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Kenza Drareni

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Kenza Drareni

Taste and Cancer **Satisfy the senses to maintain food enjoyment during** **chemotherapy**

Devant le jury composé de :

Dr. Thierry THOMAS-DANGUIN
Dr. Annemarie OLSEN
Dr. Amandine BRUYAS
Pr. Anne DIDIER
Dr. Moustafa BENSAFI
Dr. Anestis DOUGKAS
Dr. Agnès GIBOREAU

Directeur de recherche
Assistante professeur
Médecin oncologue
Professeur des universités
Directeur de recherche
Chargé de recherche
Directrice de recherche

Rapporteur
Rapporteuse
Examinatrice
Examinatrice
Directeur de thèse
Co-directeur de thèse
Co-directrice de thèse

Université Claude Bernard – LYON 1

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Institut des Sciences et Techniques de la Réadaptation	Directeur : M. Xavier PERROT
Département de Formation et Centre de Recherche en Biologie Humaine	Directrice : Mme Anne-Marie SCHOTT

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ESPE	Administrateur Provisoire : M. Pierre CHAREYRON

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Kenza

Abstract

Maintaining the pleasure of eating during a chemotherapy treatment is a major challenge for patients, their families and hospital catering professionals to avoid malnutrition. However, the sensory alterations frequently observed in patients and expressed differently from one patient to another can interfere with the taste of food and reduce the pleasure resulting from food consumption.

The aim of this work is to contribute to define a model of the effect of chemotherapy during cancer on olfactory and gustatory abilities of patients, and the consequences that this may have on their eating behavior.

The first part of this work focuses on understanding the variability of sensory changes and their consequences on patients' eating behavior. Our results highlighted three main sensory profiles: patients with no sensory impairment, patients with hyposensitivity, and patients with hypersensitivity to olfactory / gustatory stimuli. Patients with impaired olfactory / gustatory abilities expressed also changes in their food behavior.

The classification of patients based on their self-reported sensory abilities highlighted the negative impact of hyposensitivity on food taste perception. The classification based on psychophysical assessment of olfactory abilities showed a change in consumption habits in patients with hyposmia. Both approaches found a general downward trend in perceptual abilities of cancer patients treated with chemotherapy.

In the second part of this work, we examined the effect of food sensory enhancement as a coping strategy to sensory alterations. The results suggest that taste or aroma enhancement increases food liking in patients with decreased olfactory / taste sensitivity, and patients who did not report taste and smell deficits but has no effect on the hedonic rating of food in the group of control subjects.

This work highlights the interindividual diversity existing between patients and confirms the involvement of olfactory / taste alterations in patients' food behavior modification. Our results stresses the importance of personalized nutritional management of patients considering their sensory alteration profile.

Résumé

Le maintien du plaisir à s'alimenter durant un traitement par chimiothérapie est un enjeu majeur pour les patients, leurs familles et les professionnels de la restauration en hôpital afin de lutter contre la dénutrition. Or, les altérations sensorielles fréquemment observées chez les patients et exprimées différemment d'un patient à l'autre peuvent interférer avec le goût des aliments, impactant négativement le plaisir résultant de leur consommation.

L'objectif de ce travail est de contribuer à définir un modèle exhaustif de l'effet de la chimiothérapie pendant le cancer sur les capacités olfactives et gustatives des patients, et des conséquences que cela peut avoir sur leur comportement alimentaire.

Une première partie porte sur la compréhension de la variabilité des modifications sensorielles et de leurs conséquences sur le comportement alimentaire des patients. Nos résultats ont conclu à l'existence de divers profils sensoriels chez les patients sous chimiothérapie : les patients ne présentant pas d'altérations sensorielles, les patients présentant une hyposensibilité, et les patients présentant une hypersensibilité aux stimulations olfactives/gustatives. Les patients ayant des altérations des capacités olfactives/gustatives ont également montré des modifications du comportement alimentaire.

D'une part, la classification des patients sur la base de leurs capacités sensorielles auto-déclarées a mis en évidence l'impact négatif de l'hyposensibilité aux stimulations olfactives et gustatives sur la perception des aliments. D'autre part, une classification basée sur les capacités olfactives évaluées par des tests psychophysiques a montré une modification des habitudes de consommation chez les patients atteints d'hyposmie. Les deux approches ont conclu à une tendance générale à la baisse des capacités perceptives chez les patients atteints de cancer et traités par chimiothérapie.

Une seconde partie plus opérationnelle a permis de tester l'enrichissement sensoriel comme stratégie de palliation des déficits sensoriels. Les résultats suggèrent qu'un enrichissement en saveur ou en arôme augmente l'appréciation de l'aliment pour le groupe de patients ayant reporté une baisse de la sensibilité olfactive/gustative, ainsi que les patients n'ayant pas déclaré avoir de déficits sensoriels mais pas dans le groupe de sujets contrôles.

Ces travaux mettent en évidence la diversité interindividuelle existante entre les patients et confirment l'implication des altérations olfactives/gustatives dans la modification du comportement alimentaire. Nos résultats soulignent l'importance d'une prise en charge nutritionnelle personnalisée des patients selon leur profil d'altérations sensorielles.

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General introduction

General introduction

According to the WHO estimations, 18.1 million new cases of cancer were diagnosed worldwide in 2018, with a 5-year survival prevalence of 43.8 million [1]. This prevalence means that almost half of patients have a survival time greater than 5 years following the first diagnosis and are exposed to one or more treatments including surgery, chemotherapy, radiotherapy, and targeted therapies as a function of the type of cancer. Cancer treatments are known to induce several distressing side effects and thus to significantly alter patients' quality of life [2], [3].

Taste and smell alterations are among the most bothering side effects considering the consequences that they have on cancer patients' everyday life [4]. Patients' complaints on taste and smell perception alterations are frequent during chemotherapy. Chemosensory alterations may concern perceptual responses to one or more olfactory, gustatory or combined stimulation. Previous studies reported variable proportions of patients with chemosensory disturbances, ranging from 45 to 84% for gustatory disturbances and from 5 to 60% for olfactory disturbances [5]. Within these proportions, the modifications in taste and smell perceptions differ from one patient to another and even in the same patient. In fact, chemosensory alterations are expressed in different ways: while some patients complain about a decrease in their ability to perceive smells and/or taste modalities (i.e. sweet, salty, sour, bitter, umami), others are bothered by disturbingly intense perceived tastes and smells. These large individual differences in taste and smell alterations between patients, combined with the variability of assessment methods and primary endpoint resulted in heterogeneous outcomes. Indeed, in the literature, a wide range of variation exists in the proportion of patients reporting sensory alterations. This may be attributed to several factors including study design and sample size, type of cancer and chemotherapy, stage of the treatment at the time point of assessment, and factors intrinsic to the subject [6]. The observed inconsistency makes it considerably more difficult to have an accurate idea of the side effect size and constitute an obstacle regarding patients' general and nutritional care.

Besides modifying the food experience per se, taste and smell alterations influence indirectly food enjoyment and intake by affecting social and emotional processing [7], with a prominent effect on patient nutritional status and quality of life. Taste and smell alterations were found to be significantly linked with indicators of quality of life deterioration such as loss of appetite, fatigue [2], [8], and nausea [9]. Food enjoyment, which is closely linked to the perceived sensory properties of food, is an important motivation for eating. From visual and olfactory

cues to taste and texture sensations, sensory characteristics of food shape the food experience and play a functional role in energy intake regulation [10]. Consequently, disturbed olfactory and gustatory perceptions potentially lead to a modified food experience, hence, to adaptive food behavior.

In fact, in parallel to chemosensory complaints, modifications in patients' food behavior are observed. These include adding or removing food from the usual diet, changes in culinary and consumption habits, modifications in food preferences, and even the development of food aversions [11], [12]. In some cases, the dietary modifications stem from the patient's desire to embrace a healthier diet or to follow the dietary advice of a doctor, dietician, friend or family member. However, a considerable part of these dietary modifications is coping strategies adopted to overcome various side effects, including the modification of the perceived taste of food. Indeed, food could be described by the patient as "bland", "tasting the same", "too sweet", "bitter", "metallic" and sometimes the sensations are even mixed "some food are heightened and some food are dulled" [13]. This raises the question about the extent to which chemotherapy-induced taste and smell disturbances interfere with the motivation to eat and the subsequent pleasure, and most importantly, how to deal with the observed heterogeneity in this symptom expression when it comes to patients' nutritional care.

The present Doctoral project is a joint initiative between the Institute Paul Bocuse Research Center (IPBR) and Neuroscience Research Center of Lyon (CRNL), with the financial support of Elixir, Apicil and the National Association of Research and Technology (ANRT). The Ph.D. thesis addresses the link between chemotherapy-induced *chemosensory alterations* (particularly taste and smell) and the observed modifications in patients' *food behavior*. Particular attention is paid to the individual differences in chemosensory alterations that exist between patients related to their perceptive abilities and consequently their relationship to food.

Three approaches were used to address this main aim: a *theoretical* approach assessed the totality of available scientific evidence on the relationship between chemosensory alterations and food behavior and determined patterns of taste and smell disorders in cancer patients undergoing chemotherapy. An *experimental* approach described taste and smell alterations assessed by either subjective self-reported or objective psychophysical methods and their consequences on food perception and food habits. Finally, an *operational* approach allowed testing a strategy to cope with chemosensory deficits and improve patients' food liking.

Chapter I. The cancer context

1. Cancer nowadays: a worldwide health issue

Cancer is a major public health issue worldwide nowadays. At the cellular level, it corresponds to a quick and uncontrollable cell proliferation and survival of old non-functional cells to the process of their programmed death (apoptosis). The cell at the origin of the tumor is initially a healthy cell that undergoes a chemical DNA damage due to internal environmental influences [14]. This induces a DNA mutation and allows the cell to circumvent the molecular system that governs cells' birth and death. After a multistage process, the tumor becomes malignant and is referred to as a cancer [1].

The term cancer encompasses multiple types of malignant tumors and it is not possible to say why one person develops the pathology and not another. Among the proven and the highly suspected risk factors, lifestyle and diet are the most prominent. Behaviors such as smoking, alcohol consumption, diet that is rich/low in certain components and a reduced physical activity increase the risk of developing malignancies. Other risk factors that are independent of the individual's behavior and professional activity include age, gender, and genetic heritage. Finally, environmental and occupational factors such as air pollution, and exposure to some specific molecules are also listed as risk factors and contribute to the variability of cancer prevalence across countries and socio-professional categories [15].

In France, the prevalence of cancer in adults' population (all cancer types gender and age above 15 years) was estimated at 6.5 % of the general population (3 598 306 cases) in 2018 [16]. Considering both genders, colorectal cancer is the most frequently diagnosed cancer type (11.95 %) followed by lung cancer (7.5 %). When looking at prevalence by gender, prostate cancer is the most common in male population (24.9%) followed by colorectal (12.4%) and lung cancer (9.2%) while in female population breast cancer is the most commonly diagnosed (30.9%) followed by colorectal cancer (11.4%) and corpus uteri (6.7%). Lung cancer occupies the fourth position in the female population (5.6%) [16].

2. Living with cancer: the progressive shift from a fatality to a chronic disease

The evolution of cancer treatments, the identification of certain cancer risk factors, and the early diagnosis contributed to the improvement of patients' care, leading to a progressive shift of cancer from a life-threatening disease to a chronic condition [17]. The World Health Organization that considers cancer as one of the four types of chronic illness defines a chronic disease as a disease of long duration with a slow progression [1]. Thus, the notion of chronicity could not encompass all cancers, since some aggressive cancers have an unpredictable

evolution and may induce a rapid degradation of the patient’s condition. However, the low death rate in comparison to the incidence of certain commonly diagnosed cancer types (e.g. breast, prostate, and colorectal cancers) supports the classification of not all, but numerous cancers in the list of chronic conditions (figure 1).

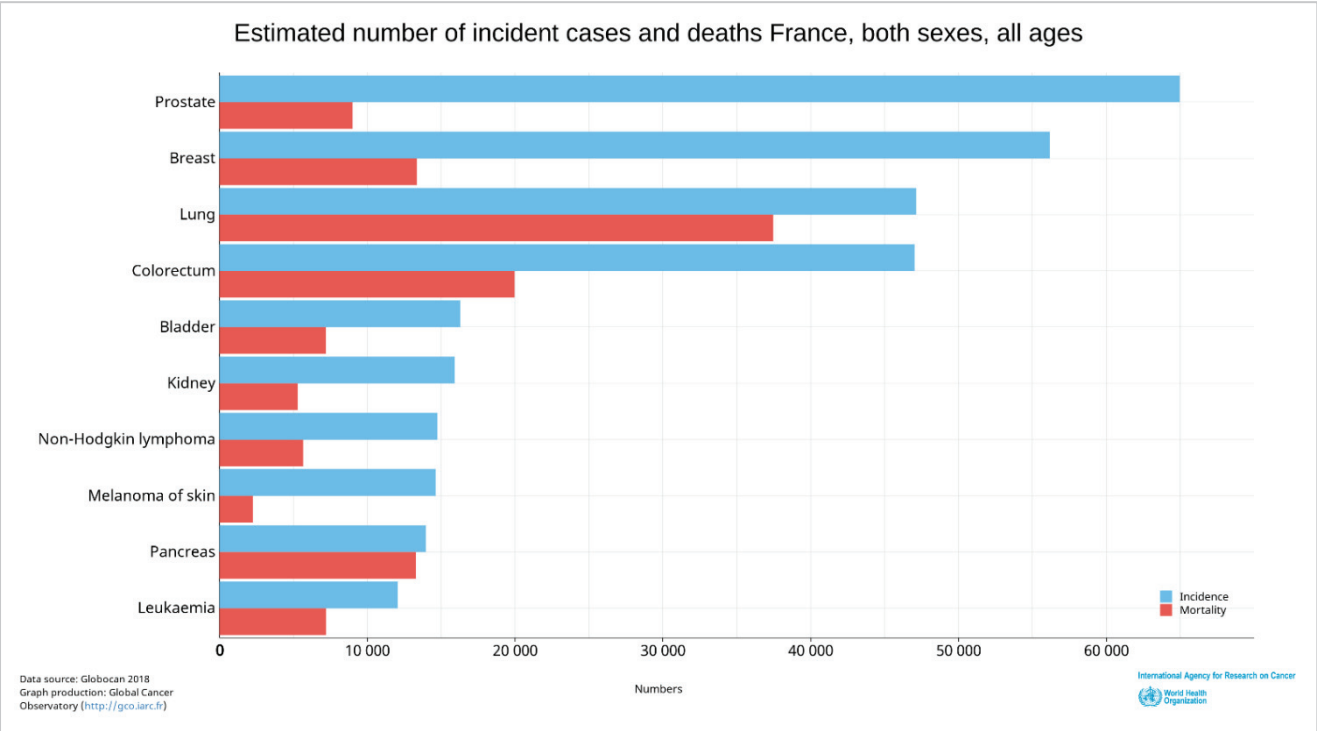


Figure 1. Estimated number of incident cases (blue) vs. estimated number of death (red) for the most prevalent cancer types in France (data relative to 2018)

Source: *Global Cancer Observatory - World Health Organization, 2018*

The American Cancer Society came with more adapted features of “chronic cancer”, describing it as a disease that can be managed for months or years, with the possibility to become stable with a treatment, or to alternate cycles of remission and recurrence [18]. This means that the cancer diagnosis is no more threatening for the patient’s life, but it has negative consequences on its quality of life, especially due to the cancer treatment side-effects [19], [20]. Thus, living with cancer often means living with long-lasting therapies and reduced quality of life for a non-defined period of time [17].

3. The evolution of cancer treatments: where are we today?

The interest in chemotherapy as anticancer therapy started in the early 20th century, but its first use was around the 1930s. In the middle of the century, research on anticancer drugs accelerated with the emergence of the Cancer Chemotherapy National Service Center in the USA, dedicated to preliminary toxicologic and pharmacologic evaluation of experimental cancer chemotherapeutic agents. This resulted in development of many molecules for cancer treatments based on different mechanisms of action (Table 1) and opened the door to molecule combination trials to improve the treatment efficiency around the 1970s. The 1990s were characterized by a decline in cancer death rate, thanks to a critical evolution in cancer therapy with the discovery of targeted therapies. In addition to being more efficient by blocking the development of cancerous cells, targeted therapy minimizes the cytotoxic effect of chemotherapy agents, limits their side effects and so, the consequences on patients' quality of life. Currently, innovative anticancer therapies are focused on developing immunotherapy approaches. This therapy acts by boosting immunity to help patients' immune system eliminate tumor cells [21]–[24]. Although anticancer therapies have evolved and new options of treatments emerged, cytotoxic chemotherapies are still widely used in clinical practice alone or combined with other treatments to increase their efficiency [24].

- **Cytotoxic chemotherapies**

Overall, chemotherapy works by targeting and killing cells that divide quickly. Chemotherapy agents interfere with the cell division process (mitosis) at the DNA level through various mechanisms (table 1). The fact that cancer cells have a high mitotic index (the number of cells undergoing mitosis divided by the total number of cells) makes them particularly sensitive to chemotherapy's potent agents, which explain the efficiency of this treatment [25].

Four main uses of chemotherapy are found in clinical settings: primary induction, neoadjuvant therapy, adjuvant therapy, and site-directed perfusion.

In the case of primary induction, cytotoxic drugs are administered as a primary treatment for advanced cancer. This approach is commonly used in cases of advanced metastatic cancers with the aim of palliating the tumor symptoms, slowing down the tumor progression and improving patient's quality of life. Chemotherapy is said neoadjuvant when it is used as a first step before the main treatment (usually surgery) with the aim to shrink the tumor. Adjuvant chemotherapy is chemotherapy administered after the main treatment to optimize its efficiency and ensure the

removal of the remaining cancer cells in order to avoid the cancer recurrence. Finally, the site-directed perfusion of a specific organ corresponds to the introduction of a therapeutically effective amount of a chemotherapeutic agent directly into a vascular access of the organ having metastatic cells. The combination of chemotherapy with a local treatment modality (surgery or radiotherapy) optimizes the chance of total remission and reduces the recurrence risk [25].

Table 1. Chemotherapy cytotoxic agents' classification and mechanism of action

Drug class	Subgroup	Mode of action
Alkylating agents	<ul style="list-style-type: none"> • Oxazaphosphorines 	<ul style="list-style-type: none"> • Alkylation of DNA/RNA → cross-links DNA at guanine N-7 → impaired DNA synthesis • Cyclophosphamide and ifosfamide require activation in liver
	<ul style="list-style-type: none"> • Nitrogen mustards 	
	<ul style="list-style-type: none"> • Hydrazine 	
	<ul style="list-style-type: none"> • Platinum-based agents 	<ul style="list-style-type: none"> • Cross-links between DNA strands → ↓ DNA replication
Topoisomerase inhibitors	<ul style="list-style-type: none"> • Topoisomerase I inhibitors 	<ul style="list-style-type: none"> • Inhibition of topoisomerase I → ↓ DNA replication and degradation (ss-DNA breaks)
	<ul style="list-style-type: none"> • Topoisomerase II inhibitors 	<ul style="list-style-type: none"> • Inhibition of topoisomerase II → ↑ DNA degradation (ds-DNA breaks) and ↓ DNA replication
Mitotic inhibitors	<ul style="list-style-type: none"> • Vinca alkaloids 	<ul style="list-style-type: none"> • Binding and destruction of tubulin in microtubules → mitotic arrest in metaphase
	<ul style="list-style-type: none"> • Taxanes 	<ul style="list-style-type: none"> • Stabilization of microtubules → ↓ mitotic spindles → mitotic arrest in metaphase
Antimetabolites	<ul style="list-style-type: none"> • Antifolates 	<ul style="list-style-type: none"> • Inhibition of dihydrofolate reductase by displacing dihydrofolate → ↓ formation of purine nucleotides
	<ul style="list-style-type: none"> • Pyrimidine antagonists 	<ul style="list-style-type: none"> • Incorporation of false pyrimidine analogs into DNA → ↓ DNA replication
	<ul style="list-style-type: none"> • Purine antagonists 	<ul style="list-style-type: none"> • Incorporation of false purine analogs into DNA → ↓ DNA replication

	<ul style="list-style-type: none"> • Purine analogs 	<ul style="list-style-type: none"> • Inhibition of DNA polymerase → DNA strand breaks
	<ul style="list-style-type: none"> • Ribonucleotide reductase inhibitor 	<ul style="list-style-type: none"> • Inhibition of ribonucleotide reductase → ↓ DNA replication → massive cytoreduction
Antibiotics	<ul style="list-style-type: none"> • Bleomycin 	<ul style="list-style-type: none"> • Induces formation of free radicals → DNA strand breaks, arrests the cell cycle at G₂ phase
	<ul style="list-style-type: none"> • Actinomycin D 	<ul style="list-style-type: none"> • DNA intercalation → interference with DNA transcription → ↓ RNA synthesis
	<ul style="list-style-type: none"> • Anthracyclines 	<ul style="list-style-type: none"> • Induces formation of free radicals → DNA strand breaks • DNA intercalation → DNA strand breaks and ↓ DNA replication • Topoisomerase II inhibitor
Other	<ul style="list-style-type: none"> • Enzymes 	<ul style="list-style-type: none"> • Cleavage of the amino acid L-asparagine by L-asparaginase
	<ul style="list-style-type: none"> • Proteasome inhibitors 	<ul style="list-style-type: none"> • Inhibit degradation of ubiquitinated apoptotic proteins such as p53 → programmed cell death
	<ul style="list-style-type: none"> • Tyrosine kinase inhibitors 	<ul style="list-style-type: none"> • Prevents phosphorylation and activation of multiple proteins by tyrosine kinases → cell dysfunction and death

Source: https://www.amboss.com/us/knowledge/Chemotherapeutic_agents

The efficiency of chemotherapy is increased when different chemotherapy agents are combined [26]. The understanding of the molecular mechanism of action of several anticancer agents (table 1) allowed the identification of chemotherapy cocktails that reach more curative goals than single-agent therapies [27]. Moreover, in some cases, the synergistic combination of different agents can inhibit the specific toxicity of molecules, reducing side-effects [28]. The toxicity toward non-targeted tissues constitute a serious limitation of chemotherapy agents' use.

- **Chemotherapy side-effects**

Regardless of their mechanism of action, all cytotoxic chemotherapy drugs result in the death of sensitive cells by damaging their DNA, thus, inhibiting their ability to live and proliferate. However, this mechanism is non-selective and influences at the same time non-cancerous fast-

growing cells of the body including hair follicles, digestive tract cells, and mucous membranes [28], [29].

To date, chemotherapy side effects are not accurately predictable because of their variation in occurrence from one patient to another. As this treatment modality is systemic, the symptoms may concern different areas of the body depending on the cell type impacted by chemotherapy drugs. The most common side effects are categorized in 2 main groups: short-term side effects and long-term side effects and are summarized in Table 2.

Table 2. Common cytotoxic chemotherapy side effects

	Short-term side effects	Long-term side effects
Gastrointestinal dysfunction	Diarrhea [30] Constipation [30] Nausea and vomiting [31]	
Symptoms related to food behavior	Bodyweight changes [32], [33] Appetite loss [34] Modifications in food preferences [7], [35]	Modification of body composition [32], [36]
Oro-nasal problems	Taste and smell alterations (see table 3) Xerostomia [37], [38] Mucositis [30]	
other	Fatigue [39] Alopecia [40]	Fatigue [41], [42] Sensory neuropathy [43] Cardiotoxicity [44] Nephrotoxicity [45]

Interestingly, some chemotherapy molecules are more likely to induce side-effects than others [46]–[48]. For instance, 5-fluorouracil (5-FU), used for digestive, gynecological, and breast cancers is known to cause diarrhea [30], while Cyclophosphamide, generally indicated for breast malignancies has a high emetogenic level [31]. Cisplatin, used as a treatment for lung, ovary and testicular cancers is a potent anticancer drug, discovered by accident in the 1960s¹. While its efficiency has been repeatedly proven, its notable toxicity constitutes a limit of its use

¹ Barnett Rosenberg, a biophysicist at the University of Michigan was interested in the effect of electrical current on cellular division. To examine this, he applied current to Escherichia coli (E. coli) cells growing in ammonium chloride buffer through platinum electrode. After a period of time, the shape of E. coli cells began to change due to the inhibition of cellular division. After two years of investigations, Rosenberg found that this phenomenon was not due to the electrical current but to the platinum contained in the electrodes used to apply it (Alderden, 2006).

at high doses, which sparked the development of similar drugs with lower cytotoxic side effects (Carboplatin and Oxaliplatin). Yet, Cisplatin is still widely used and irreplaceable for certain cancer types. The major side effects of Cisplatin are nephrotoxicity and cardiotoxicity [49]. Additionally, patients undergoing Cisplatin chemotherapy reported distressing symptoms at the perceptual level. Particularly, patients complain about a permanent metallic taste in mouth, and a decrease in taste and smell perception abilities [36], [47], [50]. Taste and smell alterations are also induced by other molecules such as Irinotecan, used for colorectal cancers [46], and the combination of Epirubicine/Docetaxel/Capecitabine used for breast and some gynecological cancers [2].

Chapter II. Eating during cancer and
chemotherapy

1. Food enjoyment : a significant aspect of quality of life of cancer patients

Given the significant side effects of the cytotoxic chemotherapy as part of many cancer treatments, there has been a growing interest in investigating patients quality of life in the past decades [19], [20], [40], [51], [52]. Quality of life encompasses several aspects including physical, social, and psychological factors, and each of them needs to be maintained at an adequate level for the global well-being of the patient.

Although not sufficiently explored, an important aspect of quality of life is food enjoyment during cancer and chemotherapy. In France, the national cancer program « *Plan Cancer* » has been implemented from 2008 to 2013, and from 2014 to 2019, with the objective to actively work on cancer prevention, cancer care, and patients' follow-up. This program includes a quality of life improvement component in which food and nutritional care are mainly considered from a preventive point of view. Yet, when an individual is diagnosed with cancer, diet is essential for the well-being of the patient and more attention is needed.

Improving patients' food enjoyment during chemotherapy may not only help to prevent the deterioration of their nutritional status, but it also influences other quality of life dimensions, such as social and emotional. Indeed, during chemotherapy, patients often complain about being unable to join and share meals with their friends and family because of the disease related symptoms, or the treatment side-effects [13], [53]. For instance, common side effects such as appetite loss [54], food aversion [11], and taste and smell alterations [34], [38], [55]–[57] are likely to modify patients relationship with food [6], reflected by indifference toward food, inability to share meals[53], and moderate to severe cases of malnutrition [58].

Eating is an essential response to a physiological need for nutrients in order to maintain body energetic balance [59]. Food intake is regulated by a series of homeostatic and not-homeostatic factors [60], [61], among which hunger and appetite are prominent [62]. However, a malignant diagnosis may represent a turning point in an individual relationship with food, either for physiological or psychological reasons. Firstly, the systemic tumor effect related to the pathology itself alters food intake by inducing anorexia/cachexia and gastrointestinal symptoms such as nausea and vomiting [63], [64]. Furthermore, cancer treatments and especially those including cytotoxic chemotherapy may contribute to malnutrition through their resulting adverse effects (table 2). Finally, psychological factors could be associated with the decrease of patients' nutritional intake, since loss of appetite is a common consequence of anxiety and depression linked to the cancer diagnosis [65].

2. How does cancer impact patients' food behavior?

Changes in food habits during chemotherapy are observed in patients with different types of cancer [13], [66]. Those changes may concern many aspects of food behavior, including food choices, culinary practices, and energy intake, and vary from one patient to another. Indeed, studies that examined patients' food intake during chemotherapy were not consensual, with some reporting a decreased food intake [67]–[69] and others showing no difference [70]. Considering food choices, the best strategy for some patients consisted of preparing familiar recipes [13], while for other patients, trying new recipes helped with food aversions and stimulated their motivation to eat [71]. Concerning culinary and consumption habits, patients declared a variety of behaviors. The most recurrent were: eating cold food [13], eating food at room temperature [38], enhancing food flavor [38], [55], [71], or on the contrary favoring more bland food, using more sauce and fat to improve the texture and avoiding food with strong smell [38]. Some of these behaviors are contradictory, and the coping strategies that work for some patients may not work for others. This makes the nutritional counseling of patients and the management of their nutritional status throughout the treatment difficult. In addition, this diversity is likely sustained by a large variation in the factors underpinning the modification in food behavior and highlights the need to better determine factors that modulate patients' food behavior.

It is, however, worth mentioning that all the practices reported by patients indicate a desire to regain the pleasure of food consumption. Indeed, the pleasure of consuming a meal is a substantial source of motivation to eat, but in the case of cancer and chemotherapy, this pleasure may decrease [68], leading to a reduced motivation to eat. According to Boltong et al. 2014: “Food hedonics, which also contributes to flavor perception, encompasses food liking: the immediate experience or anticipation of pleasure from the oro-sensory stimulation of eating a food [72]” [34]. In other words, food hedonics is closely dependent on food flavor perception, which in turn is dependent on oral stimulation by sensory properties of food.

Since liking has an influence on food intake [73], one can hypothesize that cancer-associated weight loss is not only due to cancer cachexia (resulting from metabolic changes and inflammatory reactions related to cancer), but also a consequence of reduced food intake due to modification in food flavor perception.

*Chapter III. Taste and smell alterations during
cancer and chemotherapy*

During the three last decades, there was a growing interest in taste and smell alterations reported by cancer patients undergoing chemotherapy. Therefore, many studies examined this issue using a series of methods of assessment depending on the variable of interest [74].

1. How are chemotherapy-induced taste and smell alterations assessed?

The most commonly used tools to assess patients taste and smell abilities can be classified in two categories. The first category includes approaches based on patients' self-reports using mainly questionnaires and interviews. Currently, the most used questionnaire is the Taste and Smell Survey [75], that allows obtaining a chemosensory score based on patients' self-assessment of taste and smell abilities [9], [68], [76], [77]. The second category² includes instrumental approaches, using psychophysical tests or physiological methods such as electrophysiology and functional Magnetic Resonance Imaging that allow going further than the peripheral level in the exploration of chemosensory alterations. In general, the measurement of patients' perceptive abilities is conducted with validated sensory psychophysical tests.

