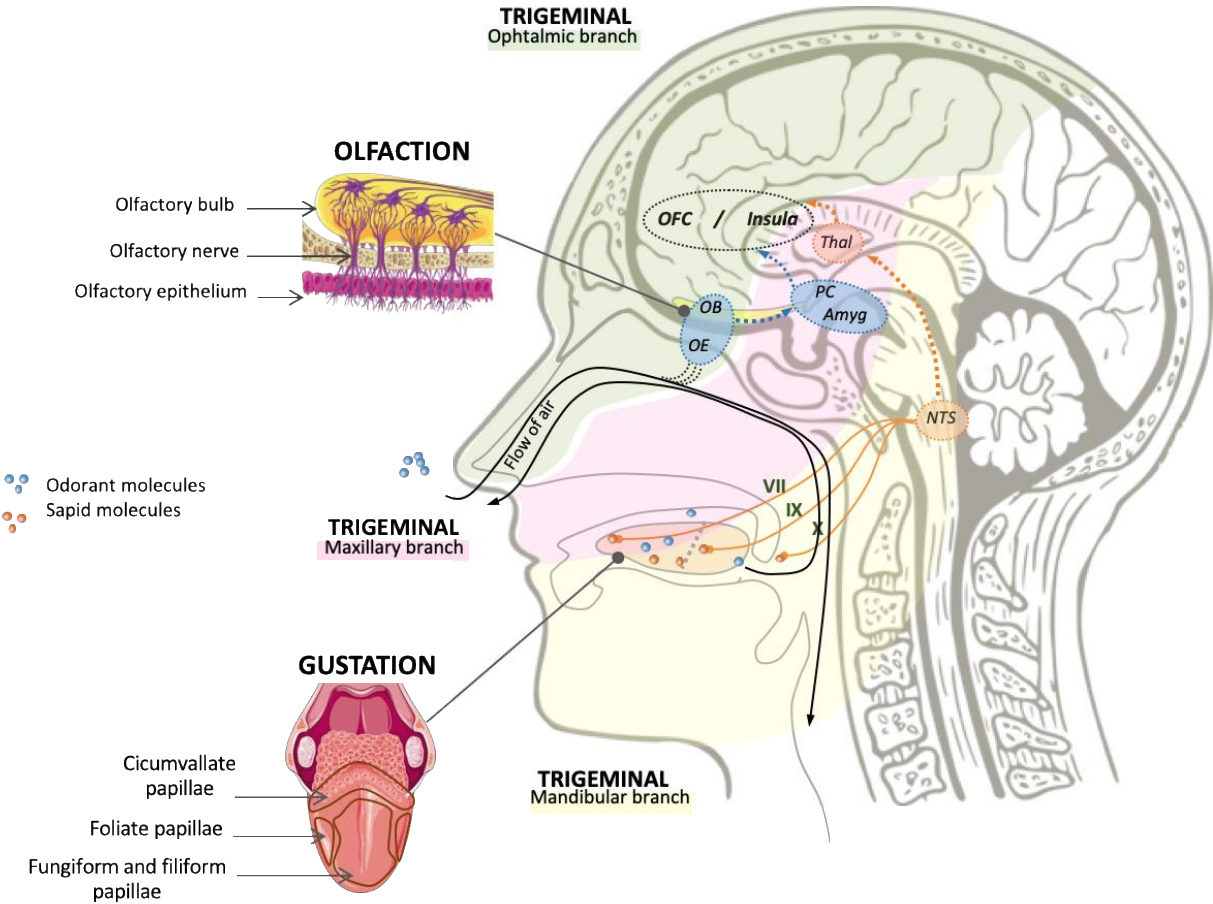


Figure 1. Chemosensory systems involved in flavor perception. The trigeminal system is composed of three branches: ophthalmic, maxillary and mandibular. In olfaction, odorant molecules are first detected in the olfactory epithelium (OE), and neural information is then transmitted to the olfactory bulb (OB) and other central structures such as the piriform cortex (PC) and the amygdala (Amyg). In gustation, sapid molecules are first treated within the different papillae on the tongue (there exist other receptor sites in the palate and esophagus), and the signal is then sent to the nucleus tractus solitarius (NTS) via different cranial nerves (VII: facial nerve (chorda tympani); IX: glossopharyngeal nerve (lingual branch); X: vagus nerve (laryngeal branch)). In both, the olfactory and the gustatory systems, high-order information is sent and processed to associative brain areas including the orbito frontal cortex (OFC) and the insula via the thalamus (THAL) for gustation.

1.1.3. *The trigeminal system*

With gustation and olfaction, the trigeminal system is the third chemosensory system that contributes to flavor perception. Trigeminal sensitivity (both proprioceptive and kinesthetic) of the face and associated cavities (i.e. oral and nasal) is transmitted via the three branches – the ophthalmic, maxillary and mandibular - of the fifth cranial nerve also called the trigeminal nerve [21] (*Figure 1*). The trigeminal nerve endings in the nasal and oral cavities are sensitive to tactile and thermic information and to several molecules known to be pungent, tingling, irritating or astringent [62]. Thus, the spiciness of pepper, the burning of ginger, the sparkling of carbonated drinks, and the astringency of red wines, are potential stimulants of the trigeminal system. Psychophysical and neurobiological investigations have revealed that interactions between the trigeminal and the olfactory system may occur at both peripheral (trigeminal fibers were identified in the nasal epithelium [63]) and central levels [64], although compared to pure olfactory stimuli, intranasal trigeminal stimuli show specific neural activations [65] .

1.2. **Food behavior: definition and determinants**

Food behavior represents food beliefs and practices linked to food choice, preparation, cooking and consumption and encompasses both nutrition and food safety knowledge, attitudes, perceptions and beliefs in the selection and handling of food [66]. Although there are several influences on food behavior related to an individual's cultural and social environment, as well as personal and food nature or food risk factors that interact these are almost impossible to disentangle [67], and most of the research linked with food behavior in pathological states is in the areas of food preferences and food intake. Food/energy intake, and food preferences and hedonics (which include choices, motives and habits) characterize not only healthy eating practices but also eating-related pathologic behaviors such as obesity,

217 eating disorders (e.g. anorexia) and malnutrition [68]. “Food/energy intake”, is considered
218 adequate when food consumption meets the energy requirements of the individual, a state
219 known as energy balance. The regulation of food intake is based on complex neuro-hormonal
220 mechanisms that allow the maintenance of the energetic balance [69] and is mainly driven
221 within the hypothalamus, and specifically the arcuate nucleus, which plays a major role in the
222 integration of hunger/satiety signals [69]. Food intake is regulated by a series of homeostatic
223 and non-homeostatic factors [70,71]. Hunger and appetite [72] are prominent regulatory
224 factors of energy balance since they modulate the energy intake side of the equation. *Hunger*
225 is the sensation of needing food, expressed at the physiological level by a complex interaction
226 between vagal signals, secretion of orexigenic hormones (ghrelin, orexin), decrease in plasma
227 concentration of leptin, and a low level of circulating glucose (hypoglycemia) [73], [74]. The
228 term appetite covers the whole process of food intake, including food selection, motivation to
229 eat, and individual preferences and is generally described as the desire to consume certain
230 foods [73]. The sensory and external environmental stimulation of appetite and thus food
231 intake has drawn attention to the hedonic dimension of appetite without underestimating the
232 importance of internal homeostatic system (energy needs) [75]. Food preferences and
233 hedonics despite being a process driven by deficits in energy, contribute to the pivotal role of
234 pleasure during an eating experience [69,70,76]. The sensory properties of food such as
235 palatability, appearance, taste, smell and texture influence hedonic expectations, and
236 contribute to the decision of food consumption: food intake is increased if food is perceived
237 as palatable, and decreased if the sensory experience is unpleasant [77,78]. Beside these two
238 dimensions, a pleasantness-based phenomenon called sensory specific satiety plays a major
239 role in the regulation of food intake [79]. Sensory specific satiety is defined as the decline of
240 liking of a specific food over the course of eating, leading to termination of its consumption,
241 in contrast to food with a different sensory profile [80,81]. Overall, it is noticeable that food

behavior is strongly modulated by sensory inputs [78,82], and especially chemosensory signals [83,84].

2. Research methodology

2.1. Data search and selection criteria strategy

The literature search was performed using PubMed and Google Scholar databases and restricted to literature for English-language articles published up to June 2018. As we aimed to understand the specific impact of cytotoxic chemotherapy on taste and smell perception and food behavior, sensory related terms were combined with food behavior related terms to identify the studies that examined the association between these two arms. The key words included 1) for the sensory arm: *taste, gustatory, smell, olfactory, trigeminal sensitivity, flavor* and 2) for the food behavior arm: *food/energy intake, hunger, appetite, satiety, food preferences, food hedonics/liking/enjoyment*. The selection of food related terms focused on the biological and hedonic determinants of food behavior, excluding other aspects such as economic, physical and social determinants. The terms *chemotherapy* and *cancer* were added to the search. Articles were eligible for inclusion if both sensory changes (including taste and smell) and food behavior determinants modifications were investigated as an explicit side effect of chemotherapy. Studies on patients with head and neck tumors, which are known to be strongly associated with taste and smell alterations, and studies on patients having any other treatment than chemotherapy were excluded. Article database was augmented by a manual search in reference lists of identified published articles, as well as previous relevant systematic and narrative reviews for citation of further eligible studies. Using these selection criteria, a total of 19 articles that cover both the sensory and the food behavior dimensions were identified. Finally, 13 eligible articles were included in this review after removing those studies that did not provide quantitative data of the variables of interest (**Table 1**).