In the early 90s, electrogustometry was the reference method for taste assessment [78], [79] while smell assessment was less common, and carried out by the mean of pyridine dilution [79]. Later, the Sniffin Sticks test³ became a popular tool to define patients' olfactory threshold because of its reliability in test re-test validation [36], [57], [80]–[84]. Another validated test is the European Test of Olfactory Capabilities (ETOC), which is an olfactory test that diagnoses hyposmia and anosmia based on detection and identification scores of 16 odors [85]. A variety of other sensory tests and questionnaires [38], [86]–[88] were developed but not all of them were used with cancer patients' population. One of the major difficulties in assessing the taste and smell abilities of cancer patients is to find a reliable tool that is adapted to clinical use, which means that it needs to be short to perform, and not too tiring for the participant. Table 3 summarizes the tools commonly used for taste and smell assessment in cancer patients' population.

² Note that during my PhD, I had the opportunity to perform a 3-month internship at the University of Dresden (Germany) under the supervision of Pr. Thomas Hummel (Jan-April 2019). During my stay, I became familiar with most objective techniques that characterize smell perception (EEG, Sniffin Sticks, etc.) and I also ran studies and analyzed different sets of data on patients with olfactory deficits. One achievement of this collaboration is a paper on patients with olfactory troubles that I wrote with Pr. Hummel and Pr. Landis (from the University Hospital of Geneva). I am the first author of this paper, which is under review in the journal *The laryngoscope* (see appendix 10).

Table 3. Self-reported and instrumental tools used for taste and smell assessment in cancer patients' population.

Method	Sensory modality	Test	Measured variable
Self-reports	Taste and Smell	Questionnaires [2], [36], [38], [47], [48], [77]	-Taste and smell abilities
		Interviews [13], [48], [53], [55], [71], [77]	-Taste and smell alterations
Instrumental assessment	Taste	Electrogustometry [78], [79]	-Taste detection threshold
		Rinsing mouth method [8], [89]	-Taste identification threshold
		Taste strips [36], [57], [90]	
		ISO 3972:2011-Sensory Analysis-Methodology-Method of Investigating Sensitivity of Taste [34]	
	Smell	Dilution of pyridine [79]	-Detection threshold
		Sniffin sticks [36], [57], [80], [81], [83], [84], [90]	-Detection threshold -Identification threshold -Discrimination threshold
		ETOC* [91]	-Detection score -Identification scores -Olfactory status

*ETOC: *European Test of Olfactory Capabilities*

2. Dealing with variability: Are taste and smell alterations homogenous across the studied population?

Interestingly, when comparing outcomes of studies focusing on cancer patients' chemosensory functions, we observed an inconsistency in terms of frequency, prevalence, intensity and type of taste and smell alterations (table 5). This 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, that could be methodological, related to the pathology and/or the treatment type or intrinsic to each individual (see chapter V).

Concerning the prevalence of taste and smell alterations, it is quite impossible to define a precise percentage of patients that present this side-effect. For instance, using the same tool

(Taste and Smell Survey Questionnaire) Hutton et al. reported taste and smell alteration in 84% of a heterogeneous group of 66 cancer patients [68] whereas Brisbois et al. reported only 60% in a group of 192 patients [9]. Moreover, olfaction is less studied than gustation, thus, it is often underestimated in cancer patients [80].

A high variability is also observed in types of alterations expressed by patients or diagnosed with sensory tests. Patients may have decreased or increased abilities to perceive tastes and smells. In less frequent cases, the taste/smell perception abilities are totally lost, inducing a state termed ageusia/anosmia. Finally, some sensory alterations are qualitative, characterized mainly by distortions in sensory perceptions, or perception of taste/smell without stimulation (table 4).

Table 4. Types of taste and smell modifications in cancer patients undergoing chemotherapy

	Taste	Smell
Modification of the perceived intensity	Ageusia: total loss of taste perception	Anosmia: total loss of smell perception
	Hypogeusia: decreased taste perception	Hyposmia: decreased smell perception
	Hypergeusia: increased taste perception	Hyperosmia: increased smell perception
Distortion of perceptions	Parageusia: distortion in the perceived quality of a taste; inability to properly identify a taste	Parosmia: distortion in the perceived quality of an odor; inability to properly identify an odor
Perceptive hallucinations	Phantogeusia: perception of taste in the absence of stimulus	Phantosmia: perception of smell in the absence of stimulus

For a better overview of the existing diversity, the main outcomes of the literature dealing with taste and smell alterations in cancer patients undergoing chemotherapy are summarized in table 5. the information displayed in the table is: the number of participants (“N”) and the study design, the cancer type (“*cancer type*”), the measured variable and the tool used for the measurement (“*measurement*”), the main outcome concerning taste and/or smell alterations (“*findings*”) and the direction of the chemosensory alteration (“*effect*”).

Design	Reference	N	Cancer types	Measurement	Findings	Effect
Cross-sectional studies	Ovesen et al., 1991 [79]	Patients N = 51 64 years Controls N= 29 62 years	Lung Ovarian Breast	Gustatory threshold: Electrogustometry Olfactory threshold: Dilution of pyridine	Higher gustatory threshold in patients compared to controls Smell threshold unchanged No impact of cancer types	Taste ↑ Smell =
	Wickham et al., 1999 [47]	Patients N= 284	Breast Colorectal Lung Lymphoma Gynecological Others	Gustatory perception : Self-reported questionnaire (FAACT)*	Effect of the treatment type on the severity of chemosensory alterations No impact of cancer types	Direction not specified
	Berteretche et al., 2004 [78] (Case-control)	Patients N = 110 58.5 years Controls N= 170 60.5 years	NS	Gustatory threshold: Electrogustometry	Higher gustatory threshold for patients compared to controls	Taste ↓
	Yakirevitch et al., 2006 [84]	Patients N= 42 67.8 years	Divers	Olfactory threshold: sniffin' sticks	Higher olfactory threshold in 60% of patients. Better scores in women/men Better scores in younger/older Unawareness of olfactory deficit in 80% of cases	Smell ↓
	Bernhardson et al., 2007 [55] Cross-sectional	Patients N=21 Age range (32-73)	Diverse	The experienced changes in taste and smell: Self-reported (interviews)	Notable differences between sensory modifications phenotypes, extent, intensity, and impact on the quality of life. Aversion for food odors and fragrance.	Taste ↑↓ Smell ↑↓
	Bossola et al., 2007 [56]	Patients N=47 65.3 years	Gastrointestinal	Gustatory perception and liking of tastes: sweet, salty,	Higher score of perceived intensity for salty, sweet and bitter in patients compared to controls.	Taste ↑

(Case-control)	Controls N = 55 64.8 years		sour, bitter solutions at different concentrations	Higher liking for higher concentrations of sweet taste. Lower liking for higher concentrations of salty bitter and sour in patients compared to controls.	
Hutton et al., 2007 [68]	Patients N=66 65.4 years	All types except digestive and oronasal area	The experienced changes in taste and smell: Self-reported (interview)	86% of patients have a taste and/or smell disturbance: 52% taste and smell 30% only taste changes 5% only smell	Taste ↑↓ Smell ↑↓
Bernhardson et al., 2008 [48]	Patients: N=518 58.7 years	Breast Gastrointestinal Gynecological	Impact of cytotoxic molecules on taste and smell perception: Self-reported (interview+ questionnaire)	75% of patients have a taste and/or smell disturbance 25% only taste changes 7.7% only smell changes	Taste ↓ Smell ↑↓
Steinbach et al., 2010 [81]	Patients N= 69 52.4 years	Breast Cervix Endometrial	Gustatory threshold: taste strips Olfactory threshold: sniffin' sticks	Effect of the treatment type on the severity of chemosensory alterations (compared to normative data) Unaltered olfactory detection score. Lower olfactory recognition score. Lower value for sour perception, no difference for other tastes.	Taste ↓ Smell ↓
Sanchez-Lara et al., 2010 [89] (Case-control)	Patients N = 30 56 years Controls N = 30 49.4 years	Breast Lung Prostate Myeloma and lymphoma	Gustatory perception: mouth rinsing method	Higher sweet detection threshold and higher bitter recognition threshold in patients compared to controls.	Taste ↓
Zabernigg et al., 2010 [46]	Patients N=197 65.2 years	Colorectal Lung Pancreatic	Taste perception: self-reported	56% of patients without taste and smell alterations 26.1% with moderate taste and smell alterations 17.6% with severe alterations	Direction not specified

						Effect of the treatment type on the severity of chemosensory alterations	
Brisbois et al., 2011 [9]	Patients N= 192 64.3 years	All types except head and neck	Taste and smell perception: Self-reported (questionnaires)	60% of patients have a taste and/or smell disturbances: 26% for taste only 3% for smell only	Taste ↑↓ Smell ↑↓		
Bernhardson et al., 2012 [13]	Patients N=12 51 years	Breast Lung Gastrointestinal Lymphoma Ovary	Taste alterations: self-reported (interviews+ questionnaires)	50% of cases of decreased sensitivity to tastes	Taste ↓		
Gamper et al., 2012 [2]	Patients N= 109 61 years	Breast Gynecological	Taste alterations: questionnaire	76.1% of patients have a taste and/or smell disturbances. Better scores in younger/older Effect of the treatment type on the severity of chemosensory alterations	Direction not specified		
Speck et al., 2013 [71]	Patients N= 25 45 years	Breast	Taste perception: self-reported (interviews)	Taste disorders in 44% of participants	Direction not specified		
Mc Greevy et al., 2014 [77]	Patients N=89 67 years	Lung Gastrointestinal	Taste and smell modifications: self-reported (interviews + questionnaires)	68.5% of patients have a taste and/or smell disturbances. Gender effect.	Taste ↓↑		
Yakirevicthet al., 2005 [83]	Patients N=21 53.6 years	Diverse	Olfactory function: Sniffin sticks	Higher olfactory threshold for 1 patient after 3 cycles	Smell =		
Jensen et al., 2008 [92]	Patients N = 45 45 years Controls N= 31 54 years	Breast	Taste modifications : self-reported (interview, questionnaire) Oral lesions: visual and microbiological analyzes	84% of cases of decreased sensitivity to tastes in patients group 22% of cases of mucosal lesions 16% of cases of mouth ulceration 11% of cases of candidiasis	Taste ↓		

Longitudinal studies	Rehwaldt et al., 2009 [38] Longitudinal	Patients: N=42 59 years	Breast Lung Lymphoma Ovary	Taste modifications: Self-reported (questionnaire)	Correlation between ageusia and xerostomia. Correlation between dysgeusia and decrease of appetite. Effect of the treatment type on the severity of chemosensory alterations.	Taste ↓
	Steinbach et al., 2009 [57] Longitudinal	Patients N=87 53.5 years	Breast Gynecological	Gustatory threshold: Taste strips Olfactory threshold: sniffin' sticks	Decrease in gustatory and olfactory function during chemotherapy compared to baseline Better scores in younger/older Salty taste more affected. Effect of the treatment type on the severity of chemosensory alterations	Taste ↓ Smell ↓
	Steinbach et al., 2012 [90] Longitudinal	Patients N=12 56.5 years	Ovary	Olfactory threshold: sniffin' sticks Gustatory threshold: taste strips (with 4 concentrations) Auditory function: Audiometric monitoring	Lower olfactory detection threshold compared to baseline. Increased olfactory identification and discrimination score compared to baseline. Decreased sensitivity to sour compared to normative data.	Taste ↓ (tendency) Smell detection ↓ Smell identification ↑
	Joussain et al., 2013 [91] Longitudinal Case-control	Patients N = 15 63.4 years Controls N' = 15 65.9 years	Lung	Olfactory detection score Olfactory identification score Liking of odors: ETOC*	Unchanged detection and identification scores Decreased liking of food odors	Smell =
Nishijima et al., 2013 [93] Longitudinal	Patients N=23 58 years	Gynecological	Gustatory disorders: serum trace element (zinc, copper, iron) levels, tongue cultures, electrogustometry, and	50% of cases of altered sensitivity to tastes during chemotherapy	Taste ↑↓ (tendencies)	

				the filter paper disc tests	Higher threshold for sweet, salty and sour detection compared to baseline Lower threshold for bitter detection through the treatment compared to baseline Lower gustatory function right after the administration of chemotherapy agents at each cycle. Decreased liking for sweet taste compared to baseline	Taste ↓
Boltong et al., 2014 [34] Longitudinal	Patients N= 52 50.4 years	Breast		Gustatory function: International Standards Organization (ISO), ISO 3972:2011- Sensory Analysis- Methodology-Method of Investigating Sensitivity of Taste	Higher olfactory detection threshold compared to baseline Better scores in younger/older	Smell ↓
Riga et al., 2015 [80] Longitudinal	Patients N=44 Groups' age 39–50 (14 %) 51–62 (34 %) 63–73 (52 %)	Breast Gastrointestinal Lung Ovarian		Olfactory threshold: sniffin' sticks	Higher olfactory threshold in patients compared to controls. Lower olfactory discrimination score during the chemotherapy compared to baseline.	Taste = Smell ↓
Ijpma et al., 2016 [36] Longitudinal Case-control	Patients N= 21 Range (27-36) Controls N = 48 Range (29-36)	Testicular		Gustatory function: taste strips + self-reported (questionnaire) Olfactory threshold: sniffin' sticks + self-reported (questionnaire)	Higher sensitivity to bitter and umami taste during chemotherapy compared to baseline	Taste ↑
Turcott et al., 2016 [8] Longitudinal	Patients N= 40 55.5 years	Lung		Gustatory function: Rinsing mouth method	Lower olfactory detection threshold during chemotherapy compared to baseline	Smell ↓
Walliczek-Dworschak et al., 2017 [82]	Patients N= 17 31 years	Testicular		Olfactory function: sniffin' sticks 5 point Likert scale		

Longitudinal					Odor discrimination and identification unchanged.	
De vries et al., 2017 [35] Longitudinal	Patients N= 15 61 years	Esophagogastric	Gustatory function: taste strips + self-reported (questionnaire) Olfactory threshold: sniffin' sticks + self-reported (questionnaire)	Ualtered olfactory and gustatory function	Taste = Smell =	
De vries et al., 2017 [67] Longitudinal Case-control	Patients N= 117 51 years Controls N= 88 53.5 years	Breast	Gustatory and olfactory function: self-reported (questionnaire)	Lower self-reported taste and smell compared to controls.	Taste ↓ Smell ↓	
Marinho et al., 2017 [94]	Patients N=55 51.5 years	breast	Gustatory modification: self-reported (questionnaire)	Alterations in taste perception	Not specified	
De vries et al., 2018 [7] (Case-control)	Patients N=28 51 years Controls N=28 51.8 years	breast	Gustatory function: taste strips + self-reported (questionnaire) Olfactory threshold: sniffin' sticks + self-reported (questionnaire)	Decreased self-reported olfaction and gustation Higher olfactory detection threshold Higher gustatory detection threshold	Taste ↓ Smell ↓	

Table 5. Summary of studies assessing taste and smell functions in cancer patients undergoing chemotherapy

We can observe in the last column that the direction of taste and smell alteration is highly fluctuant. Taste and smell abilities of patients could be increased (↑), decreased (↓), or unchanged (=). In some studies, especially those based on interviews, patients reported disturbances without specifying their direction.

3. Is there a relationship between chemosensory alterations and food behavior modifications?

The observed variability in taste and smell alterations outcomes is strongly reminiscent of the salient inconsistency in patients’ food behavior and strategies to maintain food enjoyment. This raises the fundamental question of individual variability in patients’ perception and the role of taste and smell alterations in patients’ food behavior modulation. The hypothetical link between sensory behavior (alteration and patients’ food represented in figure 2) could be established in cancer patients’ population by demonstrating that patients with altered sensory abilities present also modification of food behavior. The present Doctoral thesis is specifically interested in taste and smell alterations as a factor influencing food enjoyment and so patients’ food behavior changes.

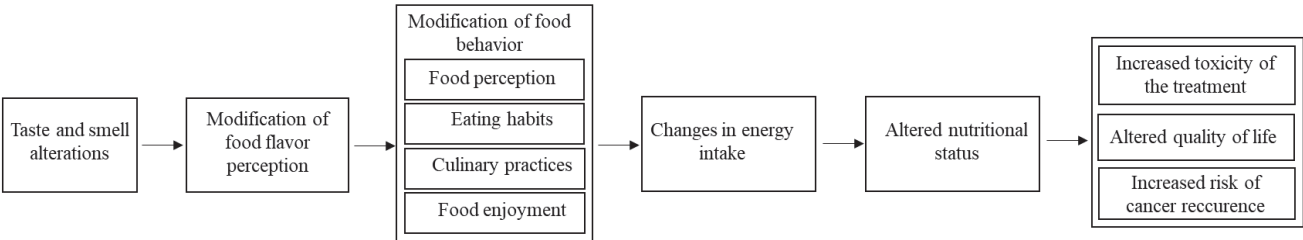


Figure 2. Hypothetical pathway by which taste and smell modifications alter cancer patients’ nutritional status

*Chapter IV. Overall objective,
research questions and hypotheses*

1. Overall objective of the project

At theoretical point of view, the objective of the present doctoral thesis is to explore the diversity between patients in the phenomenon of taste and smell alterations. In particular, we set out to understand and describe the effect of chemotherapy treatments on *olfactory and gustatory* perceptions, considering the differences between patients in terms of alteration type and intensity. At operational point of view, the objective of the project is to identify means to maintain the *food enjoyment* despite taste and smell alterations that interfere with the hedonic value of food.

2. Research questions and hypotheses

Collectively, there is evidence that taste and smell alterations are a common side effect of chemotherapy treatment. However, a high heterogeneity exists between study outcomes regarding the prevalence of this side effect, and between patients regarding the type and intensity of taste and smell alterations. In parallel, variation in patients' food behavior is also evident.

The scientific questions that have been addressed in this project, the corresponding study in the thesis, the hypothesis and specific objectives of the thesis are listed below:

Research question 1. What is the relationship between food behavior modifications and alterations in taste and smell abilities of patients during chemotherapy?

Study 1. Relationship between food behavior and taste and smell alterations in cancer patients undergoing chemotherapy: A structured review.

Hypothesis 1. The taste and smell alterations influence patients' food behavior.

Objective. To provide a critical overview of the totality of the available evidence on the association between taste and smell alterations and food behavior modifications in cancer patients undergoing chemotherapy.

Research question 2. What are the consequences of chemosensory alterations type and intensity on patients' food behavior?

Study 2.a. The impact of taste and smell alteration severity on food perception in cancer patients undergoing chemotherapy.

Hypothesis 2.a. Patients with severe taste and smell alterations report more problems related to food perception.

Objective. Examine the effect of taste and smell alterations on self-reported food behavior and food perception in a group of heterogeneous cancer patients considering different level of severity in chemosensory alterations of patients.

Study 2.b. Hyposmia in cancer patients undergoing chemotherapy affects food behavior

Hypothesis 2.b. Patients with olfactory deficits exhibit modifications in food behavior

Objective. Test clinically and experimentally relationship between olfactory deficits and patients' food habits.

Research question 3. Can we improve patients' food liking by adapting the sensory properties of food to cope with patients' taste and smell alterations?

Study 3. Flavor enhancement as a strategy to improve food liking in cancer patients with decreased taste and smell abilities.

Hypothesis 3. Enhancing food flavor by adding basic ingredients able to stimulate gustatory/olfactory receptors may improve its liking rating by patients with taste and smell deficits.

Objective. Examine the effect of flavor enhancement on food liking in a group of cancer patients undergoing chemotherapy, considering their taste and smell abilities.

3. Outline of the thesis

Although the optimization of cancer treatments focuses partly on reducing their bothering side effects, a high percentage of cancer patients still have to deal with cytotoxic chemotherapy and its induced side effects during the cancer care trajectory.

The role of taste and smell in food perception and enjoyment is established in the literature. However, the influence of taste and smell alterations on food behavior in the specific case of cancer and chemotherapy is still understudied. Therefore, after setting the context of the project in chapter I, II and III, and defining the main objective, research questions and hypotheses of the project in chapter IV, we provided a structured literature review on the relationship between taste and smell alterations and food behavior in cancer patients undergoing chemotherapy (*Chapter V*). This review starts with a summary of the mechanisms underlying taste and smell perception. The review of publications that considered both sensory alterations and food behavior of patients highlighted the high heterogeneity between patients when it comes to taste and smell alterations. We also observed that patients without sensory alterations did not have modifications in food behavior whereas patients with chemosensory alterations (either increased or decreased sensitivity to tastes and odors) did.

The relationship between sensory alterations and food perception was then assessed experimentally in a cross-sectional study, based on a self-reported approach for the assessment of patients' taste and smell ability (*chapter VI, study 2.a*). This approach had limits in some methodological aspects and needed to be completed with an instrumental approach. To circumvent these limitations, a longitudinal case-control study was conducted. The aim of this study was to examine the role of a specific type of chemotherapy (cisplatin-based chemotherapy) on taste and smell perception measured with psychophysical tests. This study examined also the consequences of the olfactory deficit on food consumption habits (*Chapter VI. Study 2.b*). The decreased taste and smell perception ability emerged as the most common chemosensory problem in the studied population, thus we examined in an interventional study the effect of flavor enhancement on food liking in a large group of patients with heterogeneous cancer types, and a sub-group of patients with breast cancer patients. This study is described and the results are discussed in *chapter VII*.

Finally, the overall findings of the thesis are discussed, considering strengths and limitations of the research work and the perspective for future works are proposed in *chapter VIII*.

*Chapitre V. Relationship between taste and
smell alterations and food behavior*



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

Kenza Drareni^{a,b}, Anestis Douglas^a, Agnes Giboreau^a, Martine Laville^c, Pierre-Jean Souquet^d, Moustafa Bensafi^{b,*}

^a Institut Paul Bocuse Research Centre, Ecully Cedex, France

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

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

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



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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 hyperchemosensation (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.

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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],

* Corresponding author. 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.

E-mail address: moustafa.bensafi@cnrs.fr (M. Bensafi).

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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.

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.

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 (Fig. 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 information 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 (Fig. 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 15–20 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].

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 2.5–10 cm^2 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 toward 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

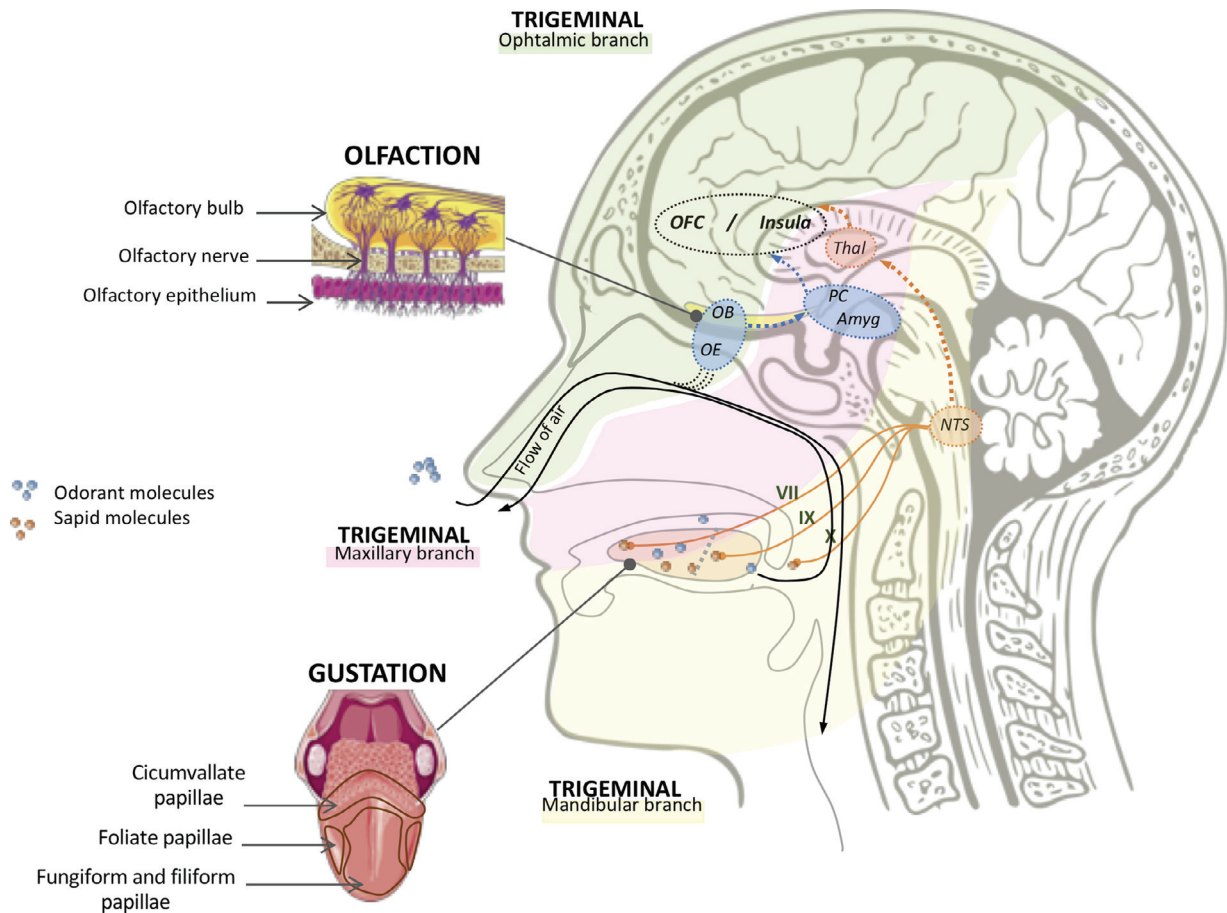


Fig. 1. Chemosensory systems involved in flavor perception. The trigeminal system is composed of three branches: ophthalmic, maxillary and mandibular. In olfaction, odorant molecules are first detected in the olfactory epithelium (OE), and neural information is then transmitted to the olfactory bulb (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.

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 (Fig. 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 (Fig. 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].

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] (Fig. 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].

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

Research methodology

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).

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.

Results

Modification in cancer patients’ taste and smell 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 versus 37% of the women declared stronger sensation, 20% of the men versus 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 an increased sensitivity or hypersensitivity to taste and smell (section D); These three types of profiles are described below.

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	Groups (n) • Mean age • Men (n) • Women (n)	Cancer histology • 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
Section A: Heterogeneous chemosensory outcomes								
Hutton et al., 2007 [31]	Cross sectional	• 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)	• 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	• Chemosensory complaints score V Energy intake: Negative correlation • Chemosensory complaints score V Food enjoyment: Negative correlation • Severity of chemosensory complaints V Energy/Protein intake: Negative correlation • Increased olfactory sensitivity V Energy intake: Negative correlation • At the time point with the highest TSS score, severity of chemosensory complaints V Energy/Protein intake: Negative correlation • From case reports: Insufficient food intake due to taste changes and loss of appetite (T2)
Brisbois et al., 2011 [9]	Cross sectional	• 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)	• Food intake: 3-day diet diary	<i>Gustation and Olfaction:</i> • Altered in 60% of the patients	• Not mentioned	• Taste and food availability are the main determinants of food choice (self-reported by 52.2% of patients at T2)
McGreevy et al., 2014 [88]	Longitudinal study T0 = baseline (before CT) T1 = 2 m T2 = 4 m T3 = 6 m	• Patients (89) • 67 years • Men (40) • Women (49)	→ Lung • CT not specified	<i>Gustatory and olfactory modifications:</i> • Interviews + TSS (subjective)	• Food intake: 3-day diet diary + PGSCA	<i>Gustation and Olfaction:</i> • Altered in 68.5% of the patients (Gender differences)	• Not mentioned	• At the time point with the highest TSS score, severity of chemosensory complaints V Energy/Protein intake: Negative correlation • From case reports: Insufficient food intake due to taste changes and loss of appetite (T2)
Belqaid et al., 2016 [127]	Longitudinal T0 = Baseline T1 = 30-99 d T2 = After 100 d	• Patients (52) • 66.8 years • Men (21) • Women (31)	→ Lung • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	• Nutritional status: FFACT + PG-SGA	<i>Gustation and Olfaction:</i> • Altered in 73% of the patients (Individual differences: weak to strong effects depending on stimuli and individuals) <i>Gustation:</i> • Changes more frequent at T1 (p = 0.044)	• Food intake/ appetite (case reports): Loss of appetite and lower food intake, lower food enjoyment (T2)	• From case reports: 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	• Patients (55) • 51.5 years • Women (55)	→ Breast • Docetaxel • Paclitaxel • FAC • CMF	<i>Gustatory modification:</i> • QS developed for the study (subjective)	• Hunger • Food enjoyment • Appetite for food categories: Visual scale developed for the study	<i>Gustation:</i> • Changes more frequent at T1 (p = 0.044)	• Food enjoyment: Decrease in meal enjoyment at T1 (p = 0.021) • Appetite: Increased overall appetite with salty food (p = 0.0028)	• Taste and food availability are the main determinants of food choice (self-reported by 52.2% of patients at T2)

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Table 1 (continued)

Reference	Study type	Groups (n) Mean age Men (n) Women (n)	Cancer histology 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
Section B: Unaltered Chemosensation	Ovesen et al., 1991 [90]	Patients (52) 57 years Men (16) Women (36)	→ Lung • Cisplatin → Ovary • Carboplatin or cisplatin → Breast • FEC • Epirubicin → Esophagogastric • Capecitabine + oxaliplatin	<i>Gustatory threshold:</i> • Electrogustometry (objective) <i>Olfactory threshold</i> • Molecule = Pyridine [128] (objective)	• Food intake: 3-day diet diary	<i>Gustation and Olfaction:</i> • Decreased gustatory threshold for Lung Cancers (Higher sensitivity) • Unchanged olfactory threshold	• Food intake: No effect	• Chemosensory thresholds (T2) V Energy/Protein intake (T2); No relationship
	De Vries, 2017 [32]	Patients (15) 61 years Men (14) Women (1)	→ Esophagogastric • Capecitabine + oxaliplatin	<i>Gustatory and olfactory functions:</i> • AHSP (subjective) • Sniffin' sticks (objective) • Taste strips (objective)	• Appetite and hunger: AHSP • Food preferences: MTPRT	<i>Gustation:</i> No effect <i>Olfaction:</i> No effect	• Food preferences: No effect	• Lower self-reported taste preference for high-protein products; Positive correlation at all time-points • Sweet threshold / Bitter recognition (Cycle 2) V Energy intake (Cycle 2); Negative correlation
Section C: Hypo- chemosensation	Lara-Sanchez et al., 2010 [10]	Patients (30) 56 years Men (16) Women (14) Controls (30) 49.4 years Men (12) Women (18)	→ Breast → Lung → Prostate → Multiple myeloma Lymphoma • CT not specified	<i>Gustatory function:</i> • Qs developed for the study (subjective) • RMT (objective)	• Appetite: Qs developed for the study • Nutrient intake: SNUT program	<i>Gustation:</i> • 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)	• Food intake: No effect	• Sweet threshold / Bitter recognition (Cycle 2) V Energy intake (Cycle 2); Negative correlation
	Bolting et al., 2014 [20]	Patients (52) 50.4 years Women (52)	→ Breast • Anthracycline and/or taxane	<i>Gustatory function:</i> • ISO 3972:2011 (objective)	• Energy and macronutrients intake: 24 h dietary recall • Food liking score and Appetite: Qs developed for the study	<i>Gustation:</i> • 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)	• Food intake/appetite: Decreased appetite at T1 (P <0.0005) Positive correlation	• Changes in taste function (T1) V Food intake and appetite (T1): Positive correlation
Ijpma et al., 2016 [85]	Longitudinal T0 = Baseline T1 = During 1 st cycle T2 = Before 2nd cycle T3A = During 2nd cycle T3B = End 2nd cycle T4 = Completion CT T5 = 7 m. after CT start T6 = 1 year after CT start	Patients (21) 32 years Men (21) Controls (48) 32 years	→ Testicular • Cisplatin	<i>Gustatory function:</i> • AHSP (subjective) • Taste strips (objective) <i>Olfactory function:</i> • AHSP (subjective) • Sniffin' sticks (objective)	• Food intake: FFQ • Food preference: Visual task developed for the study • Body composition: DEXA	<i>Gustation and Olfaction:</i> • 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	• Food intake: No effect • Food preference: No effect • Body composition: Decreased lean mass and bone density, increased fat mass	• Not mentioned

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Table 1 (continued)

Reference	Study type	Groups (n) • Mean age • Men (n) • Women (n)	Cancer histology • 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
De Vries, 2017 [92]	Case-control Time point of assessment = random days during the full cycle of CT	• Patients (117) • 51 years • Women (117) • Controls (88) • 53.5 years	→ Breast • Taxanes • Anthracyclines • Taxanes + anthracyclines	<i>Gustatory and olfactory functions:</i> • AHSP (subjective)	• Habitual intake before CT: FFQ • Food intake: 2 24h dietary recalls during the overall CT	<i>Gustation and Olfaction:</i> • Lower self-reported taste, smell in comparison with the controls; <i>Gustation:</i> • Decreased self-reported and objective gustation <i>Olfaction:</i> • Decreased self-reported and objective olfaction (lower sensitivity)	• <i>Appetite:</i> Lower self-reported appetite and hunger in patients. • <i>Food intake:</i> Patients had a lower energy intake and lower appetite during CT (not before) • <i>Food preferences:</i> Decreased liking for high fat and high protein products at T2. Higher liking for savory food at T0 and T3	• Self-reported taste perception ability V Energy intake: Positive correlation • Self-reported smell perception ability V Energy intake: No correlation • Self-reported taste perception ability V Preference for high-protein food, low energy food, savory food, sweet food: Positive correlation • Self-reported smell perception ability V Preference for low energy food and sweet food: Positive correlation at all time-points • Increase of sweet detection threshold (T1) V Decrease of protein intake (T1): Positive correlation (P=0.01)
De Vries, 2018 [91]	Longitudinal T1 = Baseline T2 = During CT T3 = 1-3 wks > CT T4 = 6 m after the end of CT	• Patients (28) • 51 years • Women (28) • Controls (28) • 51.8 years	→ Breast • Taxanes • Anthracyclines + taxanes • Platinum-containing	<i>Gustatory and olfactory function:</i> • Qs developed for the study (subjective) • Sniffin' Sticks (objective) • Taste strips (objective)	• Food preferences: MTPRT • Taste preference: Preference task [100,129]	<i>Gustation:</i> • Decreased self-reported and objective olfaction (lower sensitivity)		
Section D: Hyper-chemosensation Turcott, 2016 [8]	Longitudinal study T0 = Baseline T1 = After 2 cycles	• Patients (40) • 55.5 years • Men (20) • Women (20)	→ Lung • Paclitaxel + cisplatin	<i>Gustatory function:</i> • RMT (objective)	• Body weight • Food intake: SNUJT program impairment: PGSGA • FAACT • Body composition: Bioelectric impedance analysis	<i>Gustation:</i> • Higher sensitivity to bitter and umami tastes (P=0.02).	• <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	

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 Absorptiometry (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 + epirubicin; FFQ = Food Frequency Questionnaire (questionnaire for dietary intake assessment, [132-135]; ISO 3972:2011 = International Standards Organization 3972:2011 (a standardized sensory analysis-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]); SNUJT 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).

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 three time-points for assessments including a baseline (T0), a first follow-up before the second cycle of chemotherapy (T1) and a second follow-up 3 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 two cycles of chemotherapy, an increase in complaints about gustatory perceptions was associated with a decreased ability to identify bitter taste in patients.

The “hypersensitivity 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 hypergustatory 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.

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 three cross sectional studies and 10 longitudinal studies that followed patients for a period from 6 weeks [8] (two 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 irinotecan, a drug commonly used 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) depend on the expression of gustatory receptors. Therefore, without considering cancer histology or treatment, the status of patients (hypo vs hypersensitive) toward bitterness perception is inherently different. This

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] and umami perception [108]
Genetic variation in olfaction Density of fungiform papillae	Genetic variations in the expression of olfactory receptors lead to differences in odor perception [112] 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 Oral physiology	Flow and composition of saliva influence chemosensory perception [109–111] 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]

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 interindividual variation in a non-pathologic state, and this may explain the different olfactory phenotypes during cancer and chemotherapy. Prevalent genetic variations in olfactory receptors lead 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 physiological 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].

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 hypersensitivity), the lower was the energy intake of patients. The three 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 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 prefer-

ences, 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 two 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 two 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. Using a 24-hour dietary recall, De Vries et al. [119] reported a significantly lower energy, protein, and fat intake in 117 women with a diagnosis of breast cancer compared to 88 healthy controls. 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 1–3 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 hyposensitivity 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].

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

Declarations of interest

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Authors’ contributions

K.D. prepared and analysed the database. K.D., A.D., A.G. and M.B. drafted the manuscript. All authors contributed to, and approved, the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Supplementary materials

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*Chapter VI. Impact of taste and smell
alterations on food behavior*

Self-reported approach
Study 2.a

The impact of taste and smell alteration severity on food perception in cancer patients undergoing chemotherapy

Drareni, K.^{1,2}, Bensafi, M.², Giboreau A.¹, Dougkas, A.¹

¹Institut Paul Bocuse Research Centre, Ecully Cedex, France

²CNRS, UMR5292, INSERM U1028, Lyon Neuroscience Research Center, University Lyon, France

Abstract

Chemotherapy-induced taste and smell alterations may have a negative impact on quality of life and nutritional status. A prominent issue when dealing with taste and smell alterations and their consequences on behavior and well-being lies in the variation arising from individual differences in chemosensory perceptions. The main aim of this study is to examine the effect of taste and smell alterations on self-reported food behavior and food perception in a group of heterogeneous cancer patients considering different level of severity in chemosensory alterations of patients. Eighty-nine cancer patients completed a questionnaire subdivided into two part: a chemosensory part that allowed classification of patients in three groups (“no alteration”, “Moderat alterations” and “Severe alterations”), and a food behavior-related part. The results highlighted a negative impact of chemosensory alterations on food perception. Patients with severe chemosensory alterations reported significantly more frequent food perception problems, including modification of the perceived taste of food, finding bad taste in all food, and being unable to perceive food taste. Patients in late stage of chemotherapy reported more severe chemosensory alterations and perception of bitter taste was identified as predictor of food perception modifications. Our results underline the importance of providing specific attention to chemotherapy-induced taste and smell alterations with a consideration of the individual differences between patients.

Key words: Taste, Smell, Alterations, Food perception, Individual variability

1. Introduction

Taste and smell alterations modifications are mentioned as one of the most distressing chemotherapy side-effects in cancer patients during the treatment [1]. Changes of taste and smell perceptions have significant impact not only on quality of life, but also on nutritional status of patients and their relationship to food [2]–[4]. Previous studies reported a negative impact of taste and smell alterations on food behavior including a decrease in food intake [5], [6], a decrease in appetite [5], [7], [8] and a loss of food enjoyment [9]. Hence, it appears fundamental to better understand chemotherapy-induced taste and smell alterations in order to ameliorate this side effect and improve patients' quality of life, especially in relation to food.

A prominent issue when dealing with taste and smell alterations and their consequences on behavior and well-being lies in the variation arising from individual differences in chemosensory perceptions [10]. Indeed, whereas some patients have no taste and smell alterations [11], [12], others complain about a decrease [5], [13]–[16], or an exacerbation in taste and/or smell sensitivity [16]–[19]. Based on a Taste and Smell Survey questionnaire, Hutton et al. and Brisbois et al. showed that a higher score of chemosensory complaints (including taste and smell) was correlated with a lower energy and protein intake [20], [21] which expose patients to weight loss and a risk of malnutrition [22]. Therefore, considering chemosensory abilities of patients individually is essential to better understand how taste and smell alterations affect patient' relationship with food.

The stage of chemotherapy could further add complexity in the reported taste and smell alterations. Most of previous studies showed a decrease in patients' taste and smell abilities when assessed at different time points of chemotherapy. Particularly, a decrease in patients taste and smell abilities is observed the longer the chemotherapy treatment goes [5], [15], [23]. For instance, Steinbach et al. reported lower olfactory and gustatory function in cancer patients who received carboplatin for breast or ovarian cancer after 3 months of treatment [15], while IJpma et al. and Boltong et al. reported a lower sensitivity to salty taste in testicular and breast cancer respectively at the final cycle of chemotherapy [5], [23]. Understanding the evolution of taste and smell alterations across the treatment may enable to provide an adapted support to patients considering the fluctuations in their perceptive abilities, and the consequences that this may have on different aspects of their quality of life.

The main aim of this study is to examine the effect of taste and smell alterations on self-reported food behavior and food perception in a group of heterogeneous cancer patients considering

different level of severity in chemosensory alterations of patients. We hypothesized that patients experiencing severe taste and smell alterations have more difficulties to consume certain food and to perceive the flavor of food compared to patients without taste and smell alterations. Variation in taste and smell alteration severity was considered by running a cluster analysis of patients based on their self-reported taste and smell abilities. Moreover, in an exploratory analysis, the stages of chemotherapy were considered by examining whether taste/smell alteration level of severity can be associated with particular stages (early/late) of chemotherapy.

2. Material and methods

2.1. Participants

Participants were recruited in the oncology hospital day care of *Infirmierie Protestante* clinic in Caluire (France). Exclusion criteria comprised head and neck cancers, patients with parenteral nutrition, and patients with other cancer treatments than chemotherapy. The recruited patients were receiving chemotherapy as main treatment for different type of malignancies. The collection of data was conducted during their administration of chemotherapy treatment. All participants had the full ability to understand and participate to the experimental procedure and provided written informed consent. The study was approved by the ethical board of Hospices Civils de Lyon (N.REF: Rech_FRCH_2017; N.REF: Dossier 0024).

A total of eighty-nine patients were recruited (58.4% female and 41.6% male; mean age of 66 ± 11.7 years). The most frequent cancer type was digestive cancer ($n=35$) followed by breast (17), lung (17), gynecologic (13), lymphoma (4), bladder (2) and myeloma (1) cancers. Patients were considered at « *early stage* » of chemotherapy if they were at their third cycle of chemotherapy or less, and at « *late stage* » after the third cycle of chemotherapy. Note that mean age of the early chemotherapy group was 63 ± 10.8 whereas mean age for the late chemotherapy group was significantly higher (69.3 ± 11.9).

2.2. Study design

The study followed a cross-sectional design, where self-reported taste and smell abilities of cancer patients and their food behavior were assessed. Patients received the questionnaire prior to lunch time (between 11 a.m. and 12 p.m. for all participants). The questionnaire was a modified version of CiTAS scale (Chemotherapy induced Taste Alterations) [24] to which we added a part on olfactory capabilities assessment, since the original CiTAS scale is a tool for taste alterations measurement only. The questionnaire was subdivided into two part: the first

part was dedicated to chemosensory assessment and the second part was dedicated food behavior, oro-nasal sensations and food perception assessment as detailed below.

2.3. Assessment of taste/smell detection abilities

The 10 first items of the questionnaire were used to characterize quantitative taste/smell abilities. Here, patients were asked to answer the following question for each item: « Since the beginning of chemotherapy, I detect easily tastes (item 1), bitter taste (item 2), sour taste (item 3), salty taste (item 4), sweet taste (item 5), odors (item 6), food odors (item 7), flower odors (item 8), body odors (item 9), irritant odors (item 10) ». Patients provided their response using a four-point scale labeled as follows: 1 “never”, 2 “sometimes”, 3 “often”, 4 “always”. Responses to this questionnaire were used to reveal the profile of taste and smell alteration in the cancer patients, as described in section 2.5.

2.4. Assessment of food behavior, oro-nasal sensations, food perception

To examine food behavior, oro-nasal sensations and food perception, participants were asked to fill the second part of the questionnaire. The assessment of food behavior was made through 8 items: “Since the beginning of chemotherapy, I have less appetite (item 1), I have difficulties eating meat (item 2), I have difficulties eating fatty food (item 3), I have difficulties eating hot food (item 4), The odor of food bothers me (item 5)”, “I eat less because, I feel tired (item 6), I have mouth pain (item 7), I have nausea (item 8)”. The six following items were aimed at characterizing oro-nasal sensations: “Since the beginning of chemotherapy, I have a bitter taste in my mouth (item 1), Everything is bitter (item 2), I have an unpleasant taste in my mouth (item 3), I perceive an unpleasant odor permanently (item 4), All odors are unpleasant for me (item 5), I perceive odors without the presence of odor source (item 6)”. Finally, four items evaluated food perception: “Since the beginning of chemotherapy, Food tastes different from usual (item 1), Everything tastes bad (item 2), I hardly perceive food taste (item 3), I am unable to perceive the odor of food (item 4)”. Patients used a four-point scale (1 “never”, 2 “sometimes”, 3 “often”, 4 “always”) to provide their responses.

2.5. Data analysis

Descriptive statistics are expressed as Mean \pm Standard Deviation (SD) for all variables. The classification of patients as a function of their self-reported taste/smell abilities (based on the questionnaire presented in section 2.3) was performed using a hierarchical clustering (Ascendant Hierarchical Clustering, based on Euclidean distances, Ward method, XLStat®). Seven data points (out of 890) were missing and replaced by the mean of the distribution. This

analysis generated 3 profiles of patients (see section 3.1 below: “no alteration”, “moderate alteration”, “severe alteration”). A Pearson correlation was performed to examine the correlation between all items of the questionnaire. To examine the effect of these profiles on food behavior, oral nasal sensation and food perception, a one-way ANOVA using taste/smell profiles (3: “no alteration”, “moderate alteration”, “severe alteration”) as a between-subjects factor was performed for each item developed in section 2.3. In case of significance, Tukey post-hoc tests were performed. A multiple linear regression was run to predict food perception problems (part 3) based on chemosensory related items (questionnaire of section 2.2). Finally, to examine how taste/smell profiles are associated with chemotherapy stage, the number of patients in early/late stages of chemotherapy in each of the three profiles were compared using a Chi-square test.

3. Results

3.1. Determining taste/smell profiles

A hierarchical clustering method based on the taste/smell questionnaire (section 2.3) allowed the classification of patients in three groups (*Figure 1.a*). A *Chemosensory score* corresponding to the mean rating values for the ten items related to the detection of tastes and odors was calculated for each patient (possible range from 1 to 4 for each item, indicating ‘never’ and ‘always’ respectively). The mean values of this score were then compared across classes defined by the hierarchical clustering (*Figure 1.b*).

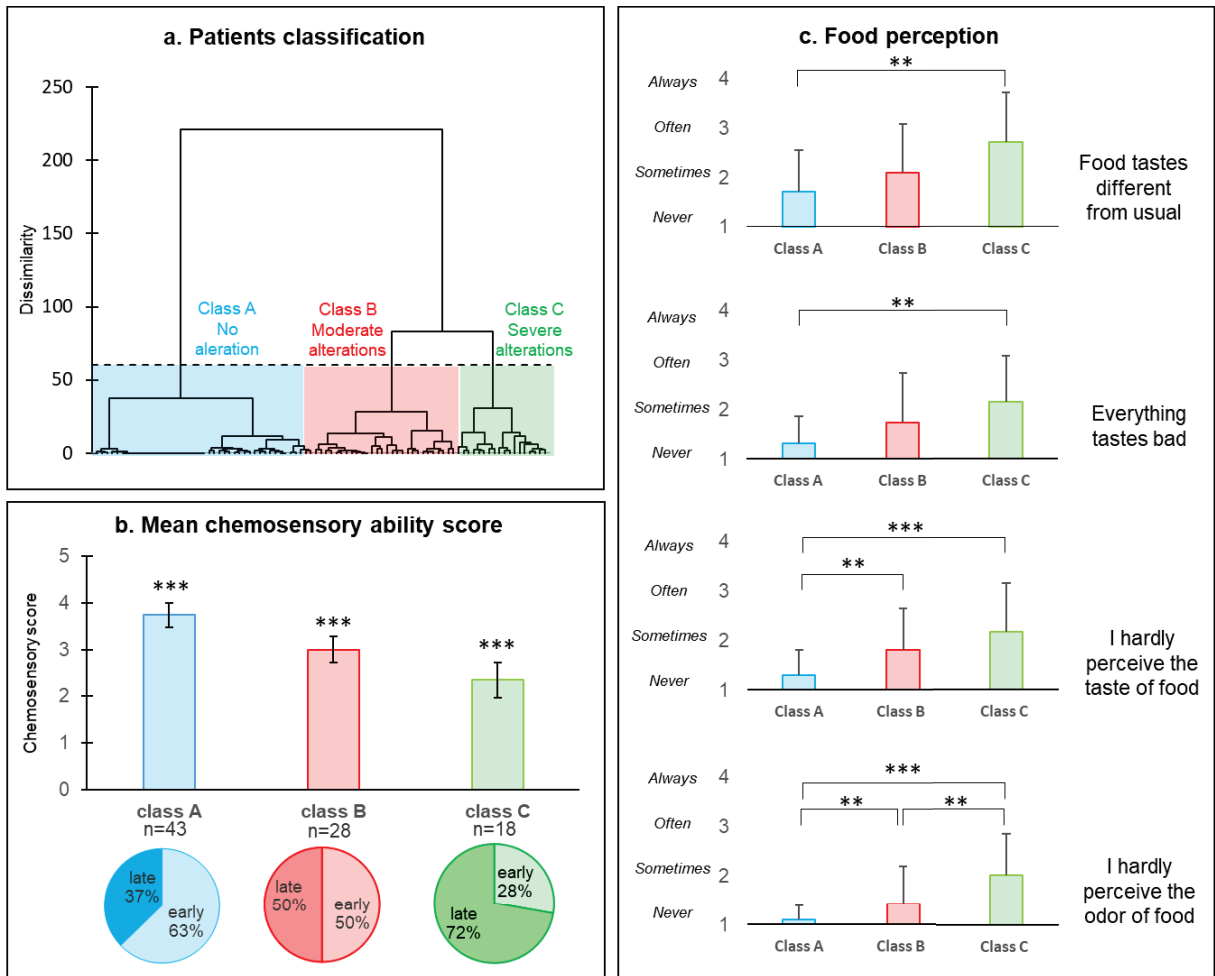


Figure 1. (a) Classification of patients based on self-reported sensory abilities. The hierarchical clustering resulted in three groups: no alteration (class A in blue), medium alterations (class B in red) and severe alteration (class C in green). (b) Mean chemosensory scores (mean \pm SD) and distribution of chemotherapy stages in each group. Chemosensory score was significantly lower in class B compared to class A and in class C compared to class A and B ($p < .001$ in all cases). A significant dependency was found between chemosensory profiles (“no alterations”, “medium alterations”, “severe alterations”). Chi-square test: $\chi^2 = 6.27$; $p = 0.04$. (c) Answers of patients to food perception related items (mean \pm SD). Patients with severe chemosensory alterations are more likely to report that food tastes different from usual ($p = 0.002$), everything tastes bad ($p = 0.002$), they hardly perceive the taste of food ($p < .001$), and they hardly perceive the odor of food ($p < .001$).

Patients in the first group (class A) had the highest chemosensory score (3.73 ± 0.26). In this group, patients reported almost always detecting easily the proposed taste modalities and smell categories. This class was thus labelled as “no alterations” profile. Patients in the second group (class B) were less consensual, reporting struggling sometimes or often in detecting tastes and odors. The mean chemosensory score was 2.99 ± 0.27 . Patients composing this group were considered as patients with “medium alterations” profile. The third group (class C) was

composed of patients who declare having difficulties in detecting tastes and odors, and so, presenting severe chemosensory alterations. The mean chemosensory score in the class C was the lowest (2.34 ± 0.37). Individuals belonging to this group were thus labelled as “*severe alterations*” profile patients.

3.2. Correlation between chemosensory- and food-related items

A Pearson correlation was performed on all the items to identify potential bias due to correlation between sensory items and the other items of the questionnaire (Table 2). For the sensory related items, strong correlation was found between the easiness to perceive sour and bitter ($R=0.72$; $p < .0001$), easiness to perceive odors in general and food odors ($R=0.79$; $p < .0001$), easiness to perceive body odors and floral odors ($R=0.77$; $p < .0001$), easiness to perceive body odors and irritant odors ($R=0.76$; $p < .0001$).

	Tastes	Bitter	Sour	Salty	Sweet	Odors	Food odors	Floral odors	Body odors	Irritant odors	Food item 1	Food item 2	Food item 3	Food item 4
Tastes	1	0,489	0,587	0,482	0,510	0,580	0,539	0,538	0,442	0,491	-0,418	-0,384	-0,453	-0,493
Bitter		1	0,729	0,436	0,515	0,268	0,257	0,427	0,509	0,427	-0,398	-0,386	-0,356	-0,294
Sour			1	0,613	0,459	0,368	0,526	0,426	0,401	0,475	-0,440	-0,412	-0,401	-0,509
Salty				1	0,457	0,283	0,410	0,264	0,216	0,256	-0,330	-0,411	-0,334	-0,309
Sweet					1	0,431	0,423	0,454	0,376	0,351	-0,238	-0,238	-0,320	-0,263
Odors						1	0,792	0,626	0,564	0,657	-0,199	-0,142	-0,230	-0,528
Food odors							1	0,561	0,462	0,556	-0,228	-0,159	-0,205	-0,549
Flower odors								1	0,775	0,676	-0,216	-0,196	-0,217	-0,519
Body odors									1	0,763	-0,188	-0,200	-0,137	-0,390
Irritant odors										1	-0,203	-0,219	-0,209	-0,486
Food item 1											1	0,773	0,770	0,418
Food item 2												1	0,733	0,361
Food item 3													1	0,531
Food item 4														1

Table 1. Pearson's correlation matrix of sensory and food perception related items. The values correspond to Pearson's R. R values that are above 0.7 were considered as reflecting a strong correlation. Food item 1: *Food tastes different from usual*; Food item 2: *Everything tastes bad*; Food item 3: *I hardly perceive food taste*; Food item 4: *I am unable to perceive the odor of food*.

For the food perception related odors, the item “Food does not taste the same as usual” was strongly correlated with the two items “everything tastes bad” ($R= 0.77$; $p < .0001$), and “I have difficulty to perceive food taste” ($R=0.77$; $p < .0001$), and the item “everything tastes bad” was correlated with the item “I have difficulty to perceive food taste” ($R=0.73$; $p < .0001$). However, no major correlation was found between the chemosensory items and the food perception related items (R value ranging from -0.14 to -0.528).

3.3. Effect of taste/smell alteration profiles on self-reported food perception

A one-way ANOVA was used to examine the effect of chemosensory alterations on food behavior, oro-nasal sensations, and food perception (respectively part 1, part 2 and part 3 of the questionnaire presented in section 2.3). Table 1 summarizes the obtained results.

	Questionnaire items related to food problems	Mean patients' ratings (possible range 1-4)			p-value
		No alterations	Medium alterations	Severe alterations	
Part 1 Food Behavior Since the beginning of chemotherapy :	I have less appetite	2.16 ± 0.9	2.57 ± 0.95	2.44 ± 0.95	NS
	I have difficulties eating meat	1.95 ± 1.06	2.39 ± 1.03	2.27 ± 0.98	
	I have difficulties eating fatty food	2.16 ± 1.13	2.46 ± 0.96	2.44 ± 0.83	p<.02
	I have difficulties eating hot food	1.55 ± 0.9	2.25 ± 1.07	1.66 ± 0.74	
	The odor of food bothers me	1.88 ± 0.98	2.25 ± 1.05	1.72 ± 0.86	
I eat less because :	I feel tired	2.20 ± 1.03	2.41 ± 0.71	2.18 ± 0.88	NS
	I have mouth pain	1.45 ± 0.76	1.88 ± 1.01	1.43 ± 0.78	
	I have nausea	1.87 ± 0.92	2.12 ± 1.01	1.82 ± 0.78	
Part 2 Oro-nasal sensations Since the beginning of chemotherapy :	I have a bitter taste in mouth	1.34 ± 0.75	1.84 ± 0.89	1.47 ± 0.77	NS
	Everything tastes bitter	1.18 ± 0.62	1.52 ± 0.82	1.50 ± 0.86	NS
	I have an unpleasant taste in mouth	1.52 ± 0.86	1.88 ± 1.01	1.87 ± 0.92	
	I perceive an unpleasant odor permanently	1.18 ± 0.5	1.28 ± 0.67	1.58 ± 0.84	NS
	All odors are unpleasant for me	1.32 ± 0.56	1.50 ± 0.7	1.52 ± 0.6	
	I perceive odors without the presence of odor source	1.20 ± 0.4	1.40 ± 0.7	1.23 ± 0.42	
Part 3 Food perception (figure 1.c) Since the beginning of chemotherapy :	Food tastes different from usual	1.71 ± 0.83	2.08 ± 0.99	2.70 ± 1.01	p<.003
	Everything tastes bad	1.30 ± 0.55	1.73 ± 1	2.12 ± 0.92	p<.003
	I hardly perceive food taste	1.30 ± 0.51	1.80 ± 0.84	2.17 ± 0.98	p<.001
	I am unable to perceive the odor of food	1.09 ± 0.29	1.42 ± 0.75	2.00 ± 0.84	p<.001

Table 2. Means (+/-SD) of patients' ratings on items related to food behavior (part 1), oro-nasal sensations (part 2), and food perception (part 3) as a function of their chemosensory profiles (No alterations/ Medium alterations/ Severe alterations). For each item, the three groups were compared using a one-way ANOVA (the column "p-value" illustrates the level of significance of the group effect).

Patients with severe chemosensory alterations reported having more often the feeling that *food tastes different from usual* ($F(2,81)= 6.95, p= 0.002$), that *everything tastes bad* ($F(2,82)= 6.83, p= 0.002$), and they have more *difficulties in perceiving food taste* ($F(2,83)= 9.57, p<.001$), and

being *unable to perceive food odors* ($F(2,83)= 14.01, p<.001$) (Figure 1.c and table 1). Note that patients with no chemosensory alterations were those reporting the lowest rating across all the items of the questionnaire. Moreover, patients with medium chemosensory alterations reported having more difficulties eating hot food ($F(2,86) = 4.82, p= 0.01$). Finally, no significant effect of chemosensory profile on self-reported appetite, fatigue, nausea, and difficulty in eating meat, fatty food and on all items related to oro-nasal sensations were observed ($p>.05$ in all cases).

Multiple linear regressions were calculated to examine more closely the involvement of sensory components on food behavior and specifically on perception of sensory characteristics of food. The dependent variables were the items composing the part 3 of the food behavior questionnaire (four items). The explicative variables included in the model were perception of: tastes in general, sweet taste, bitter taste, sour taste, salty taste, odors in general, food odors, flower odors, body odors, irritant odors. For each item, a significant regression equation was found as displayed in table 3.

The high sensitivity to bitter taste is likely to explain the increase in food perception problem. Patients who declared detecting bitter taste easily reported more that “*food tastes different from usual*”, “*everything tastes bad*”, and that they “*hardly perceive the taste of food*” (table 3).

3.1. Association between chemosensory alterations profile and chemotherapy stage

To examine how chemosensory alteration profiles are associated with chemotherapy stage, we compared the number of patients in early and late stage of chemotherapy in each of the three sensory profiles. Results showed a significant dissociation whereby: in class A (“no alteration” profile), 63% of patients were in the early stage of chemotherapy vs. 37% in the late stage, in class B (“moderate alterations” profile), 50% were in early stage vs. 50% in late stage, and in class C (“severe alterations” profile), 28% were in the early stage of chemotherapy vs. 72% in the late stage (Figure 1.b, lower panel). A Chi-square test showed a significant dependency between chemosensory profiles and stages of chemotherapy ($\chi^2= 6.27; p=0.04$).

	Food tastes different from usual <i>Estimated β ($\pm SD$)</i>	Everything tastes bitter <i>Estimated β ($\pm SD$)</i>	I hardly perceive the taste of food <i>Estimated β ($\pm SD$)</i>	I have hardly perceive the odor of food <i>Estimated β ($\pm SD$)</i>
Tastes in general	-0.332* (0.139)		-0.334** (0.114)	
Bitter	-0.277 * (0.117)	-0.244* (0.096)	-0.202* (0.095)	
Sour				
Salty		-0.315** (0.11)		
Sweet				
Odors in general				
Food odors				-0.337*** (0.085)
Floral odors				-0.188* (0.075)
Body odors				
Irritant odors				
R ²	0.213	0.248	0.236	0.335
n	89	89	89	89

Table 3. Multiple regression analysis using the food perception items of the food behavior questionnaire (columns) as dependent variables and the ten items of the sensory questionnaire (lines) as explicative variables. A stepwise method of regression was followed.