2.2. *Data extraction and processing*

The relevant information extracted from each study is related to the study characteristics, methodological characteristics and main outcomes as described in **Table 1**. Those study characteristics and outcomes are described as follows: (i) “*Reference*” (Authors and date of the studies), (ii) “*Study type*” (cross-sectional, longitudinal, following patients for a period varying from 6 weeks [8] to 1 year after the chemotherapy induction [85]), (iii) “*Groups*” characteristics (number of patients, mean age), (iv) “*Cancer type and chemotherapy regimen*”, (v) the tools used for “*Sensory assessment*” and the type of “*Approach*” used to assess taste and smell (“Objective” methods that include psychophysical tests; “Subjective” methods based on self-reported description of sensory capabilities[86]), (vi) the “*Food behavior measure*”, (vii) the “*Main effects of chemotherapy on gustatory and olfactory perceptions*” from the sensory measures, (viii) the “*Main effects of chemotherapy on food behavior*”, and finally (ix) the results of the interaction between sensory and food dimensions (“*Sensory/food interaction*”). To the best of our knowledge, alterations of the trigeminal system due to chemotherapy treatments have not been reported.

3. **Results**

3.1. **Modification in cancer patients’ taste and smell in during chemotherapy**

Eleven of the 13 studies listed in **Table 1** showed an effect of chemotherapy treatment on perceptions (including taste and smell). In studies that used subjective methods of chemosensory assessment, there was high heterogeneity in chemosensory outcomes for patients not only between the studies but also within the same study (**Table 1, Section A**). For example, Marinho et al. [87] showed that 64% of the patients reported taste changes during the chemotherapy treatment with no sensory modifications in 36%. Hutton et al. showed that 86% of the patients reported sensory abnormalities, of which 30% described only taste

abnormalities, and 5% only smell. The prevalence of olfactory and gustatory changes in patients was 60% in Brisbois et al. [9] but the sensory phenotype varied according to the participants: 42% declared a stronger sensation, 18% a weaker sensation, 14% a mixed sensation, and 26% no change in sensation. In accordance, Mc Greevy et al. [88] showed a large variability across patients, with a prominent effect of gender - for example, whereas 10% of the men vs. 37% of the women declared stronger sensation, 20% of the men vs. 6% of the women declared sensation was weaker. Finally, 73% of patients in the study by Belqaid et al. [89] declared sensory alterations with a variation in sensory phenotypes throughout the treatment - from weaker sensation to stronger sensation or no effect. Such heterogeneity in self-reported taste and smell modifications is confirmed by psychophysical studies based on objective methods of sensory assessment. Following patients' sensory capacities, three types of profiles were extracted from the papers listed in **Table 1**: (1) patients exhibiting unaltered taste and smell (section B); (2) patients exhibiting reduced sensitivity or hyposensitivity to taste and smell (section C); (3) patients exhibiting a increased sensitivity or hypersensitivity to taste and smell (section D); These 3 types of profiles are described below.

The “Unaltered taste and smell” profile

This profile characterizes patients exhibiting no changes in their olfactory and gustatory functions (**Table 1, Section B**). Two studies using an objective method of assessment showed no effect of chemotherapy on the taste and smell perception of cancer patients [32,90]. Ovesen et al. [90] reported on 52 patients with a diagnosis of cancer, including 25 lung, 21 ovarian, and 6 breast cancer. In a longitudinal study, they performed 3 time-points for assessments including a baseline (T0), a first follow up before the second cycle of chemotherapy (T1) and a second follow up three weeks after the third cycle of chemotherapy (T2). The results showed no significant difference in olfactory threshold of

patients between the three time points. However, the gustatory assessment revealed a decrease in taste threshold, but only in the patients with a diagnosis of lung cancer. Similarly, in a longitudinal study by De Vries et al. [32] using both objective and subjective methods of assessment, there was no modification of gustatory and olfactory sensitivity after 2 cycles of chemotherapy on a small but homogeneous group of patients with diagnosis of esophagogastric cancer.

The “Hyposensitivity to tastes and/or smells” profile

This profile identifies patients who experience decreased gustatory and/or olfactory function (**Table 1, Section C**). Three studies showed a decrease in both olfactory and gustatory perceptions [85,91,92], and two reported a reduced ability to identify gustatory stimuli [20,93]. In a longitudinal study, IJpma et al. [85] assessed the olfactory and gustatory capabilities in 21 patients with a diagnosis of testicular cancer undergoing cisplatin chemotherapy. The results showed a transient decrease of subjective taste and smell perception, associated with a decrease in sensitivity for salty taste. This effect was prominent during the first week of each chemotherapy cycle. Similarly, De Vries et al. [94] assessed the olfactory and gustatory functions in 28 women with a diagnosis of breast cancer, during, and 6 months after the completion of chemotherapy. Patients reported their taste and smell functions as lower during chemotherapy and shortly after chemotherapy, yet improved 6 months after the completion of chemotherapy. In the same study, objective psychophysical tests showed a lower olfactory and gustatory sensitivity during chemotherapy, especially for salty taste. The decrease of subjective taste and/or smell perception was also found in a larger group including 117 women with breast cancer [92].

Besides sensitivity, Boltong et al. [20] showed a reduced ability to identify salty, sour and umami tastes in women with breast cancer between their first and their final cycle of

chemotherapy, as well as a decrease in sweet taste liking. A difficulty recognizing tastes was also reported in a cross-sectional study by Lara-Sanchez et al. [10], who compared patients with different cancer diagnoses and healthy controls. After 2 cycles of chemotherapy, an increase in complaints about gustatory perceptions was associated with a decreased ability to identify bitter taste in patients.

The “Hyper- sensitivity to tastes and smells” profile

Only one study reported a significantly higher gustatory sensitivity for bitter and umami tastes, assessed by a Rinsing Mouth Test (RMT), in 40 patients with a diagnosis of lung cancer receiving platinum-based chemotherapy (**Table 1, Section D**). Interestingly, the increase in gustatory sensitivity was accompanied by a decrease ability to identify taste (umami). These findings suggest that a hyper gustatory sensitivity may alter taste representation and thus taste identification, which may significantly impact food recognition.

In sum, there is a high incidence of alterations in chemosensation while cancer chemotherapy is administered, as well as at times high inter-individual variability between patients and likely across treatments and cancer types. The observed heterogeneity is supported by the findings of several studies, which reported unaltered [19], decreased [18,95–99], or intensified gustatory and/or olfactory capabilities in patients who were treated with chemotherapy [15,100,101]. This inter-individual variability with regards to the effect of chemotherapy on the taste and smell perception of cancer patients could be attributable to a number of putative factors as discussed in the section below.

3.2. Putative factors modulating taste and smell profiles

At the methodological level, study design, method of assessment, variable of interest, or stage of chemotherapy at the time point of assessment may influence the results and

explain the lack of consistency between studies. For instance, we observed variability in study design, with 3 cross sectional studies and 10 longitudinal studies that followed patients for a period from 6 weeks [8] (2 chemotherapy cycles) to 1 year after the initiation of chemotherapy [85]. There was also heterogeneity in the populations studied. Eight of the selected studies had a homogeneous group of patients in terms of cancer histology, however in some, patients received different chemotherapy regimens which may have influenced the reported effects. We also noted that only five studies enrolled a control group, enabling one to examine whether the observed effect is a consequence of the pathology and/or the treatment, or if it deviates from normal fluctuations over time.

Other factors are related to the disease and treatment such as histology and chemotherapy regimen. Considering histology, studies reported a varying percentage of patients with taste and/or smell alterations: 76% of patients with breast and gynecological cancers [7]; 41.4% of patients with a diagnosis of lung cancer [96]; 68% of those with a gastrointestinal cancer [88]; and 31% of those with pancreatic cancer [96]. This factor is closely related to the type of chemotherapy used, given that certain treatment regimens are more likely to induce chemosensory impairment. For example, Zabbernig et al. [102] showed that irinocetan, a drug commonly in the management of colorectal cancer, induces more taste disorders than other drugs such as gemcitabine, commonly used for pancreatic cancer. [102]. Furthermore, the same study reported a maximal occurrence of taste dysfunction with epirubicin, docetaxel and capecitabine as neoadjuvant treatment of patients with early breast cancers.

In addition to the disease-related factors enumerated above, individual differences may be explained by intrinsic physiological factors that vary from one individual to another regardless of the cancer's histology [Table 2]. The gustatory and olfactory perception process operates at several levels, and each level is likely to present individual differences. For

instance, the perception of gustatory stimuli is based on releasing sapid molecules in contact with saliva, and their interaction with gustatory receptors located in taste buds that are held in papillae. The quantification of papillae density and more specifically fungiform papillae density allows one to detect individual variation in the number of papillae on the surface of the human tongue [103]. A high density of fungiform papillae corresponds to a higher number of taste buds, and so a higher number of taste receptors, which corresponds to a higher taste intensity perception. Thus, this physiological difference may play a role in the heterogeneity of chemotherapy-induced sensory alterations.

Another contributing factor to the observed variability is genetic variation such as the perception of bitterness [104–106]: the ability to (hypo or hyper) perceive specific molecules (phenylthiocarbamide and 6-n-propylthiouracil) depends on the expression of gustatory receptors. Therefore, without considering cancer histology or treatment, the status of patients (hypo vs. hypersensitive) towards bitterness perception is inherently different. This genetic/phenotypic status may result in differential chemotherapy effects on taste perception explaining the reported complaints of patients about sensitivity to bitterness [34,107]. Regarding the other taste modalities, a previous study showed a genetic variation in umami taste receptor that affected umami taste sensitivity [108]. Finally, considering the oral cavity, saliva, which varies in terms of flow and composition across people, may explain individual variations in the effect of chemotherapy on taste perception [109–111].

Olfactory function also exhibits inter-individual variation in a non-pathologic state, and this may explain the different olfactory phenotypes during cancer and chemotherapy. Prevalent genetic variations in olfactory receptors leads to differences in odor perception [112]. Moreover, human oral physiology and food oral processing, which determine the amount of released aroma in the nasal cavity are not similar across people [113,114].

Finally, other physiologic factors that may explain the variability in chemosensory profile are intrinsic to patients and include gender [115] and importantly age [116,117]. For example, during chemotherapy treatment, women were found to have a higher sensitivity in sweetness, bitterness perception than men [88] and younger patients showed less taste and/or smell impairments than older patients [97].

3.3. Food behavior as a function of taste and smell profiles

Of the 13 studies listed in **Table 1**, nine studies examined patients' food intake (energy or macronutrients intake), and three studies assessed food or macronutrients preferences. Surprisingly, most of these studies did not report difference in patients' energy and macronutrients intake: three studies showed no effect of chemotherapy on food intake [85,90,93], and four studies did not mention the results related to food intake at the group level [8,9,31,88]. Four studies reported a decrease in food intake but only when the group was stratified following the severity of chemosensory complaints [9,20,31,88]. The more severe were the sensory complaints (hypo or hyper sensitivity), the lower was the energy intake of patients. The 3 sub-sections that follow summarize the effects of chemotherapy on food behavior as a function of sensory profiles (unaltered, hypo, hyper) in patients with a diagnosis of cancer.

The “unaltered taste and smell” profile

Using a 3-day diet diary, Ovesen et al. [90] assessed food intake in patients with a diagnosis of cancer of the lung, ovary, or breast cancer but did not find a significant difference in food intake between baseline and follow-up at cycle 3. Also, there were no within group differences when nutritional data were analyzed as a function of diagnostic group [90]. These authors argued that the mean values of the group concealed the wide range

of intake at the individual level, noting that about one-third of the patients consumed less energy than they should have consumed. Considering food preferences, De Vries et al. [32] showed that patients had a higher preference toward high protein than high carbohydrate or low energy products, but there was no difference in macronutrient preference between baseline and after 2 cycles of treatment. No difference was observed in preferences for sweet food and savory food [32]. In sum, the unaltered taste and smell profile is unlikely to present significant alterations in food behavior at a group level.

The “hyposensitivity to tastes and/or smells” profile

Studies showing a decrease in patients’ taste and/or smell function reported either an unchanged [10,85] or a decreased energy intake [92] throughout the treatment. Ijpma et al. [85] showed that food intake assessed by the Food Frequency Questionnaire in 21 men with a diagnosis of testicular cancer remained stable over time. Lara-Sanchez et al. [10] showed that nutrient intake assessed with the SNUT program [118] of patients after 2 cycles of chemotherapy and controls were similar. However, a positive correlation between modification in sweet threshold/bitter recognition score and food intake was highlighted in some patient groups. While De Vries et al. [119] using a 24-h dietary recall reported a significantly lower energy, protein, and fat intake in 117 women with a diagnosis of breast cancer compared to 88 healthy controls [119]. This decrease in food intake was significantly correlated with a reduced self-reported taste function. Similarly, Boltong et al. [20] reported reduced energy intake in accordance with a reduced ability to identify tastes.

Regarding food and macronutrients preferences, DeVries et al. [94] noted a decreased liking for high fat and high protein products and an increased liking for savory food 1 to 3 weeks after chemotherapy in women with a diagnosis of breast cancer [91]. Furthermore, De Vries et al. [94] observed that a higher subjective rating of taste function was correlated with

a higher liking of high protein, low energy, savory and sweet products, whereas a higher rating of subjective smell function was significantly correlated with a higher liking for low energy and sweet products only. This suggests that the olfactory and the gustatory impairments affect food preferences and likings differently.

Overall, these results indicate that when considered as a group, patients with a profile of hypo-sensitivity to *tastes and/or smells* do not exhibit modifications in food intake. However, once the strength of the sensory alteration within this group is considered, a decrease in food intake and liking of certain food is apparent suggesting the more taste and smell are altered, the more food intake and liking is decreased.

The “hypersensitivity to taste and smell” profile

Only one study showed an increase in gustatory sensitivity using RMT [8]. This study assessed food intake of 40 patients with a diagnosis of lung cancer and showed a negative correlation between the sweet detection threshold and protein intake, which means that patients with higher sensitivity to sweet taste consumed less proteins, and specifically animal proteins. The difference in protein intake was not observed between patients with increased or decreased umami or bitter taste.

This is in agreement with three studies, which used a subjective assessment of chemosensory function and linked significantly self-reported taste and/or smell complaints with a lower food consumption [9,31,88]. Hutton et al. [31], Brisbois et al. [9] and McGreevy et al. [88] adapted the “Taste and Smell Survey” questionnaire (initially designed for patients infected with the HIV [120] to cancer patients and showed a strong correlation between the severity of patients’ chemosensory complaints and the decrease of energy intake. Interestingly, using the same assessment tools these three studies came to the same conclusions although the size of patient groups and cancer histology were different.

In summary, results suggest a negative impact of taste and/or smell changes (hyper or hypo profile) on energy intake [8,9,20,31,88,93] and food preferences [32,92,94,121].

4. Conclusions and perspectives

In conclusion, the available scientific literature provides no evidence for a systematic and unvarying/consistent impact of chemotherapy on gustatory and olfactory functions in patients with a diagnosis of cancer. Additionally, the existence of different sensitivities in taste and smell profiles is highlighted in various studies, which used subjective and objective methods and showed unchanged, increased or decreased sensitivity to tastes and smells in various cancers. This diversity in the chemosensory profiles of patients may be attributable to various factors including those related to methodology and those that are inherent to the physiological state of the patient (structural and functional aspects of the olfactory and the gustatory systems, saliva composition, etc).

The sensitivity of each patient to olfactory and gustatory stimuli is likely to modulate patients' food behavior and preferences by modifying the representation of foods (from sensitivity, to recognition and preferences). This may lead to an individual "food trajectory" that differs between patients and throughout the treatment. Interestingly, when patients are admitted in clinical departments for chemotherapy treatments, their "food" trajectory during and after the treatment is unpredictable. Thus, an important challenge in the oncology field is to develop strategies to help health practitioners predict potential food behavior changes of patients by being more vigilant and provide appropriate dietary and culinary solutions tailored to each patient in order to maintain a healthy relationship with food and improve quality of life.

Exploiting the relationship between taste and smell alterations and changes in eating behavior could be part of the developed strategies. For example, by systematically screening patients' senses of smell and taste at arrival at the clinic, and after the first cycles of chemotherapy, it is possible to categorize patients according to the aforementioned chemosensory profiles and therefore describe, anticipate or predict a subsequent development of changes in eating behavior.

It is notable that relationships between taste and smell alterations and changes in food behavior have already been demonstrated in physiological and/or pathological conditions other than cancer. For instance, odor hedonic perception is altered in patients suffering from Alzheimer's disease [122,123], elderly individuals [124], and children with autism [125]. Interestingly, patients with a diagnosis of Alzheimer's disease who perceived smells as less intense showed a tendency towards a decreased nutritional status [122], and elderly individuals who did not properly categorize smells exhibited a significant decrease in nutritional score [124]. Moreover, altered hedonic discrimination of odors in children with autism was associated with a higher level of food neophobia defined as refusal to consume novel foods [125]. Finally, individuals with no oncological or neurological pathologies but presenting olfactory alterations (dysosmic patients), also exhibit significant modifications in food behavior reflected in a reduced attraction towards novel foods, a tendency to experience less pleasure when eating, and a significantly higher use of condiments such as sugar, mayonnaise, or sour cream to make their dishes tasty [126].

Although the present review highlights a clear relationship between the occurrence of taste and smell alterations with the energy intake of patients with a diagnosis of cancer, experimental studies are still needed. Once validated in patients with cancer, such descriptive (or predictive) models relating olfactory and/or gustatory alterations and future modifications in food behavior may be applied in clinical settings by developing rapid and sensitive

540 chemosensory assessments combined with efficient measures of food behavior. Such
541 screening approaches and the resulting recommendations should be done using a patient-
542 centered intervention approach rather than a group approach in order to meet the needs of
543 each patient.

544 **Declarations of interest:** none

545 **Funding:** A funding contribution was provided by Elior, Apicil, Region Rhone-Alpes (ARC1
546 call), and Métropole de Lyon/Region Rhone-Alpes/Cancéropôle Lyon Auvergne Rhône-
547 Alpes (CANUT project). The funding sources were not involved in the writing and the
548 publication of this review.

549 **Authors' contributions:** K.D. prepared and analysed the database. K.D., A.D., A.G. and
550 M.B. drafted the manuscript. All authors contributed to, and approved, the final version of the
551 manuscript.