* $p < .05$ ** $p < .01$ *** $p < .001$

4. Discussion

The aim of the present study was to examine the influence of chemosensory alterations on food behavior and food perception of cancer patients undergoing chemotherapy. To this end, patients were first classified as a function of their self-reported taste/smell abilities. A cluster analysis enabled to categorize patients in three classes: patients expressing no taste and smell alterations, patients with moderate alterations and patients with severe alterations.

A first result of interest stems from the analysis that highlighted a negative impact of chemosensory alterations on food perception. This analysis has not only replicated previous studies [3], [5], [14], [19], but it has also shown that taking into account the heterogeneity in taste/smell alterations is essential. If the analysis had focused on the sample as a whole, the effect on food perception would have been attenuated because some participants have no chemosensory alterations, which does not affect their perception of food. Considering different profiles of individuals, we showed that patients with severe chemosensory alterations reported

significantly more frequent food perception problems, including modification of the perceived taste of food, finding bad taste in all food, and being unable to perceive food taste. Note that complaints about food being tasted different during chemotherapy are recurrent in cancer patients [25]–[27]. For instance, a group of patients with breast cancer reported major changes in eating habits as a consequence of taste and smell disturbances; these changes were mainly due to the presence of metallic taste in mouth, and the fact that food does not taste like it should [27]. Moreover, many patients complained about perceiving food as bland, and consequently having no longer satisfaction, comfort or pleasure from eating, and most importantly a decreased ability to distinguish fresh and spoiled food or beverage [25]. The perception of taste and smell plays a prominent role in food intake and maintaining the pleasure of eating. It is therefore of great importance to determine the severity of these chemosensory disturbances (by determining taste/smell profiles) in order to find the best strategy to support patients and improve their daily lives.

The results of the multiple regression showed that the perception of bitter taste is a common predictor of food perception problems. Patients who declared detecting bitter taste easily reported more that “*food tastes different from usual*”, “*everything tastes bad*”, and that they “*hardly perceive the taste of food*”. This result suggests that the difference in food perception is mainly related to the perception of bitter taste. The perception of bitter taste to be more strong was previously reported in patients with different types of cancer [20]. Interestingly, bitter taste perception was found to be highly variable between individuals: the ability to (hypo or hyper) perceive specific molecules (phenylthiocarbamide and 6-n-propylthiouracil) depend on the expression of gustatory receptors [28]–[30]. Therefore, without considering cancer histology or treatment, the status of patients (hypo vs hyper-sensitive) toward 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 [31], [32].

A second result of interest deals with the observed interaction between the taste/smell alteration profiles and the stage of chemotherapy. In our study, the major part of patients that reported no taste and smell perception problems were at an early stage of chemotherapy whereas the group of patients that reported more chemosensory difficulties was mainly composed of patients at a late stage of chemotherapy. Although the present study design is cross-sectional, our results are in line with a series of longitudinal studies that reported a degradation of chemosensory abilities with the progression of the chemotherapy [5], [15], [23]. Chemosensory disturbances

have been described in patients with different cancer types [5], [15], [23], with different chemotherapy regimens [33], [34] and using different methodologies [35]. However, the etiology of this side-effect remains a topic highly addressed in the literature. Some type of chemotherapies such as cisplatin were shown to induce more toxicity at a cumulative dose [13], [36] resulting in an evolutive cytotoxic effect with the progression of the treatment. Considering the cytotoxic effect of chemotherapy on rapidly dividing cells, and so, on taste and smell receptors [37], the observed dependency between chemotherapy stage and chemosensory alterations is not surprising, since patients at late stage of chemotherapy received a higher dose of cytotoxic molecules. Another explanation could be related to the age of participants. In the studied sample, the mean age of patients in the “late chemotherapy” group was significantly higher than the mean age of patients in the “early chemotherapy” group. Given the effect of sensory ageing on taste and smell abilities [38], [39], age of participants could also contribute to the observed decrease in their taste and smell abilities.

Although our study provides evidence that taste/smell alteration profile influences food perception, some of our methodological choices require discussion. A first limitation of our experiment deals with the subjectivity of the method of assessment. Indeed, our taste/smell ability classification is based on patients’ self-reports, and therefore reflected a subjective feeling of alteration rather than an objective chemosensory dysfunction. The use of subjective approach for taste and smell assessment is controversial, especially for the olfactory function [40]. Olfaction is a part of flavor elaboration and olfactory inputs are of most importance in the food experience. Giving the limited ability of human to report olfactory disturbances and more generally the limitations of olfactory language [41], it would be important in future studies to use objective approaches (e.g. psychophysics type) for a more reliable classification. Although objective physiological measurements could assist with developing strategies to prevent or treat disturbances, patients self-reported experiences of taste and smell alterations has been suggested to be a more appropriate predictor of food behavior [26], [42]. A second limitation is the heterogeneity within the sample in term of cancer site. Although homogeneous group would have brought stronger results, our group of participants allowed to respond to our research questions, since the focus of the study was to examine the effect of chemosensory abilities on food perception and food behavior regardless of other factors including cancer type and chemotherapy regimen. Furthermore, a multiple regression model showed no effect of age, gender, cancer type on patients’ chemosensory score in the studied sample (data not shown).

5. Conclusion

Notwithstanding the above limitations, our study offers new insights into the effect of taste and smell alterations on food perception in cancer patients, showing that considering diversity in chemosensory profiles is crucial. We showed in a group of 89 cancer patients undergoing chemotherapy, that 48% exhibited no taste and smell alteration, 31.5% had moderate alterations and 20,5% had severe alterations. The distribution of chemotherapy stages was not similar within these three groups suggesting a cumulative effect of cytotoxic chemotherapy on taste and smell perception throughout the treatment. The intensity of alteration in taste and smell perceptions had an impact on patients' food perception. Patients with severe chemosensory alterations declared more often that food has an unpleasant taste, that it does not taste the same as before, and reported difficulties in detecting food tastes and odors. Our results highlighted the negative effect of sensory alterations on patients' food behavior and underline the importance of providing specific attention to this chemotherapy side effect, with a consideration of the individual differences between patients. An important question that will need to be addressed in future studies is whether improving the perception of tastes and smells in patients whose taste and olfaction are most affected can improve their perception of food. This issue deserves to be evaluated by using, for example, protocols in which flavored dishes are proposed to patients suffering from cancer. Such an enterprise should be designed in an interdisciplinary manner combining skills in oncology, nutrition, food science, culinary art, psychology and neuroscience.

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Objective approach
Study 2.b

Hyposmia in cancer patients undergoing chemotherapy impacts food behavior

Drareni K.^{1,2}, Dougkas A.¹, Laville M.³, Souquet P.J.³, Nazare, J.A.⁴, Fournel, P.⁵, Hummel T.⁶, Giboreau A.¹, Bensafi M.²

¹Institut Paul Bocuse Research Centre, Ecully Cedex, France

²CNRS, UMR5292, INSERM U1028, Lyon Neuroscience Research Center, University Lyon, France

³CH Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France

⁴Centre de Recherche en Nutrition Humaine Rhone-Alpes and CENS, CH Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France

⁵Institut de Cancérologie de la Loire Lucien Neuwirth, Centre Hospitalier Universitaire de Saint-Étienne, France

⁶Smell and Taste Clinic, Department of Otorhinolaryngology, University Hospital Dresden, Germany

Abstract

Cancer patients undergoing cytotoxic chemotherapies exhibit a series of adverse side effects including modifications in taste and smell perception. Particularly, olfactory alterations are often underestimated, although declared as frequent by cancer patients. Given the influence of smell alterations on quality of life, especially related to food behavior, cancer and chemotherapy induced smell alterations need to be further studied for a better management of this side effect. The main aim of the present study was to test clinically and experimentally relationship between olfactory deficits and patients' food habits. Forty-four bronchial cancer patients receiving cisplatin and 44 controls age and gender matched participants were tested olfactory and gustatory function using the European Test of Olfactory Capabilities and the Taste Strips test. Participants reported their food and dietary habits by filling a self-administered questionnaire. Patients were tested under two different sessions: the first session was conducted before the beginning of the treatment, and the second one 6 weeks later, after 2 cycles of chemotherapy. Controls were tested under the same protocol with two sessions separated by 6 weeks. The

results highlighted a decreased taste and smell abilities in almost half of the lung patients' group even before the exposition to Cisplatin. Patients rated typical food odors as less edible compared to controls, possibly involving alterations in odor cognitive processing due to cancer. Within the patients' group, hyposmics reported using more condiments, possibly as a compensatory mechanism to their decreased sensory abilities. Our results confirm the effect of chemosensory alterations on patients' food behavior and underlie the involvement of olfaction in food perception and more specifically, the impact of reduced olfaction on dietary practices including seasoning. Experimental studies are needed to better understand the sensory compensatory mechanisms, and how using condiments may improve patients' food enjoyment.

Key words: Taste, Smell, Bronchial cancer, Cisplatin chemotherapy, Food behavior

1. Introduction

Cancer patients undergoing cytotoxic chemotherapies exhibit a series of adverse side effects including modifications in taste and smell perception [1]–[6]. The methodological and individual differences through studies examining taste and smell alterations in cancer patients undergoing chemotherapy [7] resulted in a wide range of prevalence of this side effect [8]. Particularly, olfactory alterations are often underestimated, although declared as frequent by cancer patients [9]. Furthermore, different types and severity of olfactory disturbances are reported or diagnosed in cancer patients (hyposmia: partial loss of smell; anosmia: total loss of smell, phantosmia: unpleasant smell without presence of stimuli). Smell alterations are observed in patients with different types of cancers and chemotherapy regimens, but certain molecules are more likely to induce this side effect than others [8], [10]. Cisplatin chemotherapy is known to induce distressing side effects comprising qualitative and quantitative chemosensory perception disturbances [11]–[16]. It is a common part of the treatment for several cancer types such as lung, ovary, testicle, bladder, and some types of digestive cancers. These cancers (and especially lung cancer) are among the most frequent cancer types, thus the proportion of patients that are exposed to Cisplatin, thus to its consequences on chemosensory abilities, is non-negligible.

Literature examining the interaction between cancer, chemotherapy, smell and food behavior suggests that before and/or during chemotherapy treatment, the sensitivity of a patient to olfactory stimuli is likely to modulate his/her food behavior [17]–[22] [2] [18] [19]. However, these studies often analyzed smell without dissociating it from taste [23], [25], and used self-

reported questionnaires [17], [18], [20]–[22], which is more likely to report odor annoyance, rather than smell perception ability [9]. Given the influence of smell alterations on quality of life, especially related to food behavior [9] [10], cancer and chemotherapy induced smell alterations need to be further studied for a better quantification, diagnosis and management of this side effect. Whereas some previous studies examined patients' food behavior during chemotherapy [24], [28]–[30], the question of whether smell alterations influence food behavior in cancer patients undergoing chemotherapy is less explored.

The main aim of the present study was to test clinically and experimentally relationship between olfactory deficits and patients' food habits by combining objective psychophysical tools (to assess olfactory function) with interview-based methods (to assess food habits). Since the olfactory information is processed at different levels from stimulus detection (peripheral level) to identification and more perceptual ratings (central level: estimates of odor pleasantness, odor familiarity and odorous object edibility), we also aimed to examine how cancer and chemotherapy affect these different stages of odor processing. Moreover, as the above described olfactory alterations during chemotherapy is very often accompanied by changes in taste perception, we further aimed to examine how both cancer and chemotherapy influence gustatory function.

2. Methods

2.1. Participants

The study included forty-four patients treated for bronchial cancer and forty-four healthy control participants without any history of cancer and chemotherapy. The recruitment of patients was conducted in two centers: 22 patients were treated at Lyon Sud Hospital Center, and 22 patients at Saint-Etienne hospital (France). Criteria for patient selection were as follows: Patients scheduled for Cisplatin-based chemotherapy for small or non-small cell lung cancers, with no previous chemotherapy treatment, no prior oro-nasal impairment, and no gastrointestinal disorders. Control individuals were age- and gender-matched with patients and had no history of oro-nasal impairment and/or neurologic pathology. Patients were recruited during the medical consultation preceding the chemotherapy launching, after having received oral explanation of the study and an information note from their doctor. Controls were recruited via posters and flyers distributed in Lyon (France).

All participants had the full ability to understand the study. The experimental procedure was conducted according to the Declaration of Helsinki and was approved by the local Ethics

Committee in Lyon. The protocol was registered on clinicaltrials.gov (NCT02368509) and it was explained in detail to all volunteers, who provided written consent prior to participation.

2.2. Sample size

The number of patients required for the study was calculated using PASS 2008 software (NCSS, LLC. Kaysville, Utah), based on the rating of odors by bronchial cancer patients in a previous exploratory study (Laville et al., 2010; data not published). The analysis revealed that thirty-nine patients were needed for 80% power, an alpha level of 0.05, and an expected difference of -0,55 points in odor pleasantness rating (standard deviation: 1,2) for cancer patients vs. 0 (standard deviation: 0,25) for control subjects. In each group, we recruited five more subjects to remedy a possible discontinuation from the study.

2.3. Experimental protocol

Study design. The present study considered a homogeneous group of patients (lung cancer) undergoing Cisplatin chemotherapy. The study followed a longitudinal design, with two assessments of sensory functions (olfaction and taste) and food behavior: baseline (T0) before the beginning of chemotherapy, and follow-up (T1), six weeks after the first chemotherapy cycle. The group of patients was compared to a control group of age- and gender-matched healthy participants. Such experimental design enabled us to: 1/ To characterize smell and taste alterations in a homogenous group of cancer patients undergoing chemotherapy (vs. controls), 2/ To characterize changes in food behavior in these cancer patients undergoing chemotherapy (vs. controls), 3/ To examine how smell alterations can influence changes in food behavior in cancer patients undergoing chemotherapy.

Assessment of olfactory function. Participants' olfactory performance was estimated at T0 and T1, using the European Test of Olfactory Capabilities (ETOC) [31]. Odorous solutions (volume: 5 ml) were dissolved in mineral oil and poured into a 15 ml flask (1.7 cm diameter at opening; 5.8 cm high). Each flask contained a synthetic absorbent (polypropylene) to optimize odor diffusion. The ETOC test is composed of 16 odors: 8 typical food odors (vanilla, apple, garlic, anise, orange, fish, lemon and mint) and 8 less typical food odors (cloves, eucalyptus, cinnamon, fuel-oil, pine, cut grass, rose, thyme). The ETOC is based on 16 blocks of 4 flasks. Only one flask per block contains an odorant. For each block, participants are asked firstly to

detect the flask containing the odor, and secondly to identify the detected smell. Identification is assessed by a multiple-choice procedure in which participants select the correct descriptor among 4 options, with the list of 4 descriptors being different for each row of 4 flasks. Detection and identification scores range from 0 to 16 and provide an indicator of olfactory function. To reduce the probability of fortuitous correct identification, only odors that had been correctly detected were considered in the identification score. Then, participants were asked to rate the pleasantness, intensity, familiarity and edibility of each of the 16 odors on a scale from 1 (not at all pleasant/intense/ familiar/ edible) to 9 (very pleasant/intense/ familiar/ edible). Olfactory status of participants (anosmia, hyposmia or normosmia – the latter being defined as a normal sense of smell) was defined using ETOC cut-off values defined in Joussain et al. [32]. Thus, patients with a total loss of olfactory perception abilities were categorized as anosmic. Hyposmic patients are those with reduced smell abilities. Patients with preserved olfactory abilities were considered as normosmic patients.

Assessment of gustatory function. Taste detection and identification abilities were assessed at T0 and T1 with a short version of the Taste Strips test [33]. Strips made from filter paper were impregnated with four taste solutions (sweet, salty, sour and bitter). The length of a taste strip is 8 cm and an area of 2 cm² is impregnated with a taste stimulant. The taste strips were presented in a randomized order, and the impregnated part of the strip was placed on the subject tongue. Then, subjects were asked to close the mouth and say if they detect a taste. If so, they had to choose one of four possible answers (sweet, sour, salty, bitter). Before assessment of each taste strip the mouth was rinsed with water. Detection and identification scores ranged from 0 to 4 and provided an indicator of gustatory function. After the identification task, participants were asked to rate the pleasantness, intensity, and familiarity of each of the 4 taste stimuli on a scale from 1 (not at all pleasant/ intense/ familiar) to 9 (very pleasant/ intense/ familiar).

Assessment of eating habits. A self-administered questionnaire was specifically designed for the study, with the aim to collect data on cooking, culinary and dietary habits. To examine patients' general food habits at T0 and T1 participants were asked to fill the questionnaire composed of the following items: "(1) Several months ago, who used to cook in your home? ; Over the last few weeks: (2) who is in charge of cooking in your home? (3) Do you take food supplements? (4) Have you modified your food and beverage purchasing habits? (5) Have you modified any of your dietary habits? (6) Have you modified any of your culinary habits? (6) have you added any food/beverage to your usual diet? (7) Have you removed any food/beverage

from your usual diet?”. After completing the above questionnaire, participant’s seasoning habits were examined by asking the following question: “In general, what do you like to add to your dishes to make them tastier?” To answer this question, a list of 14 condiments commonly used among French consumers was proposed to the participants: salt, sugar, pepper, mustard, ketchup, vinegar, soy sauce, lemon, mayonnaise, butter, oil, cream, herbs, and spices (several choices possible). Here, the total number of chosen condiments was used for statistical analyses (possible range: from 0 to 14).

2.4. Data analysis

The effect of cancer and chemotherapy treatment on the ability to detect and identify olfactory and gustatory stimuli was examined with a two-way ANOVA with “Group” (2: Patients vs. Controls) as a between-subject factor and “Time” (2: T0 and T1) as a within-subject factor. For perceptual ratings of odors and tastes, a three-way ANOVA model was used to examine the effect of cancer and/or chemotherapy on pleasantness, intensity, familiarity and edibility ratings. For both odors and tastes, “Group” (2: Patients vs. Controls) and “Time” (2: T0 and T1) were included as respectively between-subject and within-subject factors. An additional “Stimuli” within-subject factor was used for odors (2: food odors and non-food odors) and for tastes (4: sweet, salty, sour, bitter). For all ANOVAs, the significant effect of group*time or group*stimuli interactions was tested.

For patients’ general food behavior, the statistical analysis was firstly descriptive and secondly, when the number of individuals respond positively (i.e. “yes”) to a specific question was of at least 5, a chi-square test was used to examine the dependency between proportions of answers and time of assessment (T0 vs. T1) in patients and controls separately. For food seasoning, the number of added condiments was analyzed using a two-way ANOVA with “Group” as a between factor and “Time” as a within-factor.

To ask how olfactory alterations influenced food behavior in cancer patients we set out to characterize patients’ olfactory status (using odor detection and odor identification scores of the ETOC test; cut-off values were taken from Jousain et al., 2016) and compared - within the patients’ group - food behavior of individuals with a normal sense of smell vs. food behavior of individuals with altered olfaction. Because of its non-binary nature, the food behavior variable retained was the number of added condiments. Here, the statistical analysis used was an ANOVA with “Olfactory status” (2: normosmia, hyposmia) as a between-subject factor and

“Time” (2: T0, T1) as a within-subject factor. For all statistical analyses, the alpha level was set at $p < .05$. Statistical analyses were performed using JASP 0.9.0.1. Descriptive statistics are expressed as Mean \pm Standard Deviation (SD) for all variables unless otherwise indicated.

3. Results

3.1. Demographics and clinical data

A total of 44 bronchial cancer patients and 44 age- and gender-matched healthy controls were included for the analysis (63,5% men and 36.5% women in each group). Characteristics of participants, including age, gender, smoking status,

and body mass index are summarized in *table 1*. No difference in BMI was observed between the two groups at T0, but patients’ BMI was significantly lower in the patients’ group at T1 compared to T0 ($p=0.01$). Moreover, since there was a higher proportion of smokers in the patients’ group, all statistical analyses were accompanied by a complementary analysis considering only non-smokers patients ($n=26$) and controls ($n=41$).

Table 1. Characteristics of the study participants. * means $p < .050$.

	Patients	Controls	p-value
Age (years)			
Mean (\pm SD)	63.5 (\pm 6.80)	62.4 (\pm 7.53)	> .05
Range	(46-74)	(47-77)	
Gender (n)			
Male	28	28	> .05
Female	16	16	
Smoking status (n)			
Smokers	17	3	.001**
Non-smokers	26	41	
Not mentioned	1	0	
BMI (\pm SD)			
Baseline (T0)	23.72 (\pm 3.64)	24.97 (\pm 3.30)	.08
Follow-up (T1)	23.28 (\pm 3.46)	25.11 (\pm 3.10)	.01*

3.2.Changes in olfactory abilities

Figure 1 shows the odor detection and odor identification scores. Whereas no significant effect of “Time” was observed for odor detection ($F(1,86)=.066$, $p>.050$, $\eta^2_p<.001$) and odor identification ($F(1,86)=.005$, $p>.050$, $\eta^2_p<.001$), a significant effect of “Group” was found for both measures reflecting that patients scored significantly lower than controls for both odor detection ($F(1,86)=7.127$, $p=.009$, $\eta^2_p=.077$) and odor identification tasks ($F(1,86)=12.880$, $p<.001$, $\eta^2_p=.130$). For both odor detection and odor identification, the Time*Group interaction was not significant ($p>.050$ in both cases).

Considering only non-smokers participants ($n=26$ for patients, $n=41$ for controls), no effect of “Time” was noted ($p>.050$ in all cases), and the above observed effects of “Group” remained significant for odor identification ($F(1,65)=5.610$, $p=.021$, $\eta^2_p=.079$) and close to significance for odor detection ($F(1,65)=3.278$, $p=.075$, $\eta^2_p=.048$). Interestingly, a significant Time*Group interaction was observed for odor detection ($F(1,65)=5.465$, $p=.022$, $\eta^2_p=.076$) but paired comparisons (bilateral Student t-tests) revealed no alterations with time in patients ($t(25)=1.683$, $p=.105$) and controls ($t(40)=-1.309$, $p=.198$).

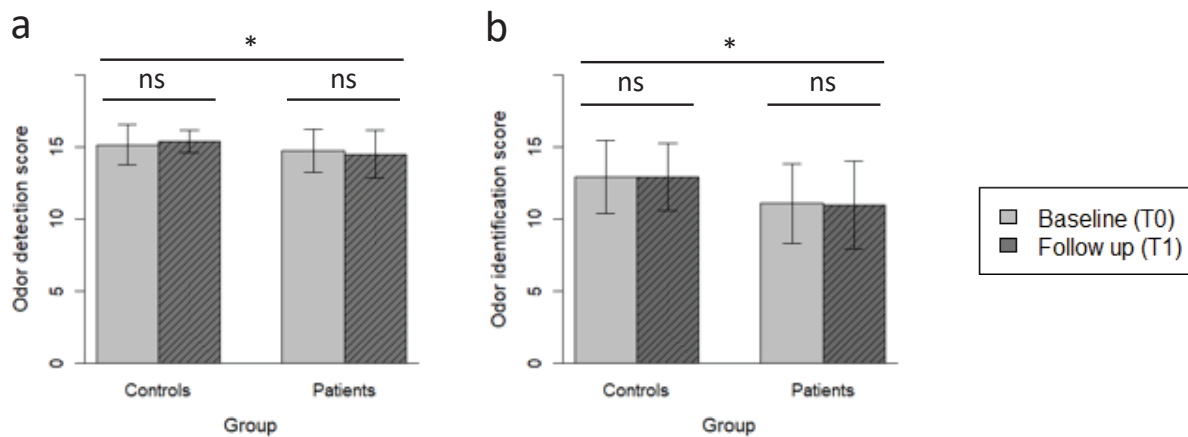


Figure 1. Mean (+/- SD) of odor detection and identification scores. (a) Odor detection; (b) Odor identification. For each of the assessed parameters, the ANOVA model showed no significant difference between T0 and T1 in patients and controls groups but patients scored lower than controls in odor detection and identification at T0 and T1. * means $p<.050$.

For odor perceptual ratings, “Stimuli” effects were observed for all 4 perceptual ratings reflecting that Food odors were rated as more intense ($F(1,86)=31.790$, $p<.001$, $\eta^2_p=.266$), familiar ($F(1,86)=491.740$, $p<.001$, $\eta^2_p=.373$), pleasant ($F(1,86)=62.686$, $p<.001$, $\eta^2_p=.426$) and edible ($F(1,86)=518.217$, $p<.001$, $\eta^2_p=.850$) than Non-food odors (see table 2 for descriptive statistics). Effects of “Time” were expressed as follow: odor intensity ($F(1,86)=10.649$, $p=.002$, $\eta^2_p=.110$), odor familiarity ($F(1,83)=3.746$, $p=.060$, $\eta^2_p=.041$), odor pleasantness ($F(1,83)=.004$, $p>.050$, $\eta^2_p<.001$) and odor edibility ($F(1,83)=1.087$, $p>.050$, $\eta^2_p=.013$) reflecting that odors were perceived as more intense (and marginally more familiar) in T0 than T1. Besides these “Odor type” and “Time” effects, effects of “Group” were significant for odor familiarity ($F(1,83)=6.243$, $p=.014$, $\eta^2_p=.070$), odor edibility ($F(1,83)=4.132$, $p=.045$, $\eta^2_p=.047$) but not odor intensity ($F(1,86)=.797$, $p>.050$, $\eta^2_p=.009$) and odor pleasantness ($F(1,83)=2.807$, $p>.050$, $\eta^2_p=.033$) reflecting lower odor familiarity/edibility ratings in patients compared to controls. Note that for odor edibility, the effect of “Group” was accompanied by a significant “Stimuli*Group” interaction ($F(1,83)=8.616$, $p=.004$, $\eta^2_p=.094$) reflecting that compared to controls, patients perceived Food odors as less edible ($t(84)=3.028$, $p=.003$) whereas no difference between groups was observed for Non-food odors ($t(84)=.413$, $p>.050$).

When the same analyses were conducted by considering only non-smoker individuals, the effects of “Group” on odor familiarity ($F(1,63)=2.058$, $p>.050$, $\eta^2_p=.032$) and odor edibility ($F(1,63)=.996$, $p>.050$, $\eta^2_p=.016$) were not significant. However, as for the main analysis, the “Stimuli*Group” interaction was significant for odor edibility ratings ($F(1,63)=5.325$, $p=.024$, $\eta^2_p=.014$) reflecting that compared to controls, patients perceived Food odors as less edible ($t(64)=1.988$, $p=.051$) whereas no difference between groups was observed for Non-food odors ($t(64)=-.410$, $p>.050$).

Table 2. Pleasantness, intensity, familiarity and edibility ratings of odors at T0 and T1 in patients and controls (mean±SD).

Olfaction	Patients (n=40)		Controls (n=40)	
	T0	T1	T0	T1
Pleasantness	5.83±1.25	5.96±1.2	6.33±0.88	6.17±1.1
Food odors	6.1±1.38	6.21±1.16	6.7±0.85	6.48±1.17
Non-food odors	5.56±1.3	5.72±1.46	5.95±1.08	5.68±1.13
Intensity	5.28±1.28	5.57±1.3	5.50±1.26	5.70±1.73

Food odors	5.48±1.33	6.01±1.37	5.61±1.27	6.12±1.33
Non-food odors	5.09±1.38	5.29±1.44	5.39±1.4	5.64±1.42
Familiarity	5.28±1.28	6.32±1.67	5.5±1.26	6.96±1.18
Food odors	6.25±1.85	6.6±1.65	7.19±1.08	7.26±1.16
Non-food odors	5.75±1.81	6.04±1.82	6.52±1.34	6.65±1.35
Edibility	5.54±1.63	5.65±1.43	6.08±1.03	6.15±1.01
Food odors	6.86±1.94	6.92±1.69	7.78±1.05	7.83±1.19
Non-food odors	4.20±1.59	4.38±1.38	4.38±1.49	4.46±1.29

3.3. Changes in gustatory abilities

As for odor detection and odor identification, whereas no significant effect of “Time” was observed neither for taste detection ($F(1,86)=.989, p>.050, \eta^2_p=.011$) nor for taste identification ($F(1,86)=.677, p>.050, \eta^2_p=.008$), the analysis revealed a significant effect of “Group” for taste detection ($F(1,86)=7.891, p=.006, \eta^2_p=.084$) and taste identification ($F(1,86)=19.160, p<.001, \eta^2_p=.182$) showing that patients exhibited lower scores of both odor detection and odor identification than controls (Figure 2). For both detection and identification, the Time*Group interaction was not significant ($p>.050$ in all 2 cases).

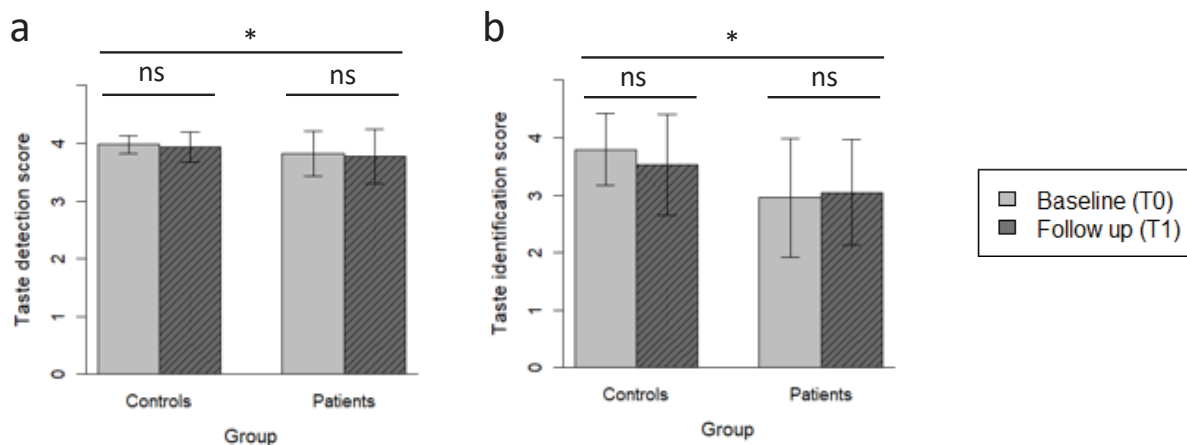


Figure 1. Mean (+/- SD) of odor detection and identification scores. (a) Odor detection; (b) Odor identification. For each of the assessed parameters, the ANOVA model showed no significant difference between T0 and T1 in patients and controls groups but patients scored lower than controls in tastes detection and identification at T0 and T1. * means $p<.050$.