552 **Ethics approval and consent to participate:** Not applicable

553

554

References

- [1] Bernhardson B-M, Tishelman C, Rutqvist LE. Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. *J Pain Symptom Manage* 2007;34:403–12. doi:10.1016/j.jpainsymman.2006.12.010.
- [2] Jensen SB, Mouridsen HT, Bergmann OJ, Reibel J, Brünner N, Nauntofte B. Oral mucosal lesions, microbial changes, and taste disturbances induced by adjuvant chemotherapy in breast cancer patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;106:217–26. doi:10.1016/j.tripleo.2008.04.003.
- [3] Bernhardson B-M, Olson K, Baracos VE, Wismer WV. Reframing eating during chemotherapy in cancer patients with chemosensory alterations. *Eur J Oncol Nurs Off J Eur Oncol Nurs Soc* 2012;16:483–90. doi:10.1016/j.ejon.2011.11.004.
- [4] Speck RM, DeMichele A, Farrar JT, Hennessy S, Mao JJ, Stineman MG, et al. Taste alteration in breast cancer patients treated with taxane chemotherapy: experience, effect, and coping strategies. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2013;21:549–55. doi:10.1007/s00520-012-1551-3.
- [5] Yakirevitch A, Bercovici M, Migirov L, Adunsky A, Pfeffer MR, Kronenberg J, et al. Olfactory function in oncologic hospice patients. *J Palliat Med* 2006;9:57–60. doi:10.1089/jpm.2006.9.57.
- [6] Riga M, Chelis L, Papazi T, Danielides V, Katotomichelakis M, Kakolyris S. Hyposmia: an underestimated and frequent adverse effect of chemotherapy. *Support Care Cancer* 2015;23:3053–8. doi:10.1007/s00520-015-2675-z.
- [7] Gamper E-M, Giesinger JM, Oberguggenberger A, Kemmler G, Wintner LM, Gattringer K, et al. Taste alterations in breast and gynaecological cancer patients receiving chemotherapy: prevalence, course of severity, and quality of life correlates. *Acta Oncol Stockh Swed* 2012;51:490–6. doi:10.3109/0284186X.2011.633554.
- [8] Turcott JG, Juárez-Hernández E, De la Torre-Vallejo M, Sánchez-Lara K, Luvian-Morales J, Arrieta O. Value: Changes in the Detection and Recognition Thresholds of Three Basic Tastes in Lung Cancer Patients Receiving Cisplatin and Paclitaxel and Its Association with Nutritional and Quality of Life Parameters. *Nutr Cancer* 2016;68:241–9. doi:10.1080/01635581.2016.1144075.
- [9] Brisbois TD, de Kock IH, Watanabe SM, Baracos VE, Wismer WV. Characterization of chemosensory alterations in advanced cancer reveals specific chemosensory phenotypes impacting dietary intake and quality of life. *J Pain Symptom Manage* 2011;41:673–83. doi:10.1016/j.jpainsymman.2010.06.022.
- [10] Sánchez-Lara K, Sosa-Sánchez R, Green-Renner D, Rodríguez C, Laviano A, Motola-Kuba D, et al. Influence of taste disorders on dietary behaviors in cancer patients under chemotherapy. *Nutr J* 2010;9:15. doi:10.1186/1475-2891-9-15.
- [11] Knowles M, Selby P. *Introduction to the Cellular and Molecular Biology of Cancer*. OUP Oxford; 2005.
- [12] Botchkarev VA. Molecular Mechanisms of Chemotherapy-Induced Hair Loss. *J Invest Dermatol Symp Proc* 2003;8:72–5. doi:10.1046/j.1523-1747.2003.12175.x.
- [13] Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *JNCI J Natl Cancer Inst* 1999;91:1616–34. doi:10.1093/jnci/91.19.1616.
- [14] Roland S, Rémi G. *Odorat et goût: De la neurobiologie des sens chimiques aux applications*. Editions Quae; 2013.
- [15] Yakirevitch A, Talmi YP, Baram Y, Weitzen R, Pfeffer MR. Effects of cisplatin on olfactory function in cancer patients. *Br J Cancer* 2005;92:1611–3. doi:10.1038/sj.bjc.6602544.
- [16] Steinbach S, Hundt W, Schmalfeldt B, Böhner C, Berkold S, Wolf P, et al. Effect of platinum-containing chemotherapy on olfactory, gustatory, and hearing function in

- ovarian cancer patients. *Arch Gynecol Obstet* 2012;286:473–80. doi:10.1007/s00404-012-2307-5.
- [17] Barlow LA, Klein OD. Developing and regenerating a sense of taste. *Curr Top Dev Biol* 2015;111:401–19. doi:10.1016/bs.ctdb.2014.11.012.
- [18] Steinbach S, Hundt W, Zahnert T, Berkold S, Böhner C, Gottschalk N, et al. Gustatory and olfactory function in breast cancer patients. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2010;18:707–13. doi:10.1007/s00520-009-0672-9.
- [19] Joussain P, Giboreau A, Fontas M, Laville M, Hummel T, Souquet PJ, et al. Cisplatin chemotherapy induces odor perception changes in bronchial cancer patients. *Lung Cancer Amst Neth* 2013;82:168–70. doi:10.1016/j.lungcan.2013.06.009.
- [20] Boltong A, Aranda S, Keast R, Wynne R, Francis PA, Chirgwin J, et al. A prospective cohort study of the effects of adjuvant breast cancer chemotherapy on taste function, food liking, appetite and associated nutritional outcomes. *PloS One* 2014;9:e103512. doi:10.1371/journal.pone.0103512.
- [21] Small DM, Prescott J. Odor/taste integration and the perception of flavor. *Exp Brain Res* 2005;166:345–57. doi:10.1007/s00221-005-2376-9.
- [22] Cullen MM, Leopold DA. DISORDERS OF SMELL AND TASTE. *Med Clin North Am* 1999;83:57–74. doi:10.1016/S0025-7125(05)70087-0.
- [23] Spence C. Multisensory flavour perception. *Curr Biol* 2013;23:R365–9. doi:10.1016/j.cub.2013.01.028.
- [24] Nicklaus S, Boggio V, Issanchou S. Les perceptions gustatives chez l'enfant. /data/revues/0929693X/00120005/05000722/ n.d.
- [25] Holmes S. Food avoidance in patients undergoing cancer chemotherapy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 1993;1:326–30.
- [26] Coa KI, Epstein JB, Ettinger D, Jatoi A, McManus K, Platek ME, et al. The impact of cancer treatment on the diets and food preferences of patients receiving outpatient treatment. *Nutr Cancer* 2015;67:339–53. doi:10.1080/01635581.2015.990577.
- [27] Schwartz MD, Jacobsen PB, Bovbjerg DH. Role of nausea in the development of aversions to a beverage paired with chemotherapy treatment in cancer patients. *Physiol Behav* 1996;59:659–63.
- [28] Fontas M, Poulain J-P, Souquet P-J, Laville M, Giboreau A, Bensafi M, et al. Perspective socio-anthropologique de la prise en charge de la dénutrition du malade cancéreux. *Bull Cancer (Paris)* 2014;101:258–65. doi:10.1684/bdc.2014.1905.
- [29] Cohen J, E. Wakefield C, G. Laing D. Smell and Taste Disorders Resulting from Cancer and Chemotherapy. *Curr Pharm Des* 2016;22:2253–63.
- [30] Mardas M, Jamka M, Mądry R, Walkowiak J, Krótkopad M, Stelmach-Mardas M. Dietary habits changes and quality of life in patients undergoing chemotherapy for epithelial ovarian cancer. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2015;23:1015–23. doi:10.1007/s00520-014-2462-2.
- [31] Hutton JL, Baracos VE, Wismer WV. Chemosensory Dysfunction Is a Primary Factor in the Evolution of Declining Nutritional Status and Quality of Life in Patients With Advanced Cancer. *J Pain Symptom Manage* 2007;33:156–65. doi:10.1016/j.jpainsymman.2006.07.017.
- [32] de Vries YC, Boesveldt S, Kampman E, de Graaf C, Winkels RM, van Laarhoven HWM. Low reported taste function is associated with low preference for high protein products in advanced oesophagogastric cancer patients undergoing palliative chemotherapy. *Clin Nutr Edinb Scotl* 2017. doi:10.1016/j.clnu.2017.12.001.
- [33] Comeau TB, Epstein JB, Migas C. Taste and smell dysfunction in patients receiving chemotherapy: a review of current knowledge. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2001;9:575–80.

- [34] Hong JH, Omur-Ozbek P, Stanek BT, Dietrich AM, Duncan SE, Lee YW, et al. Taste and odor abnormalities in cancer patients. *J Support Oncol* 2009;7:58–65.
- [35] Gamper E-M, Zabernigg A, Wintner LM, Giesinger JM, Oberguggenberger A, Kemmler G, et al. Coming to your senses: detecting taste and smell alterations in chemotherapy patients. A systematic review. *J Pain Symptom Manage* 2012;44:880–95. doi:10.1016/j.jpainsymman.2011.11.011.
- [36] Epstein JB, Hong C, Logan RM, Barasch A, Gordon SM, Oberle-Edwards L, et al. A systematic review of orofacial pain in patients receiving cancer therapy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2010;18:1023–31. doi:10.1007/s00520-010-0897-7.
- [37] Hovan AJ, Williams PM, Stevenson-Moore P, Wahlin YB, Ohrn KEO, Elting LS, et al. A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer* 2010;18:1081–7. doi:10.1007/s00520-010-0902-1.
- [38] Thorne T, Olson K, Wismer W. A state-of-the-art review of the management and treatment of taste and smell alterations in adult oncology patients. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2015;23:2843–51. doi:10.1007/s00520-015-2827-1.
- [39] Ijpma I, Renken RJ, Ter Horst GJ, Reyners AKL. Metallic taste in cancer patients treated with chemotherapy. *Cancer Treat Rev* 2015;41:179–86. doi:10.1016/j.ctrv.2014.11.006.
- [40] Boltong A, Keast R. The influence of chemotherapy on taste perception and food hedonics: a systematic review. *Cancer Treat Rev* 2012;38:152–63. doi:10.1016/j.ctrv.2011.04.008.
- [41] Altundag A, Cayonu M. Chemical Senses in Cancer Patients. *Curr Pharm Des* 2016;22:2264–9.
- [42] Ravasco P. Aspects of taste and compliance in patients with cancer. *Eur J Oncol Nurs Off J Eur Oncol Nurs Soc* 2005;9 Suppl 2:S84–91. doi:10.1016/j.ejon.2005.09.003.
- [43] Wismer WV. Assessing alterations in taste and their impact on cancer care. *Curr Opin Support Palliat Care* 2008;2:282–7. doi:10.1097/SPC.0b013e32831a6eb3.
- [44] van der Werf A, Rovithi M, Langius JAE, de van der Schueren MAE, Verheul HMW. Insight in taste alterations during treatment with protein kinase inhibitors. *Eur J Cancer* 2017;86:125–34. doi:10.1016/j.ejca.2017.09.006.
- [45] Kirk-Smith MD, Booth DA. Chemoreception in human behaviour: experimental analysis of the social effects of fragrances. *Chem Senses* 1987;12:159–66. doi:10.1093/chemse/12.1.159.
- [46] Epstein JB, Smutzer G, Doty RL. Understanding the impact of taste changes in oncology care. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2016;24:1917–31. doi:10.1007/s00520-016-3083-8.
- [47] Sugita M. Taste perception and coding in the periphery. *Cell Mol Life Sci CMLS* 2006;63:2000–15. doi:10.1007/s00018-006-6100-0.
- [48] Breslin PAS, Spector AC. Mammalian taste perception. *Curr Biol* 2008;18:R148–55. doi:10.1016/j.cub.2007.12.017.
- [49] Heck GL, Mierson S, DeSimone JA. Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. *Science* 1984;223:403–5.
- [50] Liu D, Archer N, Duesing K, Hannan G, Keast R. Mechanism of fat taste perception: Association with diet and obesity. *Prog Lipid Res* 2016;63:41–9. doi:10.1016/j.plipres.2016.03.002.
- [51] Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. Mammalian sweet taste receptors. *Cell* 2001;106:381–90.

- [52] Proctor GB. The physiology of salivary secretion. *Periodontol* 2000 2016;70:11–25. doi:10.1111/prd.12116.
- [53] Mandel ID. The functions of saliva. *J Dent Res* 1987;66 Spec No:623–7. doi:10.1177/00220345870660S203.
- [54] Salivary secretion, taste and hyposalivation - MESE - 2007 - Journal of Oral Rehabilitation - Wiley Online Library n.d. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2842.2007.01794.x/full> (accessed November 28, 2017).
- [55] Bushdid C, Magnasco MO, Vosshall LB, Keller A. Humans can Discriminate more than one Trillion Olfactory Stimuli. *Science* 2014;343:1370–2. doi:10.1126/science.1249168.
- [56] McEwen DP, Jenkins PM, Martens JR. Olfactory cilia: our direct neuronal connection to the external world. *Curr Top Dev Biol* 2008;85:333–70. doi:10.1016/S0070-2153(08)00812-0.
- [57] Nagashima A, Touhara K. Enzymatic conversion of odorants in nasal mucus affects olfactory glomerular activation patterns and odor perception. *J Neurosci Off J Soc Neurosci* 2010;30:16391–8. doi:10.1523/JNEUROSCI.2527-10.2010.
- [58] Masaoka Y, Satoh H, Akai L, Homma I. Expiration: the moment we experience retronasal olfaction in flavor. *Neurosci Lett* 2010;473:92–6. doi:10.1016/j.neulet.2010.02.024.
- [59] Landis BN, Frasnelli J, Reden J, Lacroix JS, Hummel T. Differences Between Orthonasal and Retronasal Olfactory Functions in Patients With Loss of the Sense of Smell. *Arch Otolaryngol Neck Surg* 2005;131:977–81. doi:10.1001/archotol.131.11.977.
- [60] Önerci TM. Nasal Physiology and Pathophysiology of Nasal Disorders. Springer Science & Business Media; 2013.
- [61] Zald DH, Pardo JV. Emotion, olfaction, and the human amygdala: Amygdala activation during aversive olfactory stimulation. *Proc Natl Acad Sci* 1997;94:4119–24. doi:10.1073/pnas.94.8.4119.
- [62] Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A-S, McNamara JO, et al. Trigeminal Chemoreception 2001.
- [63] Schaefer ML, Böttger B, Silver WL, Finger TE. Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. *J Comp Neurol* 2002;444:221–6. doi:10.1002/cne.10143.
- [64] Bensafi M, Iannilli E, Gerber J, Hummel T. Neural coding of stimulus concentration in the human olfactory and intranasal trigeminal systems. *Neuroscience* 2008;154:832–8. doi:10.1016/j.neuroscience.2008.03.079.
- [65] Iannilli E, Del Gratta C, Gerber JC, Romani GL, Hummel T. Trigeminal activation using chemical, electrical, and mechanical stimuli. *Pain* 2008;139:376–88. doi:10.1016/j.pain.2008.05.007.
- [66] Tepper BJ, Choi Y-S, Nayga RM. Understanding food choice in adult men: Influence of nutrition knowledge, food beliefs and dietary restraint. *Food Qual Prefer* 1997;8:307–17. doi:10.1016/S0950-3293(97)00014-1.
- [67] Food Behaviours - Report n.d. <https://www.safefood.eu/Publications/Research-reports/Food-Behaviours.aspx> (accessed January 21, 2019).
- [68] LaCaille L. Eating Behavior. In: Gellman MD, Turner JR, editors. *Encycl. Behav. Med.*, New York, NY: Springer New York; 2013, p. 641–2. doi:10.1007/978-1-4419-1005-9_1613.

- [69] Luquet S. Régulation de la prise alimentaire. *Nutr Clin Métabolisme* 2008;22:52–8. doi:10.1016/j.nupar.2008.04.011.
- [70] Levine AS, Billington CJ. Why Do We Eat? A Neural Systems Approach. *Annu Rev Nutr* 1997;17:597–619. doi:10.1146/annurev.nutr.17.1.597.
- [71] Berthoud H-R. Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. *Obes Silver Spring Md* 2006;14 Suppl 5:197S–200S. doi:10.1038/oby.2006.308.
- [72] Fromentin G, Darcel N, Chaumontet C, Marsset-Baglieri A, Nadkarni N, Tomé D. Peripheral and central mechanisms involved in the control of food intake by dietary amino acids and proteins. *Nutr Res Rev* 2012;25:29–39. doi:10.1017/S0954422411000175.
- [73] Sanger GJ, Hellström PM, Näslund E. The Hungry Stomach: Physiology, Disease, and Drug Development Opportunities. *Front Pharmacol* 2011;1. doi:10.3389/fphar.2010.00145.
- [74] Amin T, Mercer JG. Hunger and Satiety Mechanisms and Their Potential Exploitation in the Regulation of Food Intake. *Curr Obes Rep* 2016;5:106–12. doi:10.1007/s13679-015-0184-5.
- [75] Blundell J, Graaf CD, Hulshof T, Jebb S, Livingstone B, Lluch A, et al. Appetite control: methodological aspects of the evaluation of foods. *Obes Rev* 2010;11:251–70. doi:10.1111/j.1467-789X.2010.00714.x.
- [76] Lutter M, Nestler EJ. Homeostatic and Hedonic Signals Interact in the Regulation of Food Intake. *J Nutr* 2009;139:629–32. doi:10.3945/jn.108.097618.
- [77] Hurling R, Shepherd R. Eating with your eyes: effect of appearance on expectations of liking. *Appetite* 2003;41:167–74. doi:10.1016/S0195-6663(03)00058-8.
- [78] Sørensen LB, Møller P, Flint A, Martens M, Raben A. Effect of sensory perception of foods on appetite and food intake: a review of studies on humans. *Int J Obes* 2003;27:1152–66. doi:10.1038/sj.ijo.0802391.
- [79] Hetherington MM. Sensory-specific satiety and its importance in meal termination. *Neurosci Biobehav Rev* 1996;20:113–7.
- [80] Rolls BJ. Sensory-specific satiety. *Nutr Rev* 1986;44:93–101.
- [81] Brondel L, Romer M, Van Wymelbeke V, Pineau N, Jiang T, Hanus C, et al. Variety enhances food intake in humans: role of sensory-specific satiety. *Physiol Behav* 2009;97:44–51. doi:10.1016/j.physbeh.2009.01.019.
- [82] Rolls BJ, Rowe EA, Rolls ET. How sensory properties of foods affect human feeding behavior. *Physiol Behav* 1982;29:409–17.
- [83] Ramaekers MG, Boesveldt S, Lakemond CMM, van Boekel MAJS, Luning PA. Odors: appetizing or satiating? Development of appetite during odor exposure over time. *Int J Obes* 2014;38:650–6. doi:10.1038/ijo.2013.143.
- [84] Gaillet M, Sulmont-Rossé C, Issanchou S, Chabanet C, Chambaron S. Priming effects of an olfactory food cue on subsequent food-related behaviour. *Food Qual Prefer* 2013;30:274–81. doi:10.1016/j.foodqual.2013.06.008.
- [85] Ijpma I, Renken RJ, Gietema JA, Slart RHJA, Mensink MGJ, Lefrandt JD, et al. Changes in taste and smell function, dietary intake, food preference, and body composition in testicular cancer patients treated with cisplatin-based chemotherapy. *Clin Nutr Edinb Scotl* 2016. doi:10.1016/j.clnu.2016.10.013.
- [86] Spotten LE, Corish CA, Lorton CM, Ui Dhuibhir PM, O'Donoghue NC, O'Connor B, et al. Subjective and objective taste and smell changes in cancer. *Ann Oncol Off J Eur Soc Med Oncol* 2017;28:969–84. doi:10.1093/annonc/mdx018.
- [87] Marinho E da C, Custódio IDD, Ferreira IB, Crispim CA, Paiva CE, Maia YC de P. Impact of chemotherapy on perceptions related to food intake in women with breast