Considering only non-smoker participants, there was no effect of “Time” ($p > .050$ in all cases), a trend of “Group” effect on taste detection ($F(1,65)=3.015, p=.087, \eta^2_p=.044$) and a significant effect for taste identification ($F(1,65)=14.360, p<.001, \eta^2_p=.181$). The “Group” effect for taste identification was accompanied by a significant Time*Group interaction ($F(1,65)=6.359, p=.014, \eta^2_p=.089$) showing trends towards a decrease from T0 to T1 ($t(25)=-1.886, p=.071$) in patients and a trend towards an increase from T0 to T1 ($t(40)=1.777, p=.083$) in controls.

For taste perceptual ratings, statistical analyses revealed no significant effect of “Time” and “Group” factors and no significant interactions involving the “Group” factor for any of the three perceptual ratings ($p > .050$ in all cases). However, as for odors, significant main effects of “Stimuli” were observed for familiarity ($F(3,213)=49.982, p<.001, \eta^2_p=.412$), intensity ($F(3,216)=17.232, p<.001, \eta^2_p=.192$) and pleasantness ($F(3,213)=94.880, p<.001, \eta^2_p=.572$) showing as expected, that the four studied taste modalities were rated differently along the 3 perceptual ratings (see table 3 for descriptive statistics). Note that these significant effects of “Stimuli” remained significant when the analyses considered only non-smoker participants ($p < .001$ for all 3 perceptual ratings).

Table 3. Pleasantness, intensity and familiarity rating of tastes at T0 and T1 in patients and controls (mean±SD).

Taste	Patients (n=40)		Controls (n=40)	
	T1	T2	T1	T2
Pleasantness	4.70±1.81	6.60±1.56	4.92±1.38	6.57±1.46
Sweet	6.51±2.21	6.95±2.01	6.93±1.56	7.18±1.93
Salty	4.61±2.36	4.68±2.26	4.77±2.15	4.95±2.06
Sour	4.31±2.58	4.80±2.35	4.77±2.07	4.68±2.18
Bitter	3.35±2.38	3.02±2.13	3.20±1.99	3.46±1.97
Intensity	6.60±1.60	4.87±1.64	6.30±1.51	5.09±1.43
Sweet	6.23±2.41	6.34±1.99	5.72±2.14	6.59±1.72
Salty	7.09±1.63	6.83±1.73	6.68±1.93	6.56±2.03
Sour	7.13±1.87	7.15±1.50	6.81±1.48	7.27±1.63
Bitter	6.23±2.08	6.20±2.38	6.00±2.18	5.87±1.96

Familiarity	5.86±1.91	5.69±1.96	6.40±1.73	6.77±1.60
Sweet	7.12±2.35	6.60±2.46	7.15±2.24	7.61±1.89
Salty	6.38±2.54	6.17±2.51	7.13±1.85	7.43±1.79
Sour	6.02±2.65	5.78±2.76	6.45±2.19	6.70±2.40
Bitter	3.89±2.79	4.33±2.46	4.90±2.74	5.36±2.22

3.4. Changes in food behavior

Considering the first question of the questionnaire (« Several months ago, who used to cook in your home? »), responses were comparable across patients and controls, and in T0 and T1: from 45% to 50% of the participants declaring cooking themselves, from 23% to 32% declaring that their partner use to cook and from 18% to 30% declaring cooking with their partner (from 0% to 2% for the other options). For the second question (« Over the last few weeks who is in charge of cooking in your home? ») a similar pattern emerged: from 46% to 48% declaring cooking themselves, from 18% to 36% declaring that their partner cooks, and from 11% to 34% declaring that they cook with their partner (from 0% to 2% for the other options). Results based on questions 3 to 7 are displayed in Figure 3 showing the percentages of patients and controls who answered “yes” to each item of the eating habits questionnaire at T0 and T1. On a descriptive level, controls exhibited very few variations in their dietary/culinary habits in T0 and T1 (from 0% to 11% depending on the items and time of assessment), compared with patients (from 5% to 39%). A Chi-square analysis was possible for 4 out 5 items, and only in patients: Patients modified their dietary habits from T0 to T1 ($\chi^2=4.140$, $p=.040$) and removed some food / beverage from their usual diet since the beginning of the chemotherapy treatment ($\chi^2=4.520$, $p=.030$). There were no differences in the use of food supplement orbetween T0 and T1 “usual diet”). Note that because of sample size issue (some items were filled by a small number of participants) the analysis considering only non-smokers was not performed for these qualitative variables.

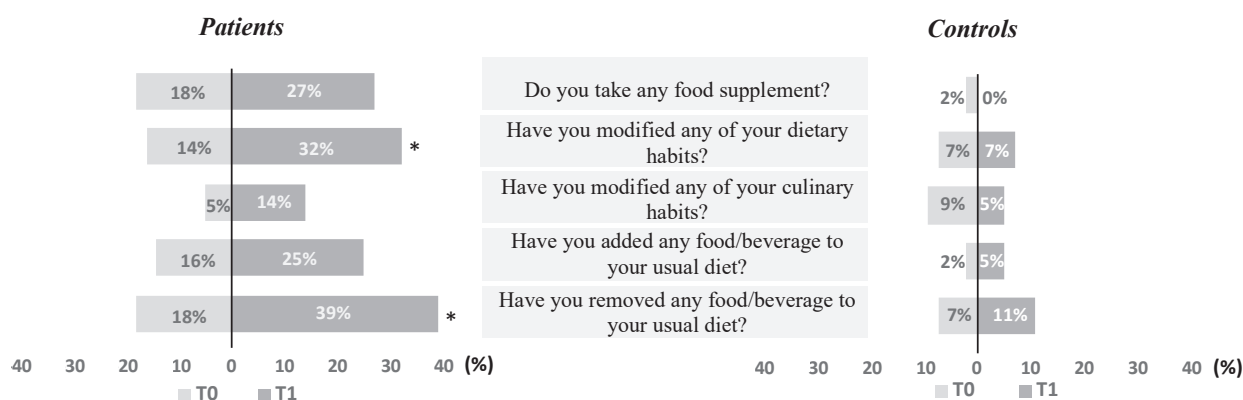


Figure 3. Food habit changes in patients (left panel) and controls (right panel) at T0 and T1 (left and right side of the mirror histograms). Horizontal bars represent the percentage of participants answering “yes” to a given item. * means $p < .050$.

Considering food seasoning, patients used less condiments than controls (3.6 ± 2.4) and 4.8 ± 2.6 , respectively). There was no effect of “Time” ($F(1,86) = 1.272, p > .050, \eta^2_p = .015$) and “Time*Group” interaction ($F(1,86) = 0.001, p > .050, \eta^2_p < .001$). Note that the effect of “Group” increased in significance when only non-smokers were considered (mean \pm SD = 2.731 ± 1.996 for patients and 4.561 ± 2.498 for controls; $F(1,65) = 9.920, p = .002, \eta^2_p = .132$).

3.5. Influence of olfactory alterations on food behavior in cancer patients

Regarding olfactory status, 48% of the patients were hyposmics at T0 and 52% at T1, with 10 out of 44 patients changing their olfactory status from T0 to T1 (6 from normosmia to hyposmia, 4 from hyposmia to normosmia). Thus, the analysis was conducted on the 34 patients that did not change olfactory status from T0 to T1 (17 normosmics, 17 hyposmics). Note that as a comparison, the prevalence of hyposmia was as follow in controls: 16% at T0 and 20% at T1 (3 controls moving from normosmia to hyposmia, 1 from hyposmia to normosmia). On a statistical level, hyposmia was significantly more prevalent in patients than in controls at both T0 ($\chi^2 = 10.270, p = .001$) and T1 ($\chi^2 = 9.620, p = .002$). An ANOVA examining the effects of “Olfactory status” (2: normosmia, hyposmia; between-subject factor) and “Time” (2: T0, T1; within-subject factor) on the number of added condiments revealed a significant of “Olfactory status” ($F(1,32) = 5.092, p = .031, \eta^2_p = .137$) reflecting that hyposmics (mean \pm SD: 4.706 ± 2.750) added significantly more condiments than normosmics (mean \pm SD: 2.853 ± 1.974). This influence of hyposmia on food behavior was independent of chemotherapy

no significant effect of “Time” ($F(1,32) = .395, p > .050, \eta^2_p = .012$) and no significant “Time*Olfactory status” interaction ($F(1,32) = .551, p > .050, \eta^2_p = .017$) were observed. Finally, smoking status could not explain these effects since there was no dependencies between this variable and olfactory status ($\chi^2 = 2.431, p > .050$).

4. Discussion

In the present study, we examined the effects of cancer and chemotherapy on odor and taste perception by comparing olfactory and gustatory scores before and after 2 cycles of Cisplatin-based chemotherapy. Using psychophysical tests, we showed a decreased sensitivity to odors and tastes in patients’ group compared to controls. Taste and smell disturbances were observed even before the beginning of chemotherapy, suggesting that the alteration of chemosensory perceptions may be related to the cancer itself before the exposition to Cisplatin. Rare cases of olfactory [34] and gustatory [35] dysfunctions in lung cancer patients were previously reported, and our study is the first longitudinal case-control study to highlight chemosensory alterations in a group of chemotherapy-naive lung cancer patients.

Given the potential impact of smoking status on smell and taste abilities [36], we systematically run additional analyses by considering only non-smokers. This selective analysis showed almost the same pattern of results found in the main analysis with very minor exceptions (decrease in odor and taste detection), likely due to lack of power. For instance, when the main analysis showed a decrease in patients vs controls in a series of variables (odor detection, odor identification, odor familiarity, edibility of food odors, taste detection, taste identification) the analysis that considered only non-smokers showed nearly the same findings with few significance differences changed to tendencies (significant effects: decrease in odor identification, edibility of food odors, taste identification; close to significance: decrease in odor detection, taste detection). When considering the effect of cancer on food habits (number of added condiments), the effect observed in the selective analysis was even stronger (from $\eta^2_p = .051$ to $\eta^2_p = .132$).

Note that our result reported no effect of Cisplatin chemotherapy after six weeks of treatment. A series of studies that evaluated the effect of Cisplatin on olfactory and gustatory perceptions showed nevertheless mixed results. In a longitudinal study, Ijpma et al. showed decreased olfactory and gustatory sensitivities (especially for salty taste) in a group of 21 testicular cancer at their fourth cycle of cisplatin chemotherapy [24]. Wallizcek-Dworschak et al. explored the influence of cisplatin on olfactory function and showed a significant decrease of olfactory

threshold in a small group of 17 testicular cancer patients on day 90 of chemotherapy [15]. In a longitudinal preliminary case-control study, Jousain et al. considered the cognitive aspects of olfactory integration, examining the effect of Cisplatin chemotherapy on the perceptual rating of odors in lung cancer patients. Results showed a decrease in the pleasantness rating of food odors in patients compared to controls after 2 cycles of chemotherapy. In another longitudinal study that considered a heterogeneous group of cancer patients (bronchial, ovary and breast) the authors did not show any effect of cisplatin on olfactory and gustatory perceptions after 3 cycles of chemotherapy [37]. Factors explaining discrepancies between studies are multiple: 1/ sample size (some investigations were conducted on small samples [15], [24], [38]), 2/ sample heterogeneity (when sample size was large, the sample was heterogeneous [37]), 3/ absence of control group (only two studies included a healthy control group [24], [38]).

Concerning the olfactory dysfunction based on detection and identification scores of the ETOC test, the analysis showed that almost half of lung cancer patients had a reduced ability to perceive odorant stimuli (hyposmia) independent of chemotherapy since olfactory dysfunction was lower in patients than controls at both baseline and T1. The observed olfactory deficit may be related to the respiration capacity, a motor and a rhythmic activity that accompanies smell perception [39]. Odorant molecules are diffuse in the surrounding air, thus, to reach the olfactory receptors they are dependent on the respiratory tract that allows the external air to penetrate in body. Since lung cancer is an impairment of the respiratory system, common consequences of the disease, such as coughing and shortness of breath might influence perception of odorant molecules by modifying the respiratory rhythmicity and the volume of air inhaled. Furthermore, taste receptors and olfactory neurons were recently identified in the bronchial tissue, more specifically in human airway smooth muscle, initiating interesting work on a novel olfactory-like chemosensory network in human airway smooth muscle cells [40], [41]. Smell and taste assessment in patients with other bronchial pathologies (e.g asthma, Chronic obstructive pulmonary disease) could help to separate whether the observed chemosensory alterations are specific to lung cancer, or generally linked to respiratory system impairments.

Considering the perceptual ratings of smells, some changes for odor familiarity and edibility but not for pleasantness were observed. This is in contrast to a study by Jousain et al., 2013, that reported changes due to cancer and/or chemotherapy on hedonic ratings of odors. However, in agreement with Jousain et al., odor familiarity was lower in patients than controls at both baseline and T1 in our study, indicating an effect of cancer and not chemotherapy. A decrease

in odor identification was also observed; suggesting that odor quality per se may have been modified by cancer. Patients may have perceived a novel and non-familiar smell and therefore exhibited difficulties in identifying it. These findings support the hypothesis of chemotherapy-induced cognitive impairments which were documented in previous studies [42], [43]. For instance, Von Ah et al. reported cognitive changes including difficulties to recognize words and pictures in newly diagnosed breast cancer patients [44]. It is therefore possible that the integration process of other stimuli is affected the same way, leading to the observed decrease in identification and familiarity of odors. Finally, another perceptual dimension modulated by cancer was edibility of odorous objects. Patients evaluated food odors as less edible compared to controls at both T0 and T1. This finding suggests that sensory alterations are likely to go beyond the peripheral level, possibly affecting conduction and integration of the olfactory/gustatory information. Interestingly, this effect was specific to food odors and not observed with non-food odors, which supports the link between chemosensory disturbances and patients' food behavior [7].

Another result of interest of our study concerns patients' food behavior. It is common that cancer patients undergoing chemotherapy exhibit modification in food behavior, mainly modifications in food intake [19] food preferences [22], [23], and culinary practices [3], [14]. Here, significantly more patients declared modifying their dietary habits and removing some food or beverage from their diet after only six weeks of chemotherapy compared with baseline. These changes were not observed in the control group. Furthermore, differences in food behavior items between patients and controls were observed even before the chemotherapy, suggesting that patients' relationship to food is modified at the point of diagnosis. Indeed, newly diagnosed patients tend to change their dietary habits, with the aim to contribute to the fight against the disease and the improvement of treatment's efficiency [45], [46]. Considering food seasoning, patients declared adding less condiments than controls at both T0 and T1. Adding condiments to enhance flavor and complement the dish in order to meet sensory expectations could be interpreted as an eating behavior related to food appreciation and seeking a subsequent pleasure from its consumption. However, cancer diagnosis and chemotherapy treatments are usually accompanied by a decrease in appetite and a lack of motivation to eat, because of physiological [47] or psychological [48] reasons. The fact that patients are less involved in the food experience, and experience a decreased food enjoyment [49] may explain that they put less effort in the meal experience and report using less condiments. Interestingly, within the

patient group, hyposmics used more condiments, suggesting a sensory deficit compensation by seasoning in order to meet sensory expectations.

Our study was designed to circumvent the methodological heterogeneity found in the literature, and have therefore numerous strengths from a methodological point of view. Firstly, its longitudinal design allowed concluding on the effect of cancer on taste and smell before and after six weeks of cisplatin treatment. Moreover, our study is one of the few studies with a homogenous cancer localization and chemotherapy regimen, reducing sources of variability between patients. The enrolment of an age- and gender- matched control group enabled us to distinguish the effect of the pathologic state from the effect of ageing on sensory abilities. Finally, the use of psychophysical approach for the sensory assessment ensured an objective evaluation of participants' perceptive abilities.

However, although designed properly, our study presents some limitations that are worth to be discussed. Firstly, the effect of chemotherapy on sensory perceptions may be observed more than six weeks of treatment, before reaching a given cumulative dose of Cisplatin, thus, a longer-term study would be more informative. Furthermore, by choosing to assess patients' chemosensory function three weeks after their previous cycle, we possibly missed the instant effect of chemotherapy that was shown to be cyclical and more severe right after the treatment administration [24], [25]. Finally, the understanding of patients' food behavior changes could be further improved by using more detailed questionnaires such as the Food Frequency Questionnaire, 24 hour recalls, [50], or tools for more accurate dietary information, or real eating context studies.

5. Conclusion

In sum, our study highlighted a decreased taste and smell abilities in almost half of the lung patients' group even before the exposition to Cisplatin. Patients rated typical food odors as less edible compared to controls, possibly involving alterations in odor cognitive processing due to cancer. Despite the sensory deficit, patients declared using less condiment than controls with unaltered chemosensory function. However, within the patients' group, hyposmics reported using more condiments, possibly as a compensatory mechanism to their decreased sensory abilities. Our results confirm the effect of chemosensory alterations on patients' food behavior and underlie the involvement of olfaction in food perception and more specifically, the impact of reduced olfaction on dietary practices including seasoning. Experimental studies are needed

to better understand the sensory compensatory mechanisms, and how using condiments may improve patients' food enjoyment.

6. References

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*Chapter V: Flavor enhancement as a strategy
to palliate sensory deficits*

Flavor enhancement as a strategy to improve food liking in cancer patients with decreased taste and smell abilities

K. Drareni ^{1,2}, A. Dougkas ¹, H. Lusson ³, D. Vansteene ³, A. Giboreau ¹, M. Bensafi ²

¹Institut Paul Bocuse Research Centre, Ecully Cedex, France

²CNRS, UMR5292, INSERM U1028, Lyon Neuroscience Research Center, University Lyon, France

³Institut de Cancérologie de l'Ouest, Nantes, France

Abstract

Prevention of malnutrition is a major challenge in oncology with 25% to 80% of cancer patients experiencing malnutrition at different degrees. Cancer treatments and especially those including cytotoxic chemotherapy may contribute to malnutrition through their resulting adverse effects including taste and smell alterations. A decline in taste/smell perceptive abilities (hyposmia/hypogeusia) is often observed in cancer patients leading to modification in food behavior. The aim of the present study is to examine the effect of flavor enhancement on food liking in a group of cancer patients undergoing chemotherapy and healthy controls. The liking of four recipes of eggplant cream enhanced with salt, lemon, garlic and cumin was evaluated in comparison to a non-enhanced eggplant cream recipe by a group of 154 cancer patients. Patients were separated in two subgroups according to their taste and smell perception abilities. Flavor enhancement resulted in a modification in liking ratings but the four types of enhancement have differential effects on food liking. Addition of salt and garlic significantly increased patients' liking of the eggplant cream, addition of lemon reduced it and enhancement with cumin did not have impact on patients' liking. Enhancing food flavor is likely to be a simple and effective way to increase food liking in cancer patients undergoing chemotherapy. Future studies should include measurements of food intake during a full meal and over a defined period to examine whether increasing food liking can be an effective strategy to improve food intake in cancer patients and prevent malnutrition.

Key words: Taste, Smell, Flavor enhancement, Cancer, Chemotherapy

1. Introduction

Prevention of malnutrition is a major challenge in oncology with 25% to 80% of cancer patients experiencing malnutrition at different degrees [1]. Cancer-related malnutrition has multiple etiology, including a loss of appetite and a decreased food enjoyment during cancer and its treatment. Cancer treatments and especially those including cytotoxic chemotherapy may contribute to malnutrition through their resulting adverse effects such as nausea and taste and smell alterations [4]. Taste and smell alterations are frequent in cancer patients undergoing chemotherapy [7]–[13], and could adversely impact patients food behavior [14] including a decreased energy intake [15], [16], a modification in food preferences [17], and a loss of food enjoyment [15], [18]. Taste and smell alterations can be expressed by a decreased sensitivity, an absence of sensation, a distortion of normal perception, or a perception of taste and smell without external stimulation. However, in most of the cases, a decline in sensory perceptive abilities termed hyposmia for olfaction and hypogeusia for gustation is observed in cancer patients [14]. Sensory properties of food strongly influence its hedonic value [19], thus, a decreased ability to perceive tastes and smells may result in modification of flavor perception and food liking, as reflected by patients' complaints on food being bland and tasteless [20]. Therefore, adapting food to the preference and sensory expectations of patients could improve their food enjoyment, increase their food intake and help to maintain an adequate nutritional status, especially for patients who experience alterations of taste and smell perceptions.

To date, the treatments of malnutrition in cancer patients are mainly food supplements enriched in calories and proteins to counter the energy deficit. However, the pleasure of eating, and the implication of sensory alterations in food perception remain unsolved [6].

The enhancement of food flavor has been tested in many studies conducted on elderly subjects with deficits in taste and smell acuity. This strategy turned out to be an effective way to increase food enjoyment and improve dietary intake in elderly population [21]–[24]. However, flavor enhancement has never been tested as a coping strategy for other population with chemosensory deficits such as cancer patients undergoing chemotherapy. Thus, remains unexplored whether manipulating food taste and smell attributes could increase its overall liking.

The main aim of the present study is to examine the effect of flavor enhancement on food liking in a group of cancer patients undergoing chemotherapy and healthy controls. The diversity in taste and smell perception abilities of patients was considered by a classification of patients in two groups based on their self-reported taste and smell abilities. In order to reduce variability

in terms of cancer type and gender, we conducted a sub-group analysis in women diagnosed with breast cancer.

2. Material and methods

2.1. Study design

The study was designed to test the impact of flavor enhancement on increasing the appreciation of food. In this study, flavor enhancement corresponds to the manipulation of an eggplant cream flavor by adding ingredients that stimulate the sensory systems involved in flavor perception (i.e. Gustation, olfaction and trigeminal sensory systems). The study encompasses two phases. Briefly, the phase I was the recipe development, determination of the ingredients used for flavor enhancement and evaluation of the recipes liking by healthy controls. In phase II, the liking of the enhanced recipes was evaluated by patients during a tasting session and compared to the liking of the non-enhanced eggplant recipe.

2.2. Phase I. development and validation of recipes

Recipes development. Professional research chefs from the Institut Paul Bocuse developed eggplant cream recipes that could be reproducible in terms of cooking process and seasoning by staff members at hospital kitchen. This eggplant based food was selected particularly because of its neutral taste that can easily be modulated to respond to the need of the study. Moreover, the creamy texture of the chosen recipe fits to all patients, even those with mouth dryness and mouth sores, which are common side effects of chemotherapy.

The non-enhanced recipe (REF) was prepared by blending oven-baked eggplant with 10% its weight of oil (70% of colza oil was mixed with 30% of olive oil to attenuate its bitterness). Eggplant and oil mixture was blended until the texture became smooth and homogeneous. The four enhanced recipes were prepared from the reference recipe to which has been added a determined amount of salt, lemon, garlic and cumin (table X). For 100 g of non-enhanced recipe (REF), was added 0.2 g of salt for the enhancement with salty taste, 2 g of lemon juice for the enhancement with sour taste, 0.2 g of garlic powder for the enhancement with garlic aroma, and 0.2 g of cumin powder for the enhancement with cumin aroma.

Validation and perceptual characterization of the recipes. A preliminary test was conducted on a group of 15 healthy individuals to make sure that the enhanced recipes were distinguishable from the reference (REF) and characterized by the flavor of the ingredient we added for the enhancement. Moreover, these 5 food samples were perceptually characterized by a group of

an additional control group of individuals composed of 36 women aged between 45 and 65 years, with no history of cancer and/or chemotherapy and without a diagnosed or noticed taste and/or smell alterations. Here, the participants rated food liking of the 4 enhanced recipes in comparison to the reference using the exact same procedure as that used by patients (see Section 3.5 below). In brief, food samples (salt, lemon, garlic and cumin, 50g container) were presented to the participants who were asked to rate the liking for each sample in comparison to the reference recipe (25g container). Results showed that whereas the cumin enhancement was significantly more appreciated than the reference ($+1.67 \pm 0.46$, $t = 3.63$, $p < .001$), this was not the case for salt ($+0.63 \pm 0.37$, $t = 1.71$, $p = .09$), lemon (-0.26 ± 0.41 , $t = -0.63$, $p = .52$) and garlic ($+0.72 \pm 0.45$, $t = 1.6$, $p = .11$).

2.3.Phase II. Experiment

Participants. Patients were recruited at Institut de Cancérologie de l'Ouest Renée Gauducheau in Nantes (France). Patients enrolled in the study were men and women diagnosed with cancer and undergoing chemotherapy as only treatment at the time of the study. Patients scheduled for radiotherapy sessions were included only if oro-nasal/ head and neck area were not concerned by radiations. The excluded patients were those with head and neck cancer, and upper aerodigestive tract cancer, patients with other treatment than chemotherapy (immunotherapy, radiotherapy...), and patients with bowel obstruction. All participant received oral and written information about the aim and the steps of the study and signed a consent form as an approval for their participation. The study was approved by the ethical board of Anger University Hospital (n°2019/38).

Assessment of taste and smell abilities. Prior to the tasting session, participants had to rate their self-perceived taste and smell abilities on a 10 cm long visual analogue scale (VAS) labeled « extremely bad » at the left edge, and « extremely good » at the right edge. Patients were divided into two sub-groups based on the self-rating of their taste and smell. Patients reported also their level of hunger before and after the tasting session by answering to the question “Are you hungry?” on a 10 cm long VAS scale going from (0) “I am not hungry at all” to (10) “I am extremely hungry”.

Liking of the reference and comparative liking of sensory enhanced recipes. The experimental sessions (tasting sessions) were scheduled from 10 to 12 a.m. in the morning, and from 3 to 5 p.m. in the afternoon, which is a usual time for snacking. Participants were free to choose one of these two slots to perform the experiment. For each participant, the tasting was

carried in two successive steps: the first step was the liking assessment of the reference recipe. A container with 50g of the reference recipe was presented to the participant who was asked to attribute a liking rating on a 10-cm-VAS scale labeled from « I do not like at all » on the left edge, to « I like it a lot » on the right edge. The second step consisted in a comparative liking task, where participants were asked to attribute a relative liking rating for each flavor enhanced recipe in comparison to the reference. Practically, the four containers with 50g of salt, lemon, garlic and cumin recipes were presented to the participant, with the instruction to attribute a liking rating compared to the reference recipe. The liking of the four enhanced recipes (salt, lemon, garlic, cumin) was assessed in comparison to the reference on a scale going from (-5) « I don't like it at all » to (+5) « I like it a lot » where the reference recipe was set at zero (0) « I like it as much as the reference ».

2.4.Data analysis

Patients were first classified as a function of their self-reported taste and smell abilities using a hierarchical clustering that allows the definition of two profiles of patients: patients without sensory alterations (unaltered) and patients with sensory alterations (altered). The comparison of the liking rating of each enhanced recipe to the reference was done for each group (altered, unaltered) using a one-sample t-test test. To examine whether the experimental session (morning vs. afternoon) was influenced by the level of hunger, we conducted a T-test to compare mean liking of the reference between participants tested in the morning and those tested in the afternoon. A one-sample t-taste was also performed for each recipe to compare liking differences of the enhanced recipes in comparison to the reference in both sessions. The same statistical analyses were firstly conducted on the entire group of patients (n=154), with heterogeneous cancer profiles), then on a homogeneous sub-group composed of breast cancer patients only (n=84). For all calculations, a p-value <0.05 was considered as statistically significant. Data are presented as mean and standard errors of the mean unless otherwise indicated. All analyses were performed using JASP 0.9.0.1.

3. 3. Results

3.1. Demographic and clinical characteristics of participants

A total of 154 patients and 36 controls were recruited. Given that 55% of patients had a breast cancer diagnosis, a subset analysis including those patients is presented separately (part 3.3). The demographic and clinical characteristics of participants are summarized in table 1.

Table 1. Demographic and clinical characteristics of participants.

	n (%)	Age (years ± SD)	Gender n (%)	Smoking status n (%)	Cancer types n (%)	Chemotherapy regimen n (%)
All patients	154 (100%)	60.36 ± 12	Female	Smoker	Breast : 84 (54.5%)	Taxol based : 76 (49.3%)
			128 (83%)	13 (8.4%)	Gynecologic : 20 (13%)	Platinum : 16 (10.3%)
			Male	Non-smoker	Digestive : 17 (11%)	Folfox : 13 (8.4%)
			28 (17%)	137 (89%)	Bronchial : 9 (5.8%)	EC / AC / FEC : 18 (11.7%)
			NA	Prostate : 6 (3.9%)	Gemcitabine : 9 (5.8%)	Others : 22 (14.5%)
			4 (2.6%)	Liver : 5 (3.3%)	Bladder : 4 (2.6%)	
				Pancreas : 4 (2.6%)		
				Others : 5 (3.3%)		

EC: Epirubicine and cyclophosphamide / AC: Adriamycin and cyclophosphamide / FEC: 5-fluorouracil, epirubicine and cyclophosphamide

3.2. Patients subgroups according to taste and smell self-ratings

A hierarchical clustering method based on the self-reported rating of taste and smell abilities resulted in a classification of patients in two groups (*Figure 1.a*). The first group was composed of 102 patients (66.2%), and rated high their taste and smell abilities (7.92 ± 1.6 cm and 7.83 ± 1.75 cm respectively). This group was labelled “unaltered”. The second group included 52 patients (33.8%) who rated poorly their taste perception ability (3.33 ± 1.64 cm) and attributed an average rating to their sense of smell (5.87 ± 2.66 cm). This second group was labelled “altered”. The taste and smell self-rating of patients with “unaltered” abilities was similar to healthy controls’ rating, whereas the altered group rating was lower (figure 1.b).

3.3. Level of hunger and liking of the reference

Patients in the “unaltered” group had a significantly higher level of hunger before the tasting session (5.71 ± 2.72 cm) compared to the “altered” (3.75 ± 2.62 cm; $p < .001$) group. Regardless of their chemosensory abilities, patients that were tested in the morning session ($n=91$) reported a higher level of hunger in comparison to patients tested in the afternoon ($n=62$) (morning: 5.44 ± 2.85 , afternoon: 4.47 ± 2.74 ; $t = -2.1$, $p = .03$). There was no significant difference in the liking of the reference recipe neither between the two groups nor between the two sessions (morning vs. afternoon) ($p > .05$).

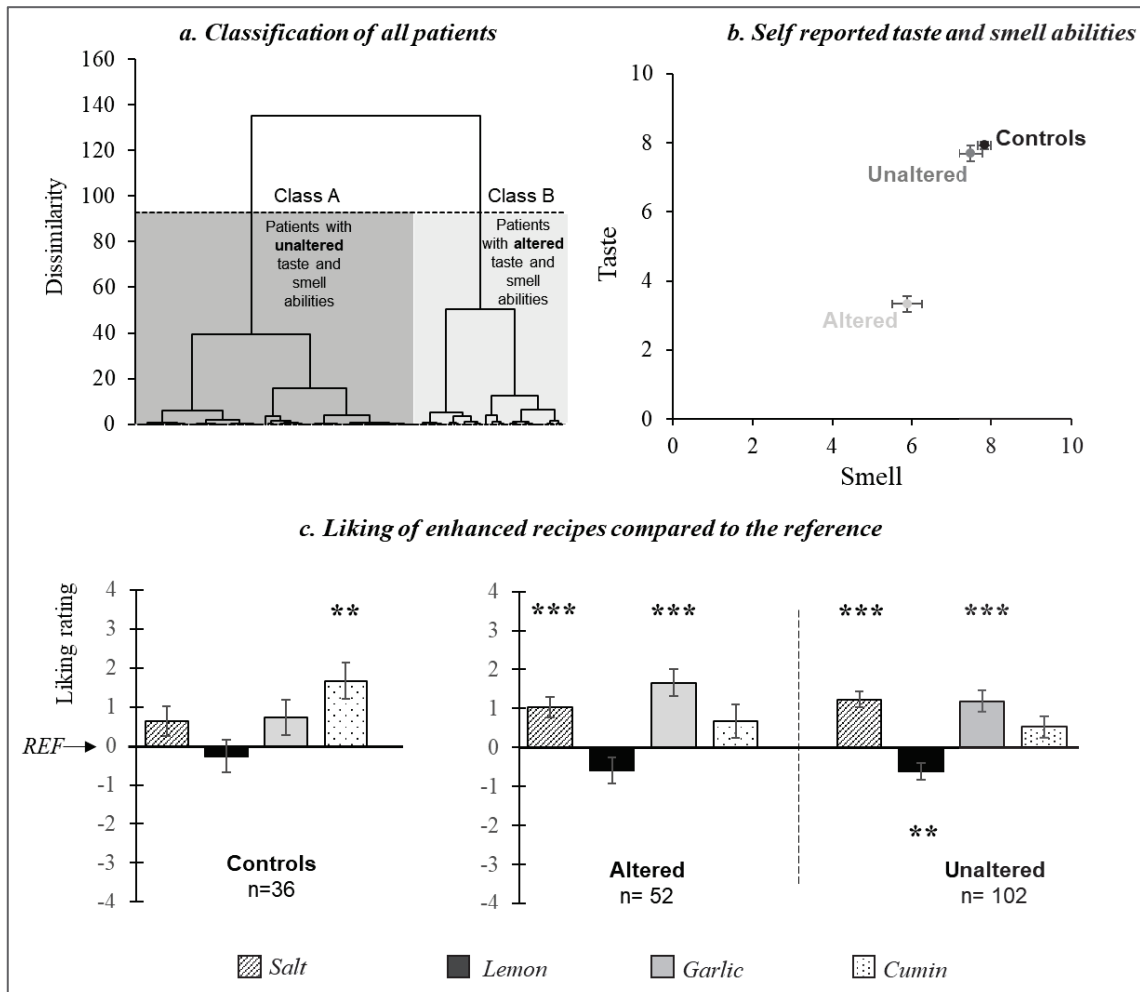


Figure 1. (a) Classification of all patients based on self-reported taste and smell abilities. The hierarchical clustering resulted in two groups: unaltered (class A in dark grey), altered (class B in light grey). (b) Chemosensory profiles of “altered”, “unaltered” and “control” groups. No difference was observed in taste and smell ratings between controls and patients with “unaltered” abilities. Patients with altered abilities ratings were significantly lower compared to controls (taste: $t=-14.88$, $p<.001$; smell: $t=-3.63$, $p=0.001$), and compared to “unaltered” patients group (taste: -19.87 , $p<.001$; smell: $t=-5.58$, $p<.001$). (c) Liking of the four enhanced recipes compared to the reference (REF) fixed at zero (0). Error bars correspond to Standard Errors.

* $p<.05$ ** $p<.01$ *** $p<.001$

3.4. Liking ratings of the enhanced recipes compared to the reference

The salt and garlic recipes were significantly more appreciated than the reference by altered and unaltered patients ($p<.001$ in both cases) but not by controls ($p>.05$). The liking of the lemon recipe was significantly lower compared to the reference in the unaltered group ($p<.001$). The comparison of liking between the sensory enhanced recipes with the reference recipe showed that the eggplant cream enhanced with cumin was not significantly more appreciated than the reference by patients in altered ($p=0.12$) and unaltered group ($p=0.06$) (figure.1.c).

Since the level of hunger was different in the two sessions and the possible influence of hunger state on food liking, we examined the effect of flavor enhancement on the recipes' liking separately in the two sessions. For the morning session, recipes enhanced with salt and garlic were more appreciated than the reference (salt: $+0.91 \pm 1.87$, $t=4.68$, $p<.001$; garlic: $+1.66 \pm 2.4$, $t=6.62$, $p <.001$). the enhancement with lemon was less appreciated (-0.774 ± 2.12 , $t= -3.5$, $p<.001$) and no difference was found for the cumin recipe ($p>.05$).

3.5. Results for breast cancer patients

In order to examine the effect of flavor enhancement in a homogenous group of patients, a subgroup of women with breast cancer was extracted from the whole group of recruited patients. The homogeneous group was composed of 84 women with breast cancer patients (mean age 55.9 ± 11). The same statistical analyzes as for the whole group were conducted on the breast cancer patients group.

Breast cancer patients' subgroups according to taste and smell self-ratings

A hierarchical clustering method based on the self-reported rating of taste and smell abilities resulted in a classification of patients with breast cancer in two groups (*Figure 2.a*). The first group was composed of 49 patients (58.3%), who attributed a high rating to their taste and smell abilities (8.31 ± 1.05 cm and 8.69 ± 0.93 cm respectively). This group is referred to as "unaltered". The second group include 52 patients (41.7%). Patients composing the second group rated poorly their taste perception ability (4.38 ± 2.36 cm) and attributed an average rating to their sense of smell (5.35 ± 2.22 cm). We referred to this group as "altered". The taste and smell self-ratings of patients with "unaltered" abilities were close to healthy controls ratings, while the altered group is lower (*figure 2.b*).

Level of hunger and liking of the reference recipe

Patients in "unaltered" group had a significantly higher level of hunger before the tasting (6.33 ± 2.1) compared to the "altered" (4.80 ± 2.66 ; $p=0.02$) group. Regardless of their chemosensory abilities, no difference in hunger rating was found between patients that were tested in the morning session ($n=48$) in comparison to patients tested in the afternoon ($n=36$) ($p >.05$). There was no significant difference in the liking of the reference recipe neither between the two groups (altered vs. unaltered) nor between the two sessions (morning vs. afternoon) ($p>.05$).

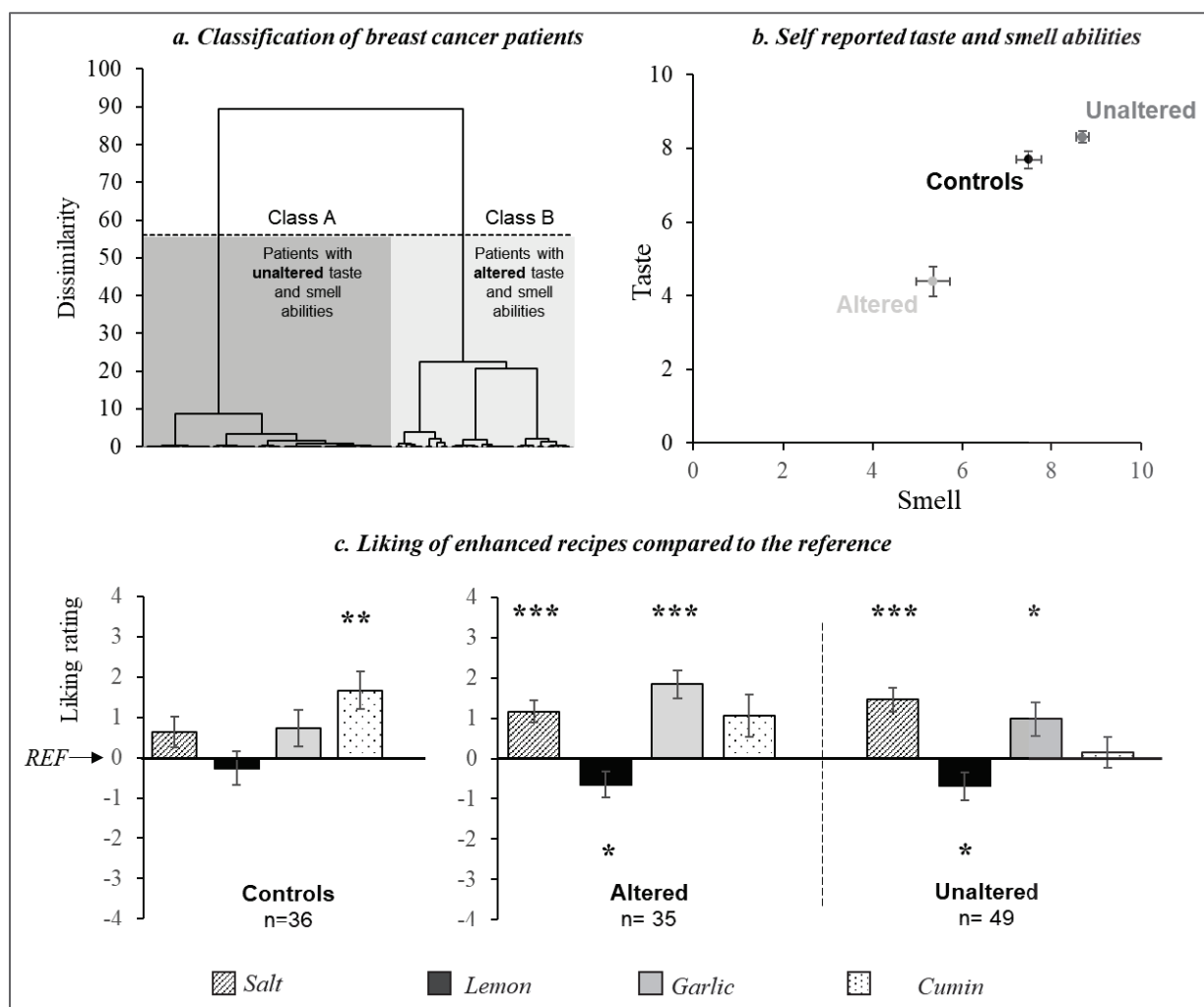


Figure 2. (a) Classification of breast cancer patients based on self-reported taste and smell abilities. The hierarchical clustering resulted in two groups: unaltered (class A in dark grey), altered (class B in fair grey). (b) Chemosensory profiles of “altered”, “unaltered” and “control” groups. No difference was observed in taste and smell ratings between controls and patients with “unaltered” abilities. Patients with altered abilities ratings were significantly lower compared to controls (taste: $t=-8.55$, $p<.001$; smell: $t=-5.45$, $p<.001$), and compared to “unaltered” patients group (taste: 10.89 , $p<.001$; smell: $t=-9.13$, $p<.001$). (c) Liking of the four enhanced recipes compared to the reference (REF) fixed at zero (0). Error bars corresponds to Standard Errors.
 * $p<.05$ ** $p<.01$ *** $p<.001$

Liking ratings of the enhanced recipes compared to the reference

The comparison of liking between the sensory enhanced recipes with the reference recipe (with zero as reference value) showed that the recipe enhanced with cumin was more appreciated than the reference by patients in altered group ($p= 0.05$) but not by patients in unaltered group ($p>.05$). The salt and garlic recipes were significantly more appreciated than the reference by

patients in altered ($p < .001$ and $p = 0.02$ respectively) unaltered groups ($p < .001$ for both recipes). The liking of the lemon recipe was significantly lower compared to the reference in altered ($p = 0.04$) and unaltered group ($p = 0.04$) (figure.1.3).

4. Discussion

To our knowledge, this is the first study that examined how manipulating the sensory attributes of food influence overall liking in cancer patients undergoing chemotherapy based on self-reported sensory alteration profile. Three major findings emerged: (i) there were differential effects of the type of flavor enhancement on food liking; (ii) The enhancement of food flavor significantly modified its liking in patient group whereas it slightly affected food liking in the control group; (iii) food liking was modified the same way regardless of patients' self-reported taste and smell abilities.

Careful consideration of the ingredients used at the manipulation of the test foods to enhance flavor that stimulate different aspects of the sensory system involved in flavor perception is the among the strengths of the study design (i.e. salt for gustation, cumin for olfaction and garlic for the trigeminal sensory system).

Overall, flavor enhancement resulted in a modification in liking ratings but the four types of enhancement have differential effects on food liking. While addition of salt and garlic significantly increased patients' liking of the eggplant cream, addition of lemon reduced it and cumin increased the liking of the eggplant cream only in the control group.

Adding salt improved significantly the liking in both altered and unaltered patients' groups. A reduced ability to perceive salty taste has already been highlighted by previous studies in cancer patients undergoing chemotherapy [25], [26]. Therefore, adding salt may compensate the deficit in salt taste perception, and fulfill patients' sensory expectations. Moreover, beyond imparting salty taste to the overall flavor, salt was found to increase liking by improving the perception of food [27]. The mechanisms that underlie this complex effect are not fully understood, however, salt was shown to enhance sweetness, mask metallic or chemical off-notes and suppress bitterness in different foods [28]. This may counter the bitter taste dysguesia and metallic taste perception frequently reported by cancer patients [29], [30], and explain the increased liking in patients' groups. Similarly, adding garlic to the eggplant cream increased its liking, but the hedonic dimension of garlic as a condiment is much less documented than salt in the literature. Garlic aroma is perceived by olfactory receptors through retro nasal way [31], but garlic has also properties that stimulate the trigeminal nerve endings. Although the role of

trigeminal perception in flavor development is prominent, this sensory modality and its possible alteration due to cancer and its treatment are not studied.

The recipe enhanced with lemon was less appreciated by patients. Cancer patients experience various modification in the oral cavity including the increased acidity of oral microflora [32], mouth ulcerations, and mucositis [33] that cause mouth pain possibly accentuated when exposed to sourness. Furthermore, in some cases, sourness accentuate the unpleasant perceived metallic taste reported by patients [29], [34] which possibly leads to sour taste aversion. Finally, the cumin recipe was significantly more appreciated than the reference in control group but not inpatient group. Overall, spices and spicy foods such as Mexican or indian dishes are often rejected by patients [34] that find them too intense. In contrast, controls liked the cumin recipe and orally reported that it was a good mix with eggplant cream.

Contrary to our hypothesis that the flavor enhancement will be more appreciated by patients who reported lower taste and smell abilities, there was no difference in liking ratings of the enhanced recipes between patients with and without taste and smell alterations. It is therefore possible that factors other than the deficit in perception of tastes and odors are involved in the increase of the liking. For instance, the trigeminal component brought by garlic, or the subjective perception of texture modification possibly due to salt adding [27] could have contributed to the modification in liking rating. Another explanation could be the method used for taste and smell function assessment that was used to classify patients. Indeed, self-reported chemosensory abilities are not always reliable, especially concerning olfaction [35]. Therefore, this method needs to be completed with psychophysical tests that provide more accurate results [36]–[39].

The analysis conducted on the sub-group of women diagnosed with breast cancer patients led to the same conclusions found in the whole group concerning the effect of flavor enhancement on food liking. However, we noted that breast cancer patients in the « unaltered » group rated their taste and smell abilities higher than controls. This may be due to the gender effect that could be more noticeable in this group than in the group including men. Indeed, female were shown to have higher sensitivity to taste and smell stimuli [40], [41], and this sensitivity tend to increase in some cases during chemotherapy [42].

In conclusion, enhancing food flavor is likely to be a simple and effective way to increase food liking in cancer patients undergoing chemotherapy. Both salt and garlic enhancement increased liking in patients but not in the control group suggesting that flavor enhancement is recommended to overcome reduced taste and smell perceptive abilities. There is evidence that food liking is a driver of food intake during lifespan and in some particular populations such as

in elderly in nursing home [22]. In the case of cancer patients undergoing chemotherapy, the enhancement of food should also take into account the specificities of this population, mainly because of the numerous oral problems patients have in addition to taste and smell alterations such as mouth dryness and mouth sores. Future studies should include measurements of food intake during a full meal and over a defined period to examine whether increasing food liking can be an effective strategy to improve food intake in cancer patients and prevent malnutrition. Moreover, manipulating other organoleptic properties of food, such as texture, to identify their role in the overall hedonic judgement of food by cancer patients with sensory deficits seems prudent.

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Chapter VIII: General discussion

General discussion

During cancer and chemotherapy, chemosensory alterations and especially taste and smell modifications constitute a disturbing side effect for patients [4]. The proportion of patients suffering from this side effect is not precisely defined because of the high variability between study outcomes on the one hand, and between individuals on the other hand. This is particularly worrisome given that taste and smell alterations impact food behavior and thus increase significantly the risk of malnutrition in cancer patients' population [58].

Given that food intake relies on the interaction between homeostatic regulation and sensory (taste and smell) hedonic pleasure, the main hypothesis tested in my thesis was that considering interindividual variability in taste and smell alterations of patients is needed to better understand the relationship between modifications in taste and smell abilities and changes in food behavior. This hypothesis had two main rationales:

Firstly, the pleasure of food consumption is shaped by diverse factors including information from sensory stimuli. Thus, we expected that the alteration of taste and/or smell perception may influence the unitary perception of flavor, involved in the acceptance or rejection of food, which in turn could alter the pleasure of consuming food.

Secondly, the high heterogeneity in both sensory and food behavior modifications observed in cancer patients undergoing chemotherapy led us to consider sample heterogeneity to explore the relationship between taste and smell alterations and patients' food behavior.

Therefore, the main aim of this Ph.D. thesis was to exploit the existing diversity between patients in taste and smell alterations and to identify means to maintain food enjoyment by considering these sensory alterations that are known to interfere with the hedonic value of food.

Within this context, we set out to explore **three objectives**:

- To identify the typology of taste and smell alterations in cancer patients undergoing chemotherapy
- To explore the relationship between taste and smell alterations and food behavior in cancer patients considering different chemosensory types (referred to as profiles in the manuscript)
- To translate the scientific evidence into application by improving food liking in cancer patients through food manipulation.

The main findings, their interpretations, and perspectives that the project opens are discussed in the following sections.

1. Main findings

Taste and smell alterations are a common side effect of chemotherapy treatment, however, a high heterogeneity exists between studies outcomes with regard to the prevalence of this side effect, and between patients in terms of type and intensity of taste and smell alterations. In parallel, diversity was also observed in patients' food behavior. Therefore, the first question that the project addresses is **whether the observed food behavior modifications could be justified by alterations in taste and smell abilities of patients during chemotherapy?**

Study 1. Relationship between food behavior and taste and smell alterations in cancer patients undergoing chemotherapy: A structured review

To answer this first research question, a literature review was conducted with the **hypothesis that taste and smell alterations impact patients' food behavior**. To consider the diversity existing between patients, the selected studies were grouped based on taste and smell assessment outcomes.

The categorization of studies depending on taste and smell assessment outcomes allowed the definition of three profiles of patients: unaltered, hypo- and hyper-chemosensation (taste and/or smell). Interestingly, patients with chemosensory alterations (either decreased or increased abilities) are those who exhibited modifications in food behavior, namely appetite loss, decreased food enjoyment, decreased food intake, and modification in food preferences.

This theoretical study allowed validating the first hypothesis and stating that taste and smell alterations affect patients' food behavior. However, it also highlighted a high variability due to different factors, a variability that could be reduced by attributing a chemosensory profile to patients.

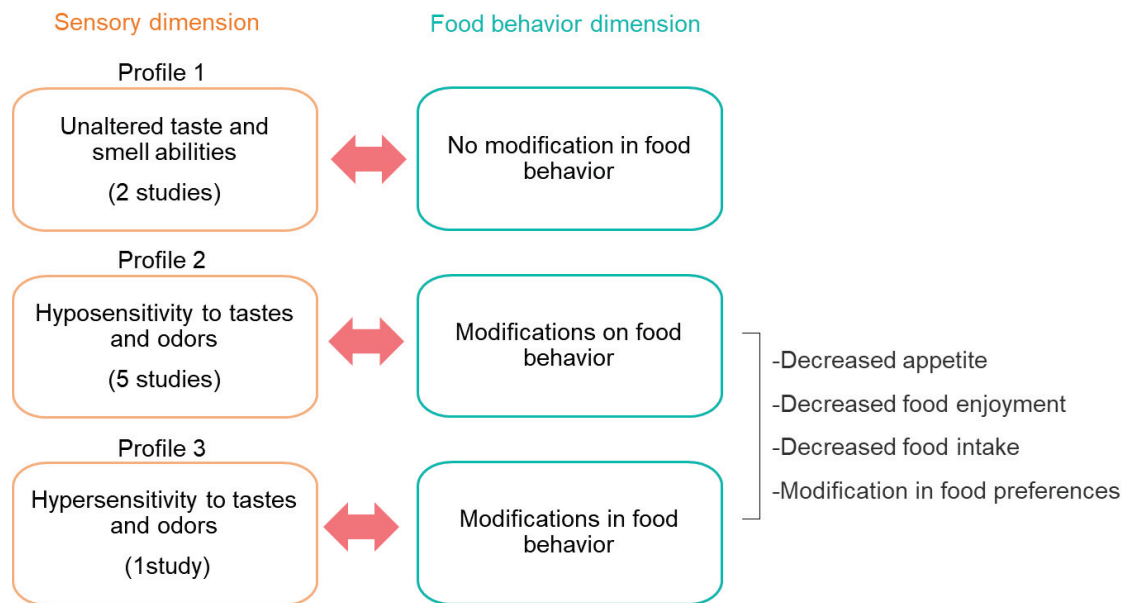


Figure 3. Relationship between taste and smell alterations and patients' food behavior from study 1

The existence of different chemosensory profiles characterized by their type (ageusia/anosmia, hypo/hyper-sensitivity) and their intensity (absent, moderate or severe), and the confirmation of the link between taste and smell alterations and food behavior modifications lead us to the second research question of the project: **what are the consequences of chemosensory alterations type and intensity on patients' food behavior?**

To answer this question, two studies based on different approaches were conducted with the hypothesis that **patients' chemosensory profile could be associated with a specific modification in his food behavior.**

Study 2.a. The impact of taste and smell alteration severity on food perception in cancer patients undergoing chemotherapy.

The main objective of this study, based on patients' self-reported method for chemosensory assessment, was to examine the effect of the intensity of taste and smell alterations on self-reported food behavior and food perception. The results showed that the intensity of taste and smell alterations have an impact on patients' food perception. Patients with severe alterations declared more often that food has an unpleasant taste, does not taste the same as before, and reported difficulties in detecting food tastes and odors. Moreover, the distribution of

chemotherapy stages (early vs. late) was not similar within these three groups, suggesting a cumulative effect of cytotoxic chemotherapy on taste and smell perception through the treatment. This effect needed to be further examined in a longitudinal study.

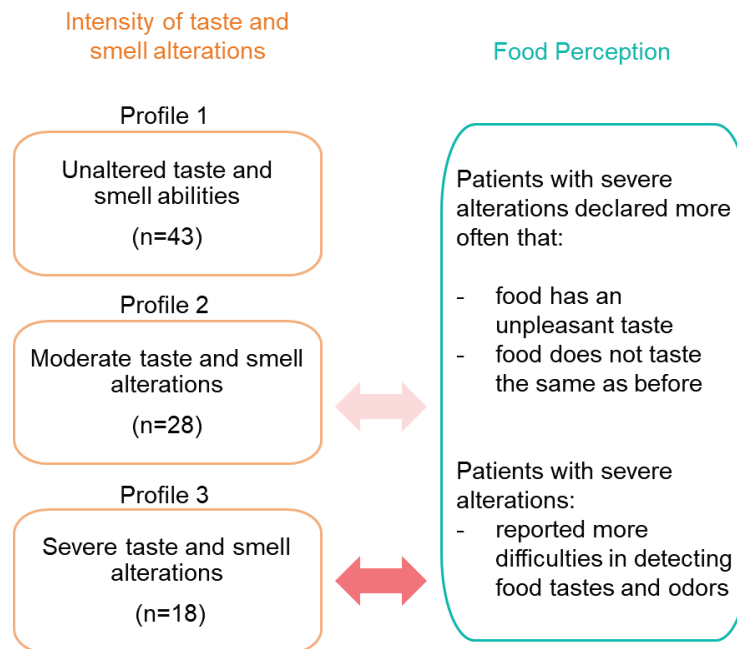


Figure 4. Relationship between taste and smell alterations and patients’ food behavior from study 2.a

Study 2.b Hyposmia in cancer patients undergoing chemotherapy impacts food behavior

To complete the previous study and palliate some of its methodological shortcomings, this third study based on a psychophysical assessment of patients’ taste and smell abilities and following a longitudinal design was conducted on a group of bronchial cancer patients and a group of age- and gender-matched controls. This study, designed to minimize the methodological variability sources has three main objectives: 1/ To characterize smell and taste alterations in a homogenous group of cancer patients undergoing chemotherapy (vs. controls), 2/ To characterize changes in food behavior of cancer patients undergoing chemotherapy (vs. controls), 3/ To examine how smell alterations can influence changes in food behavior in cancer patients undergoing chemotherapy.

Mainly, the results highlighted a decreased taste and smell abilities in almost half of the lung patients’ group even before the chemotherapy and influence of cancer/chemotherapy on odor cognitive processing, since patients rated typical food odors as less edible compared to controls. Regarding the link between sensory alterations and food behavior, the results showed that within the patients’ group, participants with lower olfactory abilities reported using more

condiments, suggesting a compensation mechanism to cope with their decreased sensory abilities. This confirms the effect of chemosensory alterations on patients' food behavior and underlines the involvement of olfaction in food perception and more specifically, the impact of reduced olfaction on dietary practices including seasoning.

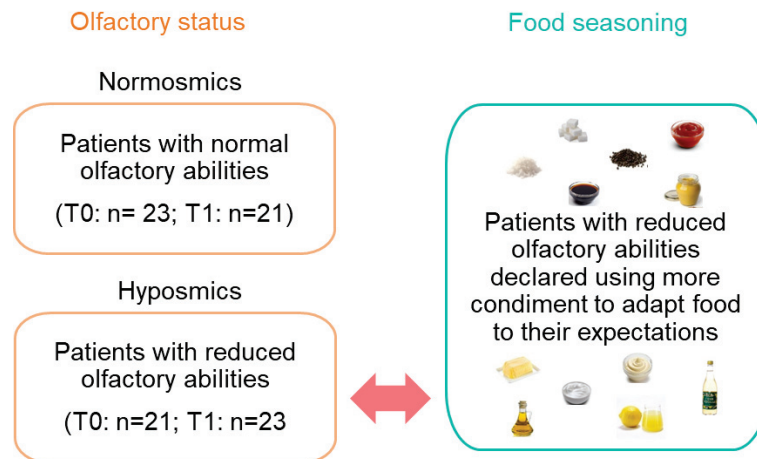


Figure 5. Relationship between smell alterations and patients' food behavior from study 2.b

In addition, to confirm the relationship between taste and smell alterations and patients' food behavior, the results from the above-mentioned studies brought two central information:

- There is a heterogeneity in the type of chemosensory alterations found in cancer patients' populations, but in most cases, taste and smell abilities are reduced (hyposmia/hypogeusia).
- Deficit in chemosensory abilities (olfactory abilities in this case) may lead to a compensation mechanism in order to adapt the taste of food to patients' sensory expectations.

These results lead to the third research question of the project: **can we improve patients' food liking by adapting the sensory properties of food to cope with patients' taste and smell alterations?**

To answer this last question, an operational study was conducted on a large group of patients undergoing chemotherapy for different types of cancer, with the hypothesis that **enhancing food flavor by adding basic ingredients able to stimulate gustatory/olfactory receptors may improve its liking rating by patients with taste and smell deficits.**

Study 3. Flavor enhancement as a strategy to improve food liking in cancer patients with decreased taste and smell abilities.

The main objective of this study was to examine the effect of flavor enhancement on food liking in a group of cancer patients undergoing chemotherapy, considering their taste and smell abilities. Patients were classified into two groups based on their self-reported taste and smell abilities: patients with unaltered chemosensory abilities and patients with altered chemosensory abilities. Patients had to taste four enhanced recipes of eggplant cream (salt, lemon, garlic, and cumin), and rate their liking for each recipe in comparison to a neutral non-enhanced eggplant cream recipe.

Regardless of their chemosensory profile, flavor enhancement resulted in a modification of liking ratings but the four types of enhancement differed in their efficiency to increase food liking. While salt and garlic significantly increased patients’ liking of the eggplant cream, lemon reduced it and adding cumin did not show any difference in patients. The opposite results were observed in the control group.