- cancer: A prospective study. PLOS ONE 2017;12:e0187573. doi:10.1371/journal.pone.0187573.
- [88] McGreevy J, Orrevall Y, Belqaid K, Wismer W, Tishelman C, Bernhardson B-M. Characteristics of taste and smell alterations reported by patients after starting treatment for lung cancer. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2014;22:2635–44. doi:10.1007/s00520-014-2215-2.
- [89] Belqaid K, Tishelman C, McGreevy J, Månsson-Brahme E, Orrevall Y, Wismer W, et al. A longitudinal study of changing characteristics of self-reported taste and smell alterations in patients treated for lung cancer. *Eur J Oncol Nurs* 2016;21:232–41. doi:10.1016/j.ejon.2015.10.009.
- [90] Ovesen L, Hannibal J, Sørensen M, Allingstrup L. Food intake, eating-related complaints, and smell and taste sensations in patients with cancer of the lung, ovary and breast undergoing chemotherapy. *Clin Nutr Edinb Scotl* 1991;10:336–41.
- [91] de Vries YC, Winkels RM, van den Berg MMGA, de Graaf C, Kelfkens CS, de Kruif JTCM, et al. Altered food preferences and chemosensory perception during chemotherapy in breast cancer patients: A longitudinal comparison with healthy controls. *Food Qual Prefer* 2018;63:135–43. doi:10.1016/j.foodqual.2017.09.003.
- [92] de Vries YC, van den Berg MMGA, de Vries JHM, Boesveldt S, de Kruif JTCM, Buist N, et al. Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2017;25:2581–91. doi:10.1007/s00520-017-3668-x.
- [93] Sánchez-Lara K, Sosa-Sánchez R, Green-Renner D, Rodríguez C, Laviano A, Motola-Kuba D, et al. Influence of taste disorders on dietary behaviors in cancer patients under chemotherapy. *Nutr J* 2010;9:15. doi:10.1186/1475-2891-9-15.
- [94] de Vries YC, Winkels RM, van den Berg MMGA, de Graaf C, Kelfkens CS, de Kruif JTCM, et al. Altered food preferences and chemosensory perception during chemotherapy in breast cancer patients: A longitudinal comparison with healthy controls. *Food Qual Prefer* 2018;63:135–43. doi:10.1016/j.foodqual.2017.09.003.
- [95] Berteretche MV, Dalix AM, d’Ornano AMC, Bellisle F, Khayat D, Faurion A. Decreased taste sensitivity in cancer patients under chemotherapy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2004;12:571–6. doi:10.1007/s00520-004-0589-2.
- [96] Bernhardson B-M, Tishelman C, Rutqvist LE. Self-reported taste and smell changes during cancer chemotherapy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2008;16:275–83. doi:10.1007/s00520-007-0319-7.
- [97] Steinbach S, Hummel T, Böhner C, Berktdorf S, Hundt W, Kriner M, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. *J Clin Oncol Off J Am Soc Clin Oncol* 2009;27:1899–905. doi:10.1200/JCO.2008.19.2690.
- [98] Riga M, Chelis L, Papazi T, Danielides V, Katotomichelakis M, Kakolyris S. Hyposmia: an underestimated and frequent adverse effect of chemotherapy. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 2015;23:3053–8. doi:10.1007/s00520-015-2675-z.
- [99] Walliczek-Dworschak U, Gudziol V, Mitzschke C, Froehner M, Hummel T. Testicular cancer patients undergoing cisplatin based chemotherapy exhibit temporary olfactory threshold scores changes. *Eur Arch Otorhinolaryngol* 2017;274:2813–8. doi:10.1007/s00405-017-4559-y.
- [100] Bossola M, Cadoni G, Bellantone R, Carriero C, Carriero E, Ottaviani F, et al. Taste intensity and hedonic responses to simple beverages in gastrointestinal cancer patients. *J Pain Symptom Manage* 2007;34:505–12. doi:10.1016/j.jpainsymman.2006.12.013.

- [101] Bernhardson B-M, Tishelman C, Rutqvist LE. Olfactory changes among patients receiving chemotherapy. *Eur J Oncol Nurs Off J Eur Oncol Nurs Soc* 2009;13:9–15. doi:10.1016/j.ejon.2008.10.002.
- [102] Zabernigg A, Gamper E-M, Giesinger JM, Rumpold G, Kemmler G, Gattringer K, et al. Taste alterations in cancer patients receiving chemotherapy: a neglected side effect? *The Oncologist* 2010;15:913–20. doi:10.1634/theoncologist.2009-0333.
- [103] Miller IJ, Reedy FE. Variations in human taste bud density and taste intensity perception. *Physiol Behav* 1990;47:1213–9. doi:10.1016/0031-9384(90)90374-D.
- [104] Kim UK, Drayna D. Genetics of individual differences in bitter taste perception: lessons from the PTC gene. *Clin Genet* 2005;67:275–80. doi:10.1111/j.1399-0004.2004.00361.x.
- [105] Bufo B, Breslin PAS, Kuhn C, Reed DR, Tharp CD, Slack JP, et al. The Molecular Basis of Individual Differences in Phenylthiocarbamide and Propylthiouracil Bitterness Perception. *Curr Biol* 2005;15:322–7. doi:10.1016/j.cub.2005.01.047.
- [106] Mennella JA, Pepino MY, Reed DR. Genetic and Environmental Determinants of Bitter Perception and Sweet Preferences. *Pediatrics* 2005;115:e216–22. doi:10.1542/peds.2004-1582.
- [107] DeWys WD, Walters K. Abnormalities of taste sensation in cancer patients. *Cancer* 1975;36:1888–96.
- [108] Shigemura N, Shirosaki S, Sanematsu K, Yoshida R, Ninomiya Y. Genetic and Molecular Basis of Individual Differences in Human Umami Taste Perception. *PLOS ONE* 2009;4:e6717. doi:10.1371/journal.pone.0006717.
- [109] Mirlohi S, Duncan SE, Harmon M, Case D, Lesser G, Dietrich AM. Analysis of salivary fluid and chemosensory functions in patients treated for primary malignant brain tumors. *Clin Oral Investig* 2015;19:127–37. doi:10.1007/s00784-014-1211-8.
- [110] Munoz C, Feron G, Canon F. Inter-individual differences in human saliva composition affect the partition of food and beverages aroma compounds. 4 Int. Conf. Food Oral Process. - “Food Oral Process. Life Interplay Food Struct. Sens. Pleas. Nutr. Needs,” Lausanne, Switzerland: 2016, p. np.
- [111] Neyraud E, Palicki O, Schwartz C, Nicklaus S, Feron G. Variability of human saliva composition: Possible relationships with fat perception and liking. *Arch Oral Biol* 2012;57:556–66. doi:10.1016/j.archoralbio.2011.09.016.
- [112] Keller A, Zhuang H, Chi Q, Vossell LB, Matsunami H. Genetic variation in a human odorant receptor alters odour perception. *Nature* 2007;449:468–72. doi:10.1038/nature06162.
- [113] Flaherty TJ, Lim J. Individual Differences in Retronasal Odor Responsiveness: Effects of Aging and Concurrent Taste. *Chemosens Percept* 2017;10:91–103. doi:10.1007/s12078-016-9206-2.
- [114] Hasin-Brumshtein Y, Lancet D, Olender T. Human olfaction: from genomic variation to phenotypic diversity. *Trends Genet* 2009;25:178–84. doi:10.1016/j.tig.2009.02.002.
- [115] Koelega HS, Köster EP. Some Experiments on Sex Differences in Odor Perception. *Ann N Y Acad Sci* 1974;237:234–46. doi:10.1111/j.1749-6632.1974.tb49859.x.
- [116] Doty RL, Kamath V. The influences of age on olfaction: a review. *Front Psychol* 2014;5. doi:10.3389/fpsyg.2014.00020.
- [117] Sergi G, Bano G, Pizzato S, Veronese N, Manzato E. Taste loss in the elderly: Possible implications for dietary habits. *Crit Rev Food Sci Nutr* 2017;57:3684–9. doi:10.1080/10408398.2016.1160208.
- [118] Hernández-Avila M, Romieu I, Parra S, Hernández-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. *Salud Publica Mex* 1998;40:133–40.

- [119] de Vries YC, van den Berg MMGA, de Vries JHM, Boesveldt S, de Kruif JTCM, Buist N, et al. Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. *Support Care Cancer* 2017;25:2581–91. doi:10.1007/s00520-017-3668-x.
- [120] Heald AE, Pieper CF, Schiffman SS. Taste and smell complaints in HIV-infected patients. *AIDS Lond Engl* 1998;12:1667–74.
- [121] Marinho E da C, Custódio IDD, Ferreira IB, Crispim CA, Paiva CE, Maia YC de P. Impact of chemotherapy on perceptions related to food intake in women with breast cancer: A prospective study. *PLOS ONE* 2017;12:e0187573. doi:10.1371/journal.pone.0187573.
- [122] Joussain P, Bessy M, Fournel A, Ferdenzi C, Rouby C, Delphin-Combe F, et al. Altered Affective Evaluations of Smells in Alzheimer’s Disease. *J Alzheimers Dis* 2016;49:433–41. doi:10.3233/JAD-150332.
- [123] Pouyet V, Cuvelier G, Benattar L, Giboreau A. Influence of flavour enhancement on food liking and consumption in older adults with poor, moderate or high cognitive status. *Food Qual Prefer* 2015;44:119–29. doi:10.1016/j.foodqual.2015.04.014.
- [124] Joussain P, Ferdenzi C, Djordjevic J, Bensafi M. Relationship Between Psychophysiological Responses to Aversive Odors and Nutritional Status During Normal Aging. *Chem Senses* 2017;42:465–72. doi:10.1093/chemse/bjx027.
- [125] Luisier A-C, Petitpierre G, Ferdenzi C, Clerc Béro d A, Giboreau A, Rouby C, et al. Odor Perception in Children with Autism Spectrum Disorder and its Relationship to Food Neophobia. *Front Psychol* 2015;6. doi:10.3389/fpsyg.2015.01830.
- [126] Manesse C, Ferdenzi C, Sabri M, Bessy M, Rouby C, Faure F, et al. Dysosmia-Associated Changes in Eating Behavior. *Chemosens Percept* 2017;10:104–13. doi:10.1007/s12078-017-9237-3.
- [127] Belqaid K, Tishelman C, McGreevy J, Månsson-Brahme E, Orrevall Y, Wismer W, et al. A longitudinal study of changing characteristics of self-reported taste and smell alterations in patients treated for lung cancer. *Eur J Oncol Nurs* 2016;21:232–41. doi:10.1016/j.ejon.2015.10.009.
- [128] Amoore JE, Ollman BG. Practical test kits for quantitatively evaluating the sense of smell. *Rhinology* 1983;21:49–54.
- [129] Trant AS, Serin J, Douglass HO. Is taste related to anorexia in cancer patients? *Am J Clin Nutr* 1982;36:45–58.
- [130] Mathey MF. Assessing appetite in Dutch elderly with the Appetite, Hunger and Sensory Perception (AHSP) questionnaire. *J Nutr Health Aging* 2001;5:22–8.
- [131] Ribaud JM, Cella D, Hahn EA, Lloyd SR, Tchekmedyian NS, Von Roenn J, et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2000;9:1137–46.
- [132] Fatihah F, Ng BK, Hazwanie H, Norimah AK, Shanita SN, Ruzita AT, et al. Development and validation of a food frequency questionnaire for dietary intake assessment among multi-ethnic primary school-aged children. *Singapore Med J* 2015;56:687–94. doi:10.11622/smedj.2015190.
- [133] Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. *Am J Clin Nutr* 1993;58:489–96. doi:10.1093/ajcn/58.4.489.
- [134] Verkleij-Hagoort AC, de Vries JHM, Stegers MPG, Lindemans J, Ursem NTC, Steegers-Theunissen RPM. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. *Eur J Clin Nutr* 2007;61:610–5. doi:10.1038/sj.ejcn.1602581.

- 953 [135] Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared
954 with actual energy intake to maintain body weight in 516 adults. *Br J Nutr*
955 2011;106:274–81. doi:10.1017/S0007114511000067.
- 956 [136] de Bruijn SEM, de Vries YC, de Graaf C, Boesveldt S, Jager G. The reliability and
957 validity of the Macronutrient and Taste Preference Ranking Task: A new method to
958 measure food preferences. *Food Qual Prefer* 2017;57:32–40.
959 doi:10.1016/j.foodqual.2016.11.003.
- 960 [137] Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global
961 Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin*
962 *Nutr* 2002;56:779–85. doi:10.1038/sj.ejcn.1601412.
- 963 [138] Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. “Sniffin” sticks’: olfactory
964 performance assessed by the combined testing of odor identification, odor
965 discrimination and olfactory threshold. *Chem Senses* 1997;22:39–52.
- 966 [139] Mueller C, Kallert S, Renner B, Stiassny K, Temmel AFP, Hummel T, et al.
967 Quantitative assessment of gustatory function in a clinical context using impregnated
968 “taste strips.” *Rhinology* 2003;41:2–6.

Table 1. Summary of studies assessing chemosensory function (taste and/or smell) and food behavior (appetite/ hunger/ food intake/ body weight/ body composition)

	Reference	Study type	<ul style="list-style-type: none"> • Groups (n) • Mean age • Men (n) • Women (n) 	Cancer histology <ul style="list-style-type: none"> • Chemotherapy (CT) regimen 	Chemosensory assessment and approach	Food behavior measure	Main effects of chemotherapy on gustatory and olfactory perceptions	Main effects of chemotherapy on food behavior	Chemosensory/Food interaction
e r r o r s	Hutton et al., 2007 [31]	Cross sectional	<ul style="list-style-type: none"> • Patients (66) • 65.4 years • Men (30) • Women (36) 	→ All types except digestive and oro-nasal cancers • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	<ul style="list-style-type: none"> • Food intake: 3-day diet diary • Food attitude and changes to food: Targeted interview 	<i>Gustation and Olfaction:</i> • Altered in 86% of the patients	• Not mentioned	<ul style="list-style-type: none"> • Chemosensory complaints score VS. Energy intake: Negative correlation • Chemosensory complaints score VS. Food enjoyment: Negative correlation
	Brisbois et al., 2011 [9]	Cross sectional	<ul style="list-style-type: none"> • Patients (192) • 64.3 years • Men (97) • Women (95) 	→ Lung → Breast → Genitourinary → Gastrointestinal → Neuroendocrine → Skin → Hematologic → Other • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	<ul style="list-style-type: none"> • Food intake: 3-day diet diary 	<i>Gustation and Olfaction:</i> • Altered in 60% of the patients	• Not mentioned	<ul style="list-style-type: none"> • Severity of chemosensory complaints VS. Energy/Protein intake: Negative correlation • Increased olfactory sensitivity VS. Energy intake: Negative correlation
	McGreevy et al., 2014 [88]	Longitudinal study T0 = baseline (before CT) T1=2 m T2=4 m T3=6 m	<ul style="list-style-type: none"> • Patients (89) • 67 years • Men (40) • Women (49) 	→ Lung • CT not specified	<i>Gustatory and olfactory modifications:</i> • Interviews + TSS (subjective)	<ul style="list-style-type: none"> • Food intake: 3-day diet diary + PGSGA 	<i>Gustation and Olfaction:</i> • Altered in 68.5% of the patients (Gender differences)	• Not mentioned	<ul style="list-style-type: none"> • At the time point with the highest TSS score, severity of chemosensory complaints VS. Energy/Protein intake: Negative correlation
	Belqaid et al., 2016 [127]	Longitudinal T0=Baseline T1=30-99 d T2=After 100 d	<ul style="list-style-type: none"> • Patients (52) • 66.8 years • Men (21) • Women (31) 	→ Lung • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	<ul style="list-style-type: none"> • Nutritional status: FAACT + PG-SGA 	<i>Gustation and Olfaction:</i> • Altered in 73% of the patients (Individual differences: weak to strong effects depending on stimuli and individuals)	<ul style="list-style-type: none"> • <i>Food intake/appetite (case reports):</i> Loss of appetite and lower food intake, lower food enjoyment (T2) 	<ul style="list-style-type: none"> • <i>From case reports:</i> Insufficient food intake due to taste changes and loss of appetite (T2)
	Marinho, 2017 [87]	Longitudinal study T0=Baseline T1=Intermediate cycle T2=Last cycle	<ul style="list-style-type: none"> • Patients (55) • 51.5 years • Women (55) 	→ Breast • Docetaxel • Paclitaxel • FAC • CMF	<i>Gustatory modification:</i> • Qs developed for the study (subjective)	<ul style="list-style-type: none"> • Hunger • Food enjoyment • Appetite for food categories: Visual scale developed for the study 	<i>Gustation:</i> • Changes more frequent at T1 (p = 0.044)	<ul style="list-style-type: none"> • <i>Food enjoyment:</i> Decrease in meal enjoyment at T1 (p= 0.021) • <i>Appetite:</i> Increased overall appetite with appetite for salty food (p = 0.0028) 	<ul style="list-style-type: none"> • Taste and food availability are the main determinants of food choice (self-reported by 52.2% of patients at T2)
e r r o r s	Ovesen et	Longitudinal study	• Patients (52)	→ Lung	<i>Gustatory threshold:</i>	• Food intake: 3-	<i>Gustation and Olfaction:</i>	• Food intake: No	• Chemosensory