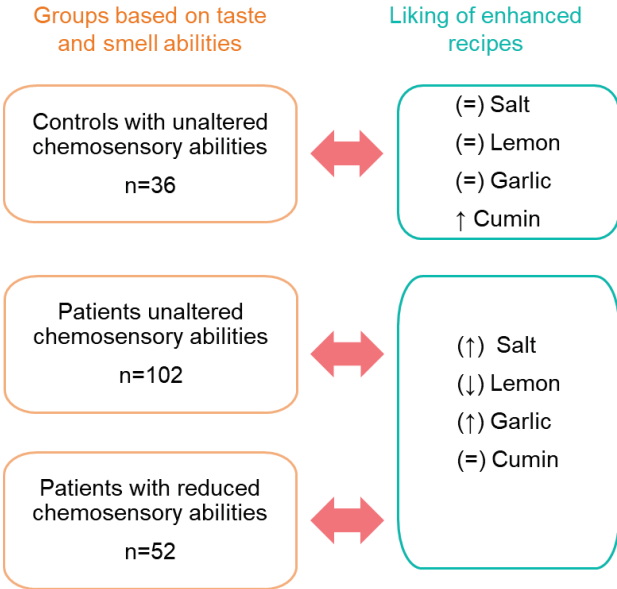


Figure 6. Relationship between taste and smell alterations and patients’ food behavior from study 3

**2. Extent and type of chemotherapy-induced chemosensory alterations:
*heterogeneity at two levels***

The literature review conducted to better understand the taste and smell alterations highlighted the high heterogeneity at two levels: i) at study outcomes and ii) at the individual level.

The prevalence of taste and smell alterations varied between studies, resulting in a wide range of percentages of patients with taste (45-84%) and smell (5-60%) alterations [95]. This

variability is likely due to methodological factors, which mainly include the study design, the approach used for sensory assessment, and the characteristics of the studied sample. Most of the studies that assessed taste and smell alterations were cross-sectional before 2012. [2], [9], [13], [46]–[48], [55], [68], [81], [84], [92]. The cross-sectional design allows data collection in a shorter time, and optimize chances to involve a higher number of patients since measurement is done at one specific point in time. Most of the recent studies followed a longitudinal design including two or more time points of assessment [8], [34]–[36], [80], [82], [90], [91], [93], [94], [96]. The longitudinal design is a more robust source of evidence and is more informative given the prospective and follow up nature of the sample population. For instance, study 2.b (chapter VI) showed an olfactory deficit in lung cancer patients before the beginning of the chemotherapy treatment, with no effect of Cisplatin treatment on their taste and smell abilities after six weeks. From a methodological, point of view, this result underly the importance of having a baseline measurement in order to not miss crucial information. Here, 50% of patients had lower olfactory and gustatory abilities before chemotherapy treatment commence, which could be caused by the cancer. In addition to the challenges entailed in the conduct of longitudinal studies such as adherence, cost and attrition, it is studying this specific population of cancer patients. Indeed, patients that are already involved in chemotherapy treatments protocols are often not able to commit and to provide the necessary effort for the study. This could explain why most of the prospective studies have been conducted either on small homogeneous groups [35], [91], [93], [97] or larger but heterogeneous groups [38], [80] and overall, few studies included a control group [36], [56], [78], [91], [98]. At the light of these elements, we ensured to have patients' groups of adequate size in order to have the power needed to provide statistically validated conclusions (study 2.a, study 2.b and study 3).

Concerning the assessment of taste and smell alterations, two main approaches are prominent: self-reports via questionnaires and interviews, and instrumental assessment using psychophysical tests (Study 2.a and b). Hutton et al. measured the chemosensory function of patients with questionnaires and identified self-reported taste and smell alterations as a predictor of decreased energy intake [68]. Brisbois et al. argued that the self-reported assessment is the best way to capture dimensions such as flavor and food enjoyment and that clinical measures of threshold are not surrogate for the complex perception of flavor [9].

The self-reported questionnaire for taste and smell assessment used in study 2.a was derived from the CiTAS scale (Chemotherapy-induced Taste Alterations Scale) [86]. CiTAS scale showed good internal consistency, and good reproducibility, which increased its clinical use in

recent studies [87]. However, it is focused on taste alterations and does not consider smell, which is a major component of flavor [99], [100] and is hard to disentangle from the taste. Thus, we added some items to assess smell at the CiTAS scale as described in detail in the questionnaire of study 2.a in order to classify patients based on both taste and smell abilities. Unlike the gustatory self-assessment, olfactory self-assessment did not allow to stratify patients in study 3 since they rated their olfactory abilities quite similarly, suggesting that self-assessment is not recommended in olfaction. Furthermore, it is common in individual with olfactory impairment to not be aware of it thus not reporting it which amplifies the underestimation of olfactory disturbances in cancer patients population [80]. Consequently, we opted for a validated psychophysical test for olfaction (ETOC) in study 2.b since the instrumental approach is effective in diagnosing alterations, even when the patient is not aware of a possible deficit.

Using self-reported approach in study 2.a and objective approach in study 2.b further revealed their strengths and weaknesses. **The underestimation of olfactory deficits was the main caveat of the self-reported approach.** The use of ETOC in study 2.b allowed the identification of hyposmia in half of the patients before and during chemotherapy whereas no major olfactory deficit was seen when patients were asked to self-rate their olfactory function in study 2.a and 3. The discrepancy between subjective and objective sensory measurements has already been highlighted in cancer patients, where taste measurements using taste strips test were not correlated with patients self-reports [96]. However, this study reported a correlation between olfactory measurement conducted with sniffin sticks test and patients' self-assessment [96]. In contrast, the discrepancy for olfaction assessment was found in other populations including hyposmic patients at risk of Parkinson disease [101], Alzheimer patients, and normal aging individual [102], confirming that the self-reported assessment often needs to be completed with an instrumental assessment.

Finally, the studied population, which differs between studies in terms of size, demographic characteristics, and specificities related to the pathology and treatment could also have contributed to the heterogeneity in study outcomes. Indeed, the prevalence of taste and smell alterations varies as a function of molecules used during chemotherapy [46]–[48], and gender [77], [103]. Nevertheless, even in homogeneous groups in terms of cancer and chemotherapy treatment, the pattern of alteration is not similar between patients [77], [94], [104]. For instance, McGreevy et al. used the taste and smell survey in a group of lung cancer patients and found taste and smell alterations in 69% of cases, among which 42% declared a stronger sensation,

18% a weaker sensation, 14% a mixed sensation, and 26% other sensations. The remaining 31% of patients did not show any sensory alterations. Similarly, our study on a homogeneous group of 44 lung cancer patients undergoing cisplatin-based chemotherapy (chapter V, study 2.b) reported olfactory deficit only in half of the participants. Taken together, this suggests that **in addition to cancer and chemotherapy type, other factors, as described below, intrinsic to the individual are likely to be involved in the occurrence of chemosensory alterations** (figure 7).

Heterogeneity was also observed at the individual level, where we found a great individual variation in patterns, severity, and impact of olfactory and/or taste changes between patients in the same study [9], [68]. Demographic characteristics (age and gender) and intrinsic factors including variation in the number of taste buds, genetic variations in olfactory and gustatory receptors and variation in saliva flow and composition may contribute to the amplification of variability in chemosensory alterations (study 1). In study 2.a, where the studied sample was composed of 52 women and 37 males undergoing chemotherapy for different types of cancer (mainly gynecological, lung, breast and digestive), no effect of age, gender and cancer type on chemosensory score was found ($p > .050$). However, a tendency of lower chemosensory abilities in patients in late stage of chemotherapy was found ($p = .07$). Similarly, no effect of age, smoking status, and cancer type was highlighted in study 3, where the group of participants was composed of 126 women and 28 men with different cancer types including breast, gynecological, lung, digestive and prostate cancers. A tendency of women reporting better sensory abilities was found in this group ($p = .06$), but giving the unbalanced sex ratio, we could not conclude to a gender effect. Thus, our results did not highlight a clear effect of physiological and demographic factors on patients taste and smell abilities.

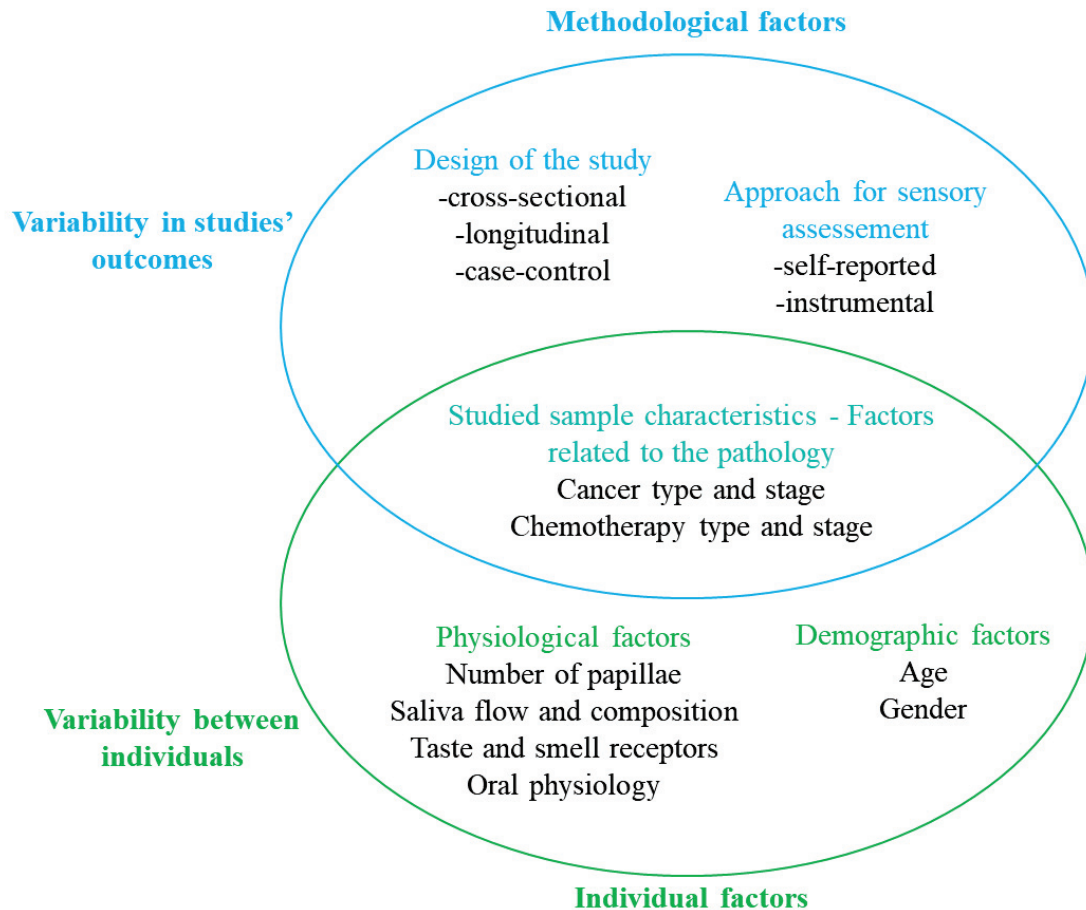


Figure 7. Factors involved in the methodologic and individual variability of taste and smell alterations in cancer patients undergoing chemotherapy

In summary, the variability with regards to the effect of chemotherapy on the taste and smell perception of cancer patients could be attributable to a number of methodologic, physiologic or demographic factors. It is important to state that **proper management of taste and smell alterations requires a proper assessment, and most importantly, to look at the individual level** rather than group level. Considering the individual variability by **identifying a typology of chemosensory abilities of patients** appeared to be a better approach to understand the consequences of taste and smell alterations on food behavior.

3. Typology of chemosensory alterations: *the importance of considering individual variability*

Based on the literature review of studies that considered both chemosensory abilities and one or more aspects of food behavior (study 1), we highlighted three main chemosensory profiles: (1) patients exhibiting unaltered taste and smell; (2) patients exhibiting reduced sensitivity (hyposensitivity) to taste and smell; (3) patients exhibiting increased sensitivity

(hypersensitivity) to taste and smell. However, we noted that a **decreased ability to perceive tastes and odors is the most frequent type of chemosensory modification across the reviewed studies** [34], [36], [96], [98], [105]. In our empirical experiments on the influence of sensory alterations on patients' eating behavior (study 2.a, 2.b, and 3), we have considered chemosensory diversity by classifying patients based on their self-reported or measured sensory capacity. In study 2.a, 51.7% of patients reported difficulties in perceiving tastes and smells, and in study 2.b, 52% of patients were hyposmic before chemotherapy and 48% after 2 cycles of chemotherapy. Almost half of the participants in both studies did not exhibit chemosensory alterations, thus, **considering the results at the group level constituted a risk of having an attenuated effect of taste and smell alterations on food perception.**

Classification of patients based on their chemosensory abilities could act as a screening tool of the existing variation in patients in order to facilitate provision of personalized management of side effects and nutritional advice. Yet, **the optimal assessment tool to characterize patients' chemosensory abilities is still required.** This tool should be reliable, user friendly so that it could be integrated into clinical routine, and not too demanding for patients. Furthermore, the assessment tool should combine objective and subjective methods in order to measure precisely smell and taste abilities and capture subjective hedonic dimension and qualitative taste and smell disturbances (e.g. phantogeusia/phantosmia).

4. Relationship between taste and smell alterations and food behavior: *a link to further explore and positively exploit*

There were only thirteen studies that assessed chemosensory abilities and patients' food behavior (chapter V) suggesting that the relationship between taste and smell alterations and food behavior of cancer patients undergoing chemotherapy is still understudied. The literature review (chapter IV) provided no evidence for a systematic and unvarying impact of chemotherapy on gustatory and olfactory functions in cancer patients given the existing individual variability. However, it highlighted that taste and smell alterations adversely influence patients' food behavior, regardless of the alteration type (hypo- or hypersensitivity). [6]. Patients with hypo- or hypersensitivity to taste and smell stimulation exhibited lower food intake [8], [9], [34], [68], [76], [98], decreased food enjoyment [94] and decreased appetite [76], [98], [105]. Patients without taste and smell alterations did not exhibit any food behavior modifications. This observation strengthens the hypothesis that food behavior changes are underpinned by chemotherapy-induced taste and smell alterations. This could be explained by the fact that the perception of food flavor derives from multiple sensory afferents, including

gustatory, olfactory, and trigeminal fibers [100], Therefore an altered ability to perceive taste/or smell could , alter food flavor liking, which is a considerable part of food overall liking [106].

It is important to consider the potential **involvement of other chemotherapy-related symptoms**. As described in *figure 8* chemotherapy-induced oro-nasal problems may **interplay with taste and smell alterations** leading to the deterioration of food enjoyment and resulting in a decreased food intake. Apart from taste and smell alterations, which modify directly the overall perception of flavor, mouth dryness (xerostomia) decrease flavor perception by causing a bad dissolution of sapid molecules and so reducing the amount of sapid molecule in contact with gustatory receptors. Mouth sores and mucositis that are frequent chemotherapy side-effects [30] may also decrease food enjoyment because of the pain when they are in contact with solid, spicy or sour food [107]. Considering those oro-nasal symptoms, when defining patients’ chemosensory profile may allow a better understanding of the contribution of other food properties such as texture and trigeminal in its overall liking.

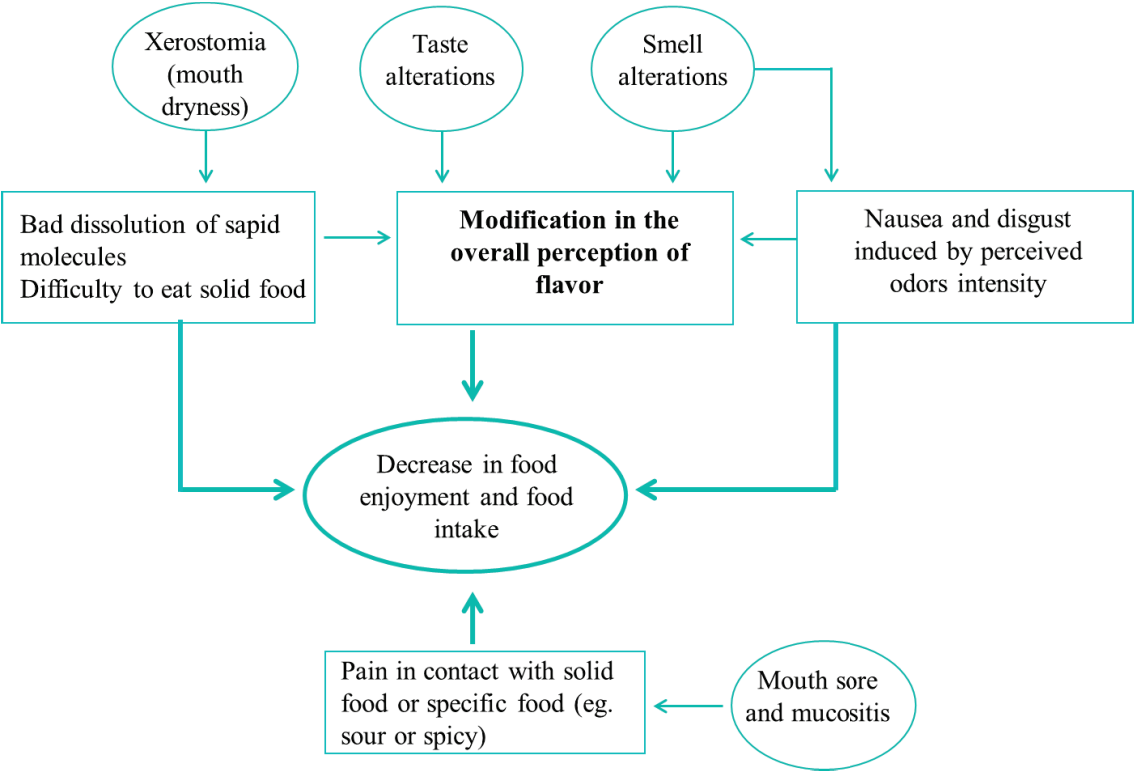


Figure 8. Oro-nasal chemotherapy-induced symptoms that influence food enjoyment and food intake

Since the term “food behavior” is broad and encompasses many aspects, we tried in study 2.a and 2.b (chapter VI) to specifically define two food aspects concerned by chemosensory alterations: food taste and odor perception, and seasoning habits.

The main objective of study 2.a was to examine the effect of the intensity of taste and smell alterations on self-reported food behavior and food perception. 89 patients with different types of cancer were recruited and classified based on their self-reported taste and smell alterations, assessed with a questionnaire developed for the study. Participants then filled a questionnaire on food behavior and food perception. We showed through this questionnaire-based study that patients with severe chemosensory alterations reported more frequent food perception problems, including modification of the perceived taste of food, finding bad taste in all food, and being unable to perceive food taste than patients with less severe chemosensory alterations. These findings underly once more the importance of classifying patients by their sensory abilities before proceeding to the analysis of food behavior modifications. The severity of chemosensory abilities had been rarely considered in previous studies. Both Hutton et al. [68] and Brisbois et al. [9] reported a negative impact of chemosensory alterations severity (assessed with Taste and Smell Survey) on patients’ energy intake. In a longitudinal study with assessment at baseline, 2, 4 and 6 months after the beginning of the treatment, McGreevy et al. [77] showed that patients had the lowest food intake at the time point at which they had the highest chemosensory complaints score. Thus, results of study 2.a provide one explanatory hypothesis to the decrease in food intake reported in previous studies [8], [34], [76], [98]. Indeed, perceiving food taste as different from usual may cause a disappointment of not meeting food sensory expectations, while being unable to perceive taste and smell in food may lead to perceive food as bland and tasteless, thus, decrease its consumption [13], [55]. However, study 2.a did not show the effect of taste and smell severity on other components of food behavior such as a difficulty of eating meat or fatty food and a decreased appetite. This is probably due to **the involvement of other parameters than taste and smell perception in food behavior changes**. For instance, the difficulty of eating meat, previously reported in cancer patients’ population [108], [109] is more likely due to the presence of metallic taste in the mouth [50], [110], or to the fact that meat requires more efforts to be chewed compared to other foods. Therefore, a classification based only on taste and smell abilities may not be effective in justifying certain food rejections.

Given that olfaction is less explored in cancer patients' population, in study 2.b the research question was focused on whether there is a link between this sensory modality and patients’

food behavior. This study examined how smell alterations can influence changes in food behavior in a homogeneous group of cancer patients undergoing cisplatin-based chemotherapy. Patients' olfactory function was assessed with the ETOC test and two major findings emerged from this assessment. Firstly, half of the patients' group was hyposmic before and six weeks after the beginning of chemotherapy, questioning the influence of the pathology itself rather than the chemotherapy treatment on the olfactory function in the case of bronchial cancer (discussed in chapter VI). Secondly, when compared to healthy controls, patients rated significantly lower two perceptual odor dimensions: familiarity and edibility. Patients judged food odors as less edible compared to controls and this effect was specific to food odors relative to non-food odors, which supports further the link between chemosensory disturbances and patients' food behavior.

Furthermore, the fact that familiarity and edibility judgments of food odors were both lower in patients' groups in comparison to controls suggests that **sensory alterations are likely to go beyond the peripheral level (olfactory and gustatory receptors)**, possibly affecting conduction and integration of the olfactory/gustatory information. This interesting finding was worth to be further investigated with an instrumental method that could provide information on the integration of odors.

Therefore, a complementary study⁴ based on Electroencephalography (EEG) was designed in order to examine the cerebral activity of cancer patients undergoing platinum-based chemotherapy when they are exposed to food odor vs. a non-food odor. Data collection for this study is ongoing and the detailed protocol is joined in appendix 6.

Hyposmic patients reported adding significantly more condiments to their dishes relative to normosmic patients, suggesting a sensory deficit compensation by seasoning in order to meet sensory expectations. However, we noted a high variability in the score and choice of added condiments, reflecting the variability in taste and smell perception, and in chemotherapy-induced chemosensory alterations.

Finally, the last study (chapter VII) was a first step to improve food liking via food sensory modulation in cancer patients through chemosensory perception.

⁴ I performed this preliminary EEG study during my 3-month internship at the University of Dresden under the supervision of Pr. Thomas Hummel.



Figure 9. Example of a tasting session at Institut de Cancérologie de l'Ouest (study 3)

Complaints about food being bland and tasteless were recurrent in cancer patients undergoing chemotherapy [13], [55]. Moreover, our results showed that in most cases, patients exhibited a decreased taste and/or smell ability (chapter V and VI), and that hyposmic patients declared using more condiments compared to normosmic patients (study 2.b, chapter VI). In this context, we examined in study 3 (chapter VII) the effect of flavor enhancement on food liking in a group of cancer patients undergoing chemotherapy exhibiting or not alterations in their taste and smell perceptive abilities. For this study, patients rated their taste and smell abilities on a Visual Analogue Scale, and were classified based on this self-rating into two groups: 66.2% of patients reported normal taste and smell abilities and 33.8% reported lower abilities in comparison to a control group without noticed or diagnosed chemosensory alterations. The liking of four flavor enhanced recipes of eggplant cream with either salt, lemon, garlic, or cumin was compared to the liking of a sensory neutral recipe of eggplant cream (without seasoning). Flavor enhancement resulted in a modification in liking ratings, but the four types of enhancement differed in their efficiency to increase food liking. While salt and garlic significantly increased patients' liking of the eggplant cream, lemon reduced it and adding cumin did not show any difference in patients but increased the liking in the control group. These results are even more interesting because no effects of sensory enhancement were observed in the control group, confirming that **the effectiveness of flavor enhancement is specific to individuals with sensory deficits**. Surprisingly, patients with and without self-reported taste and smell alterations rated the liking of the enhanced recipes almost similarly, while we hypothesized the flavor enhancement to be more appreciated by patients who reported lower taste and smell abilities. This could be due to other factors than taste and smell deficits (the trigeminal property

of garlic for instance), which could have influenced the liking rating. In addition, it could be due to the self-reported character of the chemosensory assessment method since self-reported chemosensory abilities are not always reliable, especially concerning olfaction [111]. Taken together, our results showed that **flavor enhancement may be a simple and effective way to increase food liking in cancer patients undergoing chemotherapy**, and raises an important question: does a higher liking of food increase its intake by cancer patients undergoing chemotherapy? If it is the case, flavor enhancement of food may help to prevent malnutrition in cancer patients by providing an alternative solution to food supplements, which are usually not designed to consider the sensory and hedonic aspects of the food experience.

Conclusion and perspectives

Conclusion and perspectives

The present thesis is one of the rare research to focus on the relationship between taste and smell alterations and modification in cancer patients' food behavior, with a particular attention to the inter-individual differences. While no consistent pattern of taste and smell alteration was identified, three main chemosensory profiles were prominent: unaltered taste and smell perception, hypo- and hyper- sensitivity to tastes and smell. This investigation revealed a negative effect of taste and smell alterations on food intake and preferences from the literature, and a modified food perception and dietary habits from experimentation. Furthermore, it opens a way for food flavor enhancement as a coping strategy to counter taste and smell alterations.

The thesis offered a contribution in the understanding of the relationship between taste and smell alterations and food behavior during cancer and chemotherapy, and provided some evidence for the four hypotheses put forward. This contribution will be valuable to offer culinary and dietary recommendations to patients, and to develop specific food to cancer patients' population by food industry.

Furthermore, this thesis work has opened a promising way for research to better understand the consequences of one not sufficiently studied chemotherapy side effect on cancer patient' food behavior. Our results constitute preliminary conclusions that need to be completed with additional research.

The development of standard tools for patients' chemosensory classification

The integration of taste and smell assessment into clinic routine requires an access to a suitable tool that is easy to use for medical teams. Further studies could focus on the development and the validation of such a tool. This could be done by working on a reduced version of the existing validated tests such as the Sniffin' sticks, the ETOC or the UPSIT for the olfaction, and the Taste strips test for the gustation. These tests should be associated to a questionnaire that would help to identify cases of phantosmia / phantom, or other qualitative changes. CiTAS scale which is more and more used in clinic could be a starting point to develop this questionnaire. However, the CiTAS scale should be adapted to native french speakers and completed with a part dedicated to olfactory assessment. Since patients also have symptoms that may affect eating pleasure, such as nausea and vomiting, the assessment of these symptoms should be also be assessed.

A rapid methodology to profile patients will be tested in a study designed to replicate the results obtained in Study 3, which assesses the effect of flavor enrichment on the liking of a food.

This profiling method combines a psychophysical approach with a self-declared approach. Smell abilities will be assessed with a fast olfactory test of detection and identification of two odors (lemon and rose), as well as the evaluation of their intensity. Regarding taste, patients will have to detect and identify two tastes in water (salty and sour), and evaluate their intensity. In addition to these tests, patients will self-report their olfactory and taste abilities on a Visual Analogue Scale. This study will take place in Antoine Lacassagne Center for oncology in Nice (France).

Evaluation of the influence of enhancing food liking on food intake

In our experiment, we found that the flavor enhancement improves the liking of eggplant cream, but we do not know if this is applicable to other foods, and most importantly, if improved liking improves food intake of cancer patients undergoing chemotherapy. This was not possible to examine through our study design (study 3) as the tastings were done at the time of snacking, and the quantities consumed by patients were limited.

Therefore, it would be interesting to apply the strategy of flavor enhancement on a complete meal consisting of starter, main course and dessert. In this context, the CANUT project, launched in September 2019, and associating a consortium of researchers, doctors, dietician and industrial aims to define a strategy of improving food for certain profiles of patients with chemosensory impairments. For this, a first step will consist in the definition of a suitable tool for profiling patients and the formulation of reference recipes (starter, main course, and dessert) and their variations for each type of patient. The evaluation of the food flavor enhancement effect will be done via a prospective study, in which patients will be followed at three time points: baseline (before chemotherapy), T1 (cycle 3), and T2 (cycle 5). It will be proposed to patients participating in the study to come to the living lab of the Institut Paul Bocuse Research Centre three times for a complete meal. Patients will first be assigned a chemosensory profile based on their olfactory and gustatory abilities as well as their food preferences (assessed by psychophysical tests and a complementary questionnaire). Afterwards, a starter, a dish and a dessert will be offered to the patient, who will evaluate the liking of each of them. At the end of the meal, the plates will be weighed to assess consumption, in order to examine the potential relation between liking and consumption.

The results of this project will lead to the development of a guide accessible to patients and their families that provides tasting advice, nutritional advice, foods to avoid or promote, sample recipes for each type of chemosensory profile. The impact of this guide on patient's quality of life related to food enjoyment will be evaluated by questionnaire.

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Appendix 3 : Study 2.b European Test for Olfactory Capabilities answers

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Appendix 5 : Study 2.b Food behavior questionnaire

Appendix 6 : Protocole of EEG study + flyer used for patients recruitment

Appendix 7 : Study 3 - Technical sheet for eggplant cream preparation

Appendix 8 : Study 3 – Formal consent

Appendix 9 : Study 3 – Questionnaire for taste, smell and liking assessment

Appendix 10 : Additional study on head trauma-induced olfactory disturbances

Appendix 1: Study 2.a - Questionnaire for taste and smell self-reported assesment

Date :

Code patient :

Evaluation de la perception

Avez-vous faim ?

Je n'ai pas J'ai très
du tout
faim
faim

Veillez cocher la réponse qui convient le mieux à ces affirmations selon vous.