Section C: Hypo-chemosensation	al., 1991 [90]	T0=Baseline T1=Before 2 nd CT cycle T2=3 w after 3 rd CT cycle	<ul style="list-style-type: none"> • 57 years • Men (16) • Women (36) 	<ul style="list-style-type: none"> • Cisplatin <p>-----</p> <p>→ Ovary</p> <ul style="list-style-type: none"> • Carboplatin or cisplatin <p>-----</p> <p>→ Breast</p> <ul style="list-style-type: none"> • FEC • Epirubicin 	<ul style="list-style-type: none"> • Electrogustometry (objective) <p><i>Olfactory threshold</i></p> <ul style="list-style-type: none"> • Molecule = Pyridine [128] (objective) 	day diet diary	<ul style="list-style-type: none"> • Decreased gustatory threshold for Lung Cancers (Higher sensitivity) • Unchaged olfactory threshold 	effect	thresholds (T2) VS. Energy/Protein intake (T2): No relationship
	De Vries, 2017 [32]	Longitudinal study T0=Baseline T1=After 2 cycles	<ul style="list-style-type: none"> • Patients (15) • 61 years • Men (14) • Women (1) 	<p>→ Esophagogastric</p> <ul style="list-style-type: none"> • Capecitabine + oxaliplatin 	<p><i>Gustatory and olfactory functions:</i></p> <ul style="list-style-type: none"> • AHSP (subjective) • Sniffin' sticks (objective) • Taste strips (objective) 	<ul style="list-style-type: none"> • Appetite and hunger: AHSP • Food preferences: MTPRT 	<p><i>Gustation:</i> No effect</p> <p><i>Olfaction:</i> No effect</p>	<ul style="list-style-type: none"> • <i>Food preferences:</i> No effect 	<ul style="list-style-type: none"> • Lower self-reported taste perception VS. lower preference for high-protein products: Positive correlation at all time-points
	Lara-Sanchez et al., 2010 [10]	Cross sectional T=Cycle 2	<ul style="list-style-type: none"> • Patients (30) • 56 years • Men (16) • Women (14) <p>-----</p> <ul style="list-style-type: none"> • Controls (30) • 49.4 years • Men (12) • Women (18) 	<p>→ Breast</p> <p>→ Lung</p> <p>→ Prostate</p> <p>→ Multiple myeloma Lymphoma</p> <ul style="list-style-type: none"> • CT not specified 	<p><i>Gustatory function:</i></p> <ul style="list-style-type: none"> • Qs developed for the study (subjective) • RMT (objective) 	<ul style="list-style-type: none"> • Appetite: Qs developed for the study • Nutrient intake: SNUT program 	<p><i>Gustation:</i></p> <ul style="list-style-type: none"> • Increased complaints in patients with cancer (vs controls; (p-values from 0.04 to 0.05)) • Decreased ability to identify bitter taste (compared to controls) 	<ul style="list-style-type: none"> • Food intake: No effect 	<ul style="list-style-type: none"> • Sweet threshold / Bitter recognition (Cycle 2) VS. Energy intake (Cycle 2): Negative correlation
	Boltong et al., 2014 [20]	Longitudinal study T0=Baseline T1=Early 3 rd cycle T2=Middle 3 rd cycle T3=Late 3 rd cycle T4=Early final cycle T5=8wks after CT completion	<ul style="list-style-type: none"> • Patients (52) • 50.4 years • Women (52) 	<p>→ Breast</p> <ul style="list-style-type: none"> • Anthracycline and /or taxane 	<p><i>Gustatory function:</i></p> <ul style="list-style-type: none"> • ISO 3972:2011 (objective) 	<ul style="list-style-type: none"> • Energy and macronutrients intake: 24 h dietary recall • Food liking score and Appetite: Qs developed for the study 	<p><i>Gustation:</i></p> <ul style="list-style-type: none"> • Decreased ability to identify tastes (salty at T2 and T4, sour at T4, umami at T1) • Decreased sweet liking at T1/T2/T4 (p-value: 0.002) 	<ul style="list-style-type: none"> • <i>Food intake/appetite:</i> Decreased appetite at T1 (p<0.0005) 	<ul style="list-style-type: none"> • Changes in taste function (T1)VS. Food intake and appetite (T1): Positive correlation
	Ijma et al., 2016 [85]	Longitudinal T0=Baseline T1=During 1 st cycle T2=Before 2 nd cycle T3A=During 2 nd cycle T3B=End 2 nd cycle T4=Completion CT T5=7 m after CT start T6=1 year after CT start	<ul style="list-style-type: none"> • Patients (21) • 32 years • Men (21) <p>-----</p> <ul style="list-style-type: none"> • Controls (48) • 32 years 	<p>→ Testicular</p> <ul style="list-style-type: none"> • Cisplatin 	<p><i>Gustatory function:</i></p> <ul style="list-style-type: none"> • AHSP (subjective) • Taste strips (objective) <p><i>Olfactory function:</i></p> <ul style="list-style-type: none"> • AHSP (subjective) • Sniffin' sticks (objective) 	<ul style="list-style-type: none"> • Food intake: FFQ • Food preference: Visual task developed for the study • Body composition: DEXA 	<p><i>Gustation and Olfaction:</i></p> <ul style="list-style-type: none"> • Transient Decrease of subjective taste (p=0.002), smell (p=0.04), appetite (p=0.002), and hunger feelings (p= 0.003) at T1 • Increased salt threshold at T4 • No effect on objective olfaction 	<ul style="list-style-type: none"> • <i>Food intake:</i> No effect • <i>Food preference:</i> No effect • <i>Body composition:</i> Decreased lean mass and bone density, increased fat mass 	<ul style="list-style-type: none"> • Not mentioned
	De Vries, 2017	Case-control Time point of	<ul style="list-style-type: none"> • Patients (117) • 51 years 	<p>→ Breast</p> <ul style="list-style-type: none"> • Taxanes 	<p><i>Gustatory and olfactory functions:</i></p>	<ul style="list-style-type: none"> • Habitual intake before CT: 	<p><i>Gustation and Olfaction:</i></p> <ul style="list-style-type: none"> • Lower self-reported 	<ul style="list-style-type: none"> • <i>Appetite:</i> Lower self-reported 	<ul style="list-style-type: none"> • Self-reported taste perception ability VS.

	[92]	assessment= random days during the full cycle of CT	<ul style="list-style-type: none"> • Women (117) ----- • Controls (88) • 53.5 years 	<ul style="list-style-type: none"> • Anthracyclines • Taxanes + anthracyclines 	•AHSP (subjective)	FFQ •Food intake: 2 24h dietary recalls during the overall CT	taste, smell in comparison with the controls:	appetite and hunger in patients. • <i>Food intake</i> : Patients had a lower energy intake and lower appetite during CT (not before)	Energy intake: Positive correlation •Self-reported smell perception ability VS. Energy intake: No correlation
	De Vries, 2018 [91]	Longitudinal T1=Baseline T2=During CT T3=1-3 wks > CT T4=6m after the end of CT	<ul style="list-style-type: none"> • Patients (28) • 51 years • Women (28) ----- • Controls (28) • 51.8 years 	→ Breast <ul style="list-style-type: none"> • Taxanes • Anthracyclines + taxanes • Platinum-containing 	<i>Gustatory and olfactory function</i> : <ul style="list-style-type: none"> • Qs developed for the study (subjective) • Sniffin' Sticks (objective) • Taste strips (objective) 	<ul style="list-style-type: none"> • Food preferences: MTPRT • Taste preference: Preference task [100,129] 	<i>Gustation</i> : <ul style="list-style-type: none"> • Decreased self-reported and objective gustation <i>Olfaction</i> : <ul style="list-style-type: none"> • Decreased self-reported and objective olfaction (lower sensitivity) 	<ul style="list-style-type: none"> • <i>Food preferences</i>: Decreased liking for high fat and high protein products at T2. Higher liking for savory food at T0 and T3 	<ul style="list-style-type: none"> • Self-reported taste perception ability VS. Preference for high-protein food, low energy food, savory food, sweet food: Positive correlation • Self-reported smell perception ability VS. Preference for low energy food and sweet food: Positive correlation at all time-points
Section D: Hyper-chemosensation	Turcott, 2016 [8]	Longitudinal study T0= Baseline T1= After 2 cycles	<ul style="list-style-type: none"> • Patients (40) • 55.5 years • Men (20) • Women (20) 	→ Lung <ul style="list-style-type: none"> • Paclitaxel + cisplatin 	<i>Gustatory function</i> : <ul style="list-style-type: none"> • RMT (objective) 	<ul style="list-style-type: none"> • Body weight • Food intake: SNUT program • Nutritional impairment: PGSGA • FFACT • Body composition: Bioelectric impedance analysis 	<i>Gustation</i> : <ul style="list-style-type: none"> • Higher sensitivity to bitter and umami tastes (p=0.02). 	<ul style="list-style-type: none"> • <i>Food intake</i>: Not mentioned • <i>Body weight</i>: Loss of weight at T1 (p=0.001) • <i>Body composition</i>: No effect • <i>Nutritional impairment</i>: No effect 	<ul style="list-style-type: none"> • Increase of sweet detection threshold (T1) VS. Decrease of protein intake (T1): Positive correlation (p=0.01)

AHSP: Appetite Hunger and Sensory Perception (a self-report questionnaire that measures appetite, hunger and perception including taste and smell functions, [130]); **CMF,** cyclophosphamide + methotrexate + 5-fluorouracil; **CT:** Chemotherapy, d: day(s), **DEXA:** Dual Energy X-ray Absorptimetry (objective measure of body composition); **FAACT:** Functional Assessment of Anorexia Cachexia Therapy Questionnaire (an anorexia and cachexia assessment questionnaire [131]); **FAC,** 5-fluorouracil + adriamycin + cyclophosphamide; **FEC,** 5-luorouracil + yclophosphamide + epirubicin; **FFQ:** Food Frequency Questionnaire (questionnaire for dietary intake assessment, [132–135]; **ISO 3972:2011:** International Standards Organization 3972:2011 (a standardized sensory analysis-methodology-method of investigating sensitivity of taste), m: month(s), **MTPRT:** Macronutrient and Taste Preferences Ranking Task (a computer-based preference task with food pictures[136]); **NS:** Not Specified; **PGSGA:** Patient Generated Subjective Global Assessment (questionnaire for assessing nutritional status in patients with cancer [137]); **RMT:** Rinsing Mouth Test (a test that measures gustatory threshold based on aqueous solutions); **Sniffin' Sticks:** (a pen-based test that measures olfactory function, [138]); **SNUT program:** Nutritional Assessment System Habits and Nutrient Intake (a software that calculates the daily intake of calories, macronutrients and micronutrients, [118]); **TSS:** Taste and Smell Survey (a self-report questionnaire on Taste and Smell, [120]); **Taste strips:** a paper-based test that measures gustatory function, [139]; **wks:** week(s)

Table 2. Physiological factors that can modulate smell and taste profiles

Factors	Modulation of smell and taste perception
Genetic variation in gustation	Genetic variations in the expression of gustatory receptors lead to individual differences in both bitterness perception [104–106] umami perception [108]
Genetic variation in olfaction	Genetic variations in the expression of olfactory receptors lead to differences in odor perception [112]
Density of fungiform papillae	High density of fungiform papillae is associated to a higher number of taste buds, and so a higher number of taste receptors, resulting in a higher taste intensity perception [103]
Saliva	Flow and composition of saliva influence chemosensory perception [109–111]
Oral physiology	Differences in human oral physiology and food oral processing can determine the amount of released aroma in the nasal cavity [113, 114]
Gender	Women exhibit a higher sweetness/bitterness perception than men [88, 115]
Age	Young individuals show less taste and/or smell impairments than older individuals [97, 116, 117]