1. Depuis le début du traitement :

	Jamais	Parfois	Souvent	Toujours
Je détecte facilement les goûts en général	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement la saveur amère	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement la saveur acide	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement la saveur salée	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement la saveur sucrée	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Depuis le début du traitement :

	Jamais	Parfois	Souvent	Toujours
Je détecte facilement les odeurs en général	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement les odeurs alimentaires	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement les odeurs florales	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement les odeurs corporelles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je détecte facilement les odeurs irritantes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Depuis le début du traitement :

	Jamais	Parfois	Souvent	Toujours
J'ai moins d'appétit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J'ai des difficultés à manger de la viande	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J'ai des difficultés à manger des aliments gras	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J'ai des difficultés à manger des aliments chauds	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L'odeur des plats me dérange	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Je mange moins car :

Je me sens fatigué	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je ressens une gêne/douleur dans la bouche	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je me sens nauséeux	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Depuis le début du traitement :				
J'ai un goût amer en bouche	Jamais <input type="checkbox"/>	Parfois <input type="checkbox"/>	Souvent <input type="checkbox"/>	Toujours <input type="checkbox"/>
Tout a un goût amer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J'ai un mauvais goût en bouche	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Depuis le début des traitements :				
Je perçois une odeur désagréable en permanence	Jamais <input type="checkbox"/>	Parfois <input type="checkbox"/>	Souvent <input type="checkbox"/>	Toujours <input type="checkbox"/>
Toutes les odeurs me paraissent désagréables	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je perçois des odeurs sans présence de source odorante	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Depuis le début du traitement :				
Les aliments n'ont pas le goût qu'ils ont d'habitude	Jamais <input type="checkbox"/>	Parfois <input type="checkbox"/>	Souvent <input type="checkbox"/>	Toujours <input type="checkbox"/>
Tout a mauvais goût	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J'ai des difficultés à percevoir le goût des aliments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Je suis incapable de percevoir l'odeur des aliments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci de votre participation

Appendix 2: Study 2.b –Formal consent

Protocole ARC 1 – Formulaire consentement / Patient - Version 1 du 31 juillet 2014

Page 1 sur 2 Paraphe du : _____ Paraphe de l'investigateur : _____

CONSENTEMENT ECLAIRE

1 - Je soussignée (Nom, prénom)

.....
accepte volontairement et de mon plein gré de participer à l'étude :

APPROCHE SENSORIELLE DES MODIFICATIONS ALIMENTAIRES INDUITES PAR UNE CHIMIOTHERAPIE

2- J'ai été pleinement informée par le Professeur Pierre-Jean Souquet ou le Professeur Pierre Fournel ou leurs co-investigateurs, des caractéristiques de l'étude, de ses procédures, contraintes et risques éventuels. La note d'information m'a été remise et j'en ai pris connaissance.

3 - J'ai eu la possibilité de poser des questions au Professeur Pierre-Jean Souquet ou au Professeur Pierre Fournel ou à leurs co-investigateurs sur tous les aspects de l'étude et j'ai compris les réponses et l'information qui m'ont été données.

4- S'il y a lieu et avec mon accord, mon médecin traitant sera averti de ma participation :

- J'accepte que mon médecin traitant soit averti de ma participation,
- Je refuse que mon médecin traitant soit averti de ma participation,

5- Les données qui me concernent sont strictement confidentielles. Je n'autorise leur consultation que par des représentants des Autorités de Santé ou par des personnes mandatées par le promoteur, les Hospices Civils de Lyon.

6- J'accepte, compte-tenu des nécessités de la Recherche, que les données enregistrées à l'occasion de cette étude, puissent faire l'objet d'un traitement informatisé.

7- Je sais que les données me concernant entrent dans le cadre de la Loi "Informatique et Liberté" (Loi N°2004-801 du 6 août 2004). Mon droit d'accès et de rectification s'exerce par l'intermédiaire du Professeur Pierre-Jean-Souquet ou du Professeur Pierre Fournel, auprès de qui je peux également demander toute information complémentaire.

8- J'ai aussi été informé(e) que ma participation à l'étude entre dans le cadre de la Loi française relative aux recherches biomédicales (loi n° 2004-806 du 9 Août 2004 relative à la politique de santé publique).

9- Je sais que le protocole a reçu un avis favorable du CPP SUD-EST IV le 09/09/2014 et l'autorisation de l'ANSM le 28/08/2014.

10- J'ai compris que je suis libre de me retirer de l'étude à n'importe quel moment, sans devoir donner de justification, sauf si cela est lié au produit testé.

11- J'accepte de ne me soumettre à aucun autre protocole pendant l'étude.

Protocole ARC 1 – Formulaire consentement / Patient - Version 1 du 31 juillet 2014

Page 2 sur 2 Paraphe du : _____ Paraphe de l'investigateur : _____

12- Je confirme qu'un exemplaire de ce document m'a été remis.

PATIENT

Date : _____

Lieu : _____

Signature: _____

Je soussigné <Dr.....>, Investigateur de l'étude, confirme avoir pleinement expliqué au sujet nommé ci-dessus la nature, les procédures, ainsi que les risques éventuels liés à cette étude. Je confirme qu'il (elle) a reçu la fiche d'information, en a pris connaissance et a accepté librement de participer à l'étude.

INVESTIGATEUR

Date : _____

Lieu : _____

Signature: _____

Remarque : ces deux pages doivent être paraphées par l'investigateur et le participant.



Objet n°

Code

Centre de Recherche en Neurosciences de Lyon
CNRS UMR5292-INSERM U1028, Université Claude Bernard Lyon 1
95, boulevard Pinel, F69500 Bron

Date / Heure

Age

Sexe : M F

N°	Localisation			Identification			Remarques
	A	B	C	D	Chocolat	Vanille	
1	A	B	C	D	Noix de coco	Vanille	Pain
2	A	B	C	D	Lavande	Clou de girofle	Champignon
3	A	B	C	D	Mandarine	Abricot	Pamplemousse
4	A	B	C	D	Violette	Fraise	Tomate
5	A	B	C	D	Cannelle	Noisette	Café
6	A	B	C	D	Peinture	Fioul	Tabac
7	A	B	C	D	Goudron	Lilas	Concombre
8	A	B	C	D	Chou	Ail	Céleri
9	A	B	C	D	Herbe coupée	Melon	Jasmin
10	A	B	C	D	Amande	Anis	Cumin
11	A	B	C	D	Orange	Banane	Poire
12	A	B	C	D	Oignon	Poivron	Poisson
13	A	B	C	D	Vinaigre	Carotte	Cerise
14	A	B	C	D	Thym	Réglisse	Poivre
15	A	B	C	D	Framboise	Ananas	Citron
16	A	B	C	D	Noix de muscade	Olive	Menthe

Version TOE.

Appendix 4: Study 2.b Taste strips test answers

Test gustatif

Date : _____

Heure : _____

Sujet : _____

Langue	Détection (o/n)	Identification	Intensité	Hédonique	Familiarité
1					
2					
3					
4					

QUESTIONNAIRE SUR LES HABITUDES ET COMPORTEMENTS ALIMENTAIRES

Numéro de la visite (V1 ou V2):

Numéro du patient :

Date et heure :

Bonjour,

Dans le cadre d'une étude clinique réalisée à Lyon et Saint Etienne, nous effectuons une recherche sur le comportement alimentaire. C'est important pour nous d'avoir les réponses d'un grand nombre de personnes. Nous vous demandons, pour cela, de répondre à quelques questions (environ 15 min). Vous êtes totalement libre d'accepter ou non de participer à cette recherche.

Vos réponses seront strictement confidentielles. Le traitement informatique des données sera anonyme. Il n'y a pas de bonnes ou de mauvaises réponses, répondez le plus sincèrement possible.

La seule chose qui compte pour nous c'est ce que vous pensez réellement, que vous puissiez vous exprimer librement par rapport aux différents sujets que nous allons vous proposer.

Lisez bien les consignes avant de répondre et n'hésitez pas à me demander si elles ne vous semblent pas claires.

Il y a plusieurs mois, qui faisait la cuisine dans votre foyer ? (Veuillez cocher une seule case, merci)

- Vous-même
- Votre conjoint(e)
- Vous et votre conjoint(e)
- Vos enfants
- Une autre personne

Ces dernières semaines, qui faisait la cuisine dans votre foyer ? (Veuillez cocher une seule case, merci)

- Vous-même
- Votre conjoint(e)
- Vous et votre conjoint(e)
- Vos enfants
- Une autre personne

Ces dernières semaines, des professionnels de santé vous ont-ils prescrit ou recommandé des compléments alimentaires ?

- Oui, Précisez le ou les prescripteur(s) :
- Non

Ces dernières semaines avez-vous : (*Veillez cocher une ou plusieurs cases, merci*)

Plusieurs choix possibles

- Modifié vos habitudes pour acheter les aliments et les boissons ?
- Modifié vos manières de cuisiner?
- Ajouté des aliments et/ou des boissons à votre alimentation ?
- Supprimé des aliments et/ou des boissons de votre alimentation ?
- Rien modifié
- Autres, précisez :
- Commentaires libres

Ces dernières semaines, qu'aviez-vous l'habitude d'ajouter à vos plats pour les rendre à votre goût : (Entourez votre/vos choix)

Sucre	Sel	Poivre	Moutarde
Ketchup	Vinaigre	Sauce soja	Citron
Mayonnaise	Beurre cru	Huile d'olive	Crème fraîche
Herbes de Provence	Epices	Autre	Autre

Ces dernières semaines, quelles sont les odeurs que vous aimez sentir (Entourer votre/vos choix) ? Celles que vous n'aimez pas (Barrer votre/vos choix) ?

Noix de coco	Chocolat	Vanille	Pain
Lavande	Clou de girofle	Ciboulette	Champignon
Mandarine	Abricot	Pamplemousse	Pomme
Violette	Fraise	Eucalyptus	Tomate
Cannelle	Noisette	Beurre	Café
Peinture	Fioul	Urine	Tabac
Goudron	Lilas	Pin	Concombre
Chou	Ail	Poireau	Céleri
Herbe coupée	Melon	Cassis	Jasmin
Amande	Anis	Rhum	Cumin
Orange	Banane	Mûre	Poire
Oignon	Poivron	Fromage	Poisson

Vinaigre	Carotte	Rose	Cerise
Thym	Réglisse	Persil	Poivre
Framboise	Ananas	Pêche	Citron
Noix de muscade	Olive	Basilic	Menthe
Autre odeur plaisante.....	Autre odeur déplaisante		

Ces dernières semaines, pouvez-vous préciser les aliments et boissons que vous AIMIEZ consommer en particulier pour leur goût, leur parfum, leur consistance?

- Non (aucun)
- Oui, Si oui préciser :

ALIMENTS	BOISSONS
.....
.....
.....
.....
.....

Ces dernières semaines, pouvez-vous préciser les aliments et boissons que vous N'AIMIEZ PLUS consommer en particulier pour leur goût, leur parfum, leur consistance?

- Non (aucun)
- Oui, Si oui préciser :

ALIMENTS	BOISSONS
.....
.....
.....
.....
.....

Effects of cancer and chemotherapy on neural processing of smells

Context

Cancer and chemotherapies cause alterations in the functioning of the olfactory system (Yakirevitch et al., 2005; Steinbach et al., 2009; Steinbach et al., 2010; Riga et al., 2015), and this has been associated with modifications of important aspects of quality of life including appetite loss and fatigue (Gamper et al., 2012; Turcott et al., 2016), nausea, (Brisbois et al., 2011), and decrease in energy intake (Sanchez-Lara, 2010). Although the importance of olfaction on nutrition and well-being is recognized, the neural changes sustaining effects of both cancer and chemotherapy on olfaction have not been adequately assessed. Understanding the psychological and neural underpinnings associated with olfactory changes is therefore essential to better understand the pathology and provide patients a better quality of life.

During cancer, one explanatory theory of chemotherapy on neural processing of smells suggests an interference of cytotoxic drug action with the regeneration of the olfactory neurons from the basal cells (Comeau et al., 2001). Here, it remains unclear at which stage of the cycle (early – before 3 cycles; or late from 4 cycles to at least 10) such effects of chemotherapy occur. Moreover, besides these peripheral alterations, we do not know how cancer and chemotherapy affect the functioning of the central networks involved in olfactory and emotional processing.

*The main objective of the present proposal will be to test these questions, based on the analysis of EEG responses to olfactory stimulations. This will provide an insight on the effect of cancer and chemotherapy on different stages of olfactory processing, informing on the stage to focus on for a better management of patients' olfactory disturbances.

Aim and hypothesis

*The aim of the present study will be to examine how peripheral and central neurophysiological responses to smells are altered in cancer patients in different stages of chemotherapy treatment. Here, the “peripheral effect” and the “central effect” hypothesis will be tested with electroencephalography (EEG; event-related potentials and time-frequency analysis) that enables measuring effects within different time window in a post-stimulus period of 2000ms.

*In a secondary aim, we will examine how olfactory alterations in patients are related to changes in their dietary habits (using food habit questionnaires).

Experimental groups

Three groups of participants will be tested (30 participants per group – *if possible*).

*Group 1: cancer patients in « early » stages of platinum-based chemotherapy (cycles 1-3)

*Group 2: cancer patients in « late » stages of platinum-based chemotherapy (cycles 4-10)

*Group 3: control group (individuals without cancer)

Experimental tasks

*TDI Sniffin Sticks including assessment of odor thresholds using a single-staircase, three alternative forced choice (3-AFC) procedure.

*Retronasal testing

*Quality of life questionnaires (SF32, SNOT20, QOD)

*Clinical examination – nasal endoscopy, oral status, saliva production

*Odorants through olfactometry: food odors and non-food odors (to be defined the number of odors and types)

*EGG measures: 07 channels system.

*Dietary habits: Dietary habits questionnaire

*Duration of the experiment: 1h30

Data analysis

*Univariate and multivariate statistical analyses will be used to compare the 3 groups.

*Multivariate regressions will be computed to highlight a potential relationship between the olfactory outcomes and food/quality of life items.

* Level of significance: $p < 0.05$.

Wir wollen Riechstörungen bei Chemotherapie besser verstehen und damit besser behandeln



Februar-April 2019

Wo: Univ. HNO Klinik, Haus 5, UG

Wer: Patienten mit Chemotherapie bei Lungenkarzinom

Was: Riechtest, EEG Ableitung (Hirnströme)

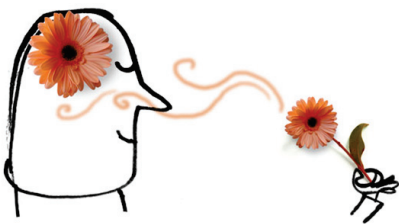
Wie lange: 90 Minuten

Bei Interesse:

Prof. Hummel, Tel. 0351 458 4189; thomas.hummel@ukdd.de

Patricia Schmidt, Tel. 0163 3326391; patricia_schmidt1991@yahoo.de

We want to better understand olfactory disorders in chemotherapy and treat it better



From February 2019

Where: Interdisciplinary Center Smelling and Tasting of the University ENT Clinic Dresden, house 5

Who: Lung cancer patients undergoing chemotherapy

What: Using a simple and non invasive EEG recording, we observe the reaction of your brain when you are exposed to different odors

How long: 1 appointments for a total of no more than 1 hours

Prof. Hummel, Tel. 0351 458 4189; thomas.hummel@ukdd.de

Patricia Schmidt, Tel. 0163 3326391; patricia_schmidt1991@yahoo.de

FICHE TECHNIQUE

Crème d'aubergine

Pour 1kg de produit fini

Recette de référence

Ingredients

1 kg d'aubergines cuites
(Obtenu à partir de 2kg 250g
d'aubergines cru)

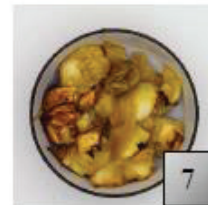
100 g d'huile
(70% colza / 30% olive)

Matériel

- Plaque de cuisson
- Four
- Papier cuisson
- Planche à découper
- Couteau
- Bols

Process

1. Couper les aubergines en deux dans le sens de la longueur.
2. Marquez le côté coupé des aubergines selon un motif hachuré en laissant un centimètre entre chaque ligne.
3. Percez le côté peau avec une fourchette.
4. Tapisser un plateau avec du papier sulfurisé et le côté coupé en haut.
5. Cuire au four préchauffé à 180 ° C pendant 25 minutes avec une ventilation élevée.
6. Mettez les aubergines cuites dans un bol et filmez-les. Laissez les aubergines dans le bol filmé pendant 15 minutes à température ambiante.
7. Pelez la peau d'aubergine.
8. Mélangez la pulpe d'aubergine et l'huile dans un mixeur jusqu'à obtention d'une pâte lisse et homogène.



Recettes enrichies:

En saveur salée

100 g de recette de référence
0.2 g de sel fin

En saveur acide

100 g de recette de référence
2 g de jus de citron

En arôme cumin

100 g de recette de référence
0.2 g de cumin en poudre

En arôme ail

100 g de recette de référence
0.2 g d'ail en poudre

A Saint-Herblain, le

Madame, Monsieur,

Vous êtes pris en charge à l'Institut de Cancérologie de l'Ouest et venez en Hôpital de jour pour votre cure de chimiothérapie.

1. Contexte et objectif de la recherche Nous vous proposons de participer ce jour à l'étude Goût et Cancer dont l'objectif principal est de mieux comprendre l'implication des perceptions sensorielles gustatives et olfactives dans l'appréciation et la consommation alimentaire. Les modifications des perceptions gustatives et olfactives sont observées chez 45 à 84% des patients sous chimiothérapie. Ces modifications peuvent se manifester de façon cyclique ou continue tout au long du traitement et peuvent persister jusqu'à quelques mois après le traitement. Cet effet secondaire de la chimiothérapie peut induire une modification des préférences et de la prise alimentaire, le goût étant un des principaux déterminants du choix alimentaire. La dénutrition est observée chez environ 40% des patients sous chimiothérapie et est en partie due à un rejet de certains aliments, jugée comme insipides, ou au contraire, trop relevés par les patients.

2. Déroulement de l'étude et nature des données recueillies L'étude se déroulera en 1 séance durant laquelle vous devrez déguster 5 recettes de caviar d'aubergine, et indiquer sur une échelle votre appréciation de ces produits. Vous pouvez par la suite, si vous le souhaitez, consommer les produits qui vous ont été donnés avec des toasts. Cette séance se déroulera durant votre hospitalisation de jour prévue dans le protocole de soin qui vous a été proposé dans le cadre de votre prise en charge. Les informations relatives à votre âge, sexe, statut tabagique, type de cancer, et nombre de cures de chimiothérapie au jour du test seront recueillies par questionnaire. En complément, nous recueillerons les données relatives à votre pathologie (localisation du cancer et type de chimiothérapie reçue) dans votre dossier médical informatisé. Le recueil de ces informations n'aura aucune incidence sur la prise en charge médicale ou sur la surveillance de votre maladie. Vous n'aurez aucun examen particulier ou consultation supplémentaire liés à cette recherche. Vous pouvez vous opposer à participer à cette recherche en le faisant savoir à la personne qui vous propose la recherche ; votre décision de participer ou pas n'aura absolument aucune incidence sur vos relations avec le médecin et l'équipe soignante et sur la qualité des soins et de la prise en charge de votre maladie. De même, vous aurez par la suite le droit de vous retirer de cette recherche à n'importe quel moment sans avoir à vous justifier.

3. Confidentialité et protection des données

Votre dossier médical restera confidentiel. Les données médicales vous concernant, nécessaires compte- tenu de l'objet de la recherche, ne seront transmises qu'au gestionnaire de l'étude ainsi que le cas échéant aux autorités sanitaires habilitées, dans des conditions garantissant leur confidentialité et ne permettant pas votre identification directe. GOUT et CANCER (ICO-2019-10 – N° CNIL) « Effet d'un enrichissement sensoriel sur l'appréciation et la consommation alimentaire » RESPONSABLE DU TRAITEMENT DES DONNEES Mme Kenza DRARENI – Doctorante responsable du projet Centre de Recherche de l'Institut Paul Bocuse 1, chemin de Calabert - 69130 ECULLY, France Tél : +33 4 72 18 54 66 REFERENTS ICO Dr Damien VANSTEENE - Oncologue Médical Mme Hélène LUSSON - Diététicienne Institut de

Cancérologie de l'Ouest (ICO) - Site de Saint Herblain Bd Jacques Monod - 44805 SAINT HERBLAIN

En vue d'analyser les résultats, dans le respect de l'objectif mentionné ci-dessus, les données à caractère personnel et médicales des patients participant à l'étude feront l'objet d'un traitement automatisé (fichier informatique) garantissant l'anonymat, conformément à la loi n°78-17 du 6 janvier 1978 modifiée relative à l'informatique, aux fichiers et à la liberté, et au Règlement Général sur la Protection des Données 2016/679 du 27 avril 2016. Les données seront conservées jusqu'à publication des résultats de la recherche ; puis archivées pendant une durée conforme à la réglementation.

Les publications qui en découleront présenteront toujours les données sous forme statistique, ne permettant pas l'identification.

Conformément à la Délibération n° 2018-155 du 3 mai 2018 portant homologation d'une méthodologie de référence relative aux traitements de données à caractère personnel mis en oeuvre dans le cadre des recherches n'impliquant pas la personne humaine, des études et évaluations dans le domaine de la santé (MR-004), l'ICO s'est engagée auprès de la Commission Nationale de l'Informatique et des Libertés à suivre cette méthodologie de référence.

Le traitement informatique des données de l'étude a été enregistré par le délégué à la protection des données de l'ICO sur le registre des traitement de données tenu à disposition de la CNIL sous le N°XXX.

Le protocole de l'étude a été soumis au Comité d'Ethique du CHU d'Angers.

4. Vos droits en tant que participant à cette recherche

Vous disposez des droits suivants sur les données vous concernant :

- droits d'accès aux données,
- droit de rectification des données erronées,
- droit d'effacement des données en cas de traitement illicite,
- droit de portabilité vous permettant d'obtenir les données que vous avez-vous-même fournies à l'établissement,
- droit de limitation du traitement des données notamment si celui-ci venait à être remis en cause.

Vous disposez également d'un droit d'opposition au traitement de vos données dans les conditions définies par le Règlement Général sur la Protection des Données 2016/679 du 27 avril 2016. Celui-ci empêche tout traitement ultérieur des données vous concernant. Cependant, si le traitement est nécessaire à l'exécution d'une mission d'intérêt public, le responsable de traitement ne pourra répondre favorablement à l'exercice de ce droit d'opposition.

Si malgré l'engagement de l'ICO à respecter vos droits et à protéger les données vous concernant, vous restez insatisfait, il vous est possible d'introduire une réclamation auprès de l'autorité de contrôle : la Commission nationale de l'informatique et des libertés (<https://www.cnil.fr/fr/notifier-une-violation-de-donnees-personnelles>).

Vous pouvez exprimer votre opposition à participer à cette étude auprès de la personne qui vous a remis cette lettre d'information. Vous pouvez exercer vos droits relatifs aux données personnelles vous concernant, à tout moment par courrier auprès du délégué à la protection des données de l'ICO (DPO), par téléphone 0241352701 ou par mail delegue.protection.donnees@ico.unicancer.fr

Note d'information remise le : I __ I __ I ____ I

à Mme/Mr : Né(e) le: I __ I __ I ____ I

Nom : Signature :

Appendix 9: Study 3 – Questionnaire for taste, smell and liking assessment



Questionnaire de satisfaction

PAUL
INSTITUT
BOCUSE

RECHERCHE
Science & Innovation

Date :

Initiales :.....

Heure :

Etes-vous : H F

Code Patient :

Quel est votre âge :.....

Etes-vous fumeur ? OUI NON

Type de cancer :.....

Cycle de chimiothérapie (n) :.....

Indiquer par un trait où vous vous situez sur l'échelle de perception :

Mon sens de l'odorat est :

Extrêmement mauvais

Extrêmement bon

Ma perception des goûts est :

Extrêmement mauvaise

Extrêmement bonne

Avez-vous faim ?

Je n'ai pas faim du tout

J'ai extrêmement faim

Etape 1 : Vous avez face à vous une coupelle contenant une crème d'aubergine étiquetée « réf ». Ce produit sera votre référence pour la suite de la dégustation.

Veillez déguster cette crème.

A quel point appréciez-vous ce produit ?

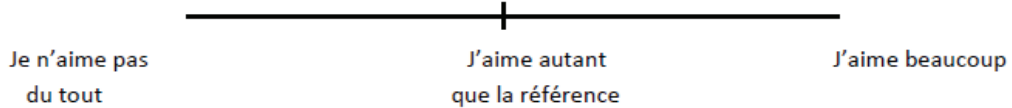
Je n'aime pas
du tout

J'aime beaucoup

Veillez boire un peu d'eau avant de passer à l'étape suivante

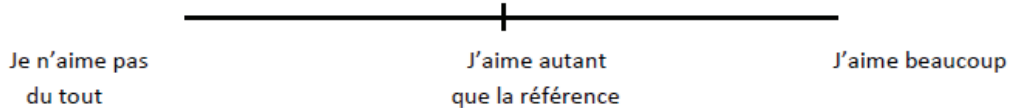
Etape 2 : Maintenant, vous avez face à vous 4 recettes différentes de crème d'aubergine.
Veuillez les déguster dans l'ordre ci-dessous

A. Dégustation du produit 221. A quel point appréciez-vous le produit 221 par rapport au produit de référence ?



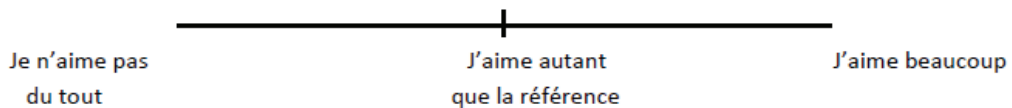
Veuillez boire un peu d'eau avant de passer à la dégustation suivante

B. Dégustation du produit 645. A quel point appréciez-vous le produit 645 par rapport au produit de référence ?



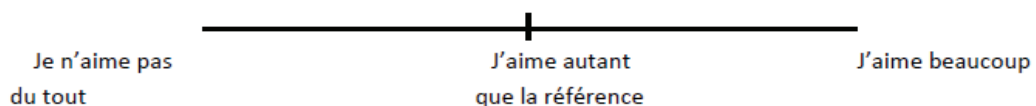
Veuillez boire un peu d'eau avant de passer à la dégustation suivante

C. Dégustation du produit 138. A quel point appréciez-vous ce produit 138 par rapport au produit de référence ?



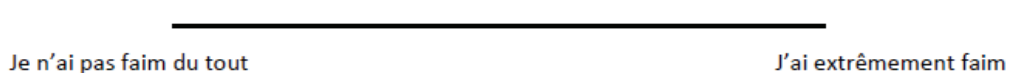
Veuillez boire un peu d'eau avant de passer à la dégustation suivante

D. Dégustation du produit 972. A quel point appréciez-vous ce produit 972 par rapport au produit de référence ?



Veuillez boire un peu d'eau avant de passer à la dégustation suivante

Avez-vous faim ?



Etape 3 : Vous maintenant consommez autant de crème d'aubergine que vous le souhaitez, accompagnée de toasts.

Merci de votre participation

Olfactory function in patients with different types of maxillo-facial traumata

Short running title: Olfaction and maxillo-facial traumata

Kenza DRARENI^{1,2}; Thomas HUMMEL¹, MD; Moustafa BENSAFI², PhD ; Charles-Arnaud SEREX^{3,4}, MD ; Marianne HUGENTOBLER⁴ ; Hergen FRIEDRICH⁵, MD ; François VORUZ^{3,4}, MD; Andrej TERZIC³, DMD, MD; Basile Nicolas LANDIS⁴, MD

1. Smell and Taste Clinic, Department of Otorhinolaryngology, University Hospital Dresden, Germany
2. Lyon Neuroscience Research Center, CNRS UMR 5292 and University Lyon I, France
3. Service of Oral and Maxillo-Facial Surgery, Department of Surgery, University of Geneva Medical School, Switzerland
4. Rhinology-Olfactology Unit, Department of Otorhinolaryngology – Head and Neck Surgery, Geneva University Hospitals (HUG), Geneva, Switzerland
5. Division of Pediatric Otolaryngology, University Children's Hospital, Zurich, Switzerland.

Corresponding Author: Kenza DRARENI, Smell & Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; phone +49-351-458-4189; fax +49-351-458-4326; kenza.drareni@institutpaulbocuse.com

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Abstract:

Objective: To investigate olfactory and gustatory functions in patients with traumata and associated fractures of the maxillo-facial region.

Methods: Olfactory and gustatory function was assessed psychophysically in 124 patients who had maxillo-facial traumata with an associated fracture. Olfaction was measured with the Sniffin' Sticks (TDI score) and gustation with the taste spray method. Patients self-rated olfactory and gustatory function on a visual analogical scale prior to testing. The different trauma types were those currently and clinically used for maxillo-facial trauma classification.

Results: Ten out of 124 patients were found to be anosmic (8%) whereas half of them were found in the group involving the skull base (Le Fort). The Le Fort fracture group had significantly lower olfactory capabilities compared to other fracture types (TDI score= 22.4 ± 10.7 ; $p=0.01$; possible range 1-48). The mean score of gustatory spray test was 3.82 ± 0.4 (possible range 0-4) without any group differences. Self-ratings of olfactory function showed a correlation with the measured scores ($r=0.61$, $p<.001$) across all groups. However, there was a variable proportion of discordant patients' olfactory self-evaluation.

Conclusion: The present data show the significant effect of the trauma and fracture type in the maxillo-facial region on the occurrence of anosmia. Maxillo-facial fractures involving the skull base such as Le Fort fractures are more prone to induce permanent smell loss, whereas the other fracture types (mandible, nose, orbit and zygomatic bone) are rarely associated with anosmia. This raises the question to which extent the maxillo-facial region may act as crumple zone in cases of head trauma.

Keywords: Smell, Anosmia, Taste, Trauma, Le-Fort, Maxillo-facial

Evidence level: 3

Introduction

Smell and taste impairments are among common neurological sequelae following head trauma [1-3]. Depending on the severity of the trauma and its localization, chemosensory impairments could be quantitative or qualitative, and of variable intensity. Quantitative modifications of smell and/or taste perception range from a slight decrease in odor/taste perception to total loss of olfactory and/or gustatory functions. Qualitative distortions of chemosensory perception are more complex but less frequent in patients with traumatic brain injury. They are described either as a distorted perception, or as a perception of smells or tastes (usually unpleasant) without any stimulation [4-5].

Due to different methodologies of assessment, and heterogeneity in terms of studied head trauma types, the reported frequency of posttraumatic olfactory and gustatory disorders varies considerably. It ranges from 0.4% to 38% for taste [6-8] and from 4% to 67% for smell dysfunction [1, 9-12]. One shortcoming of many studies investigating head trauma and chemosensory disorders is the mentioned heterogeneity of the included patients. Olfactory disorders are favored by trauma giving rise to shearing movements between the cribriform plate and the brain structures. This is the case for almost all kinds of neurosurgical trauma with brain contusion and “coup and contre-coup” movements. Besides chemosensory disorders and mainly olfactory loss these patients often also experience posttraumatic syndromes with behavioral changes, fatigue, sleep, attention and concentration problems.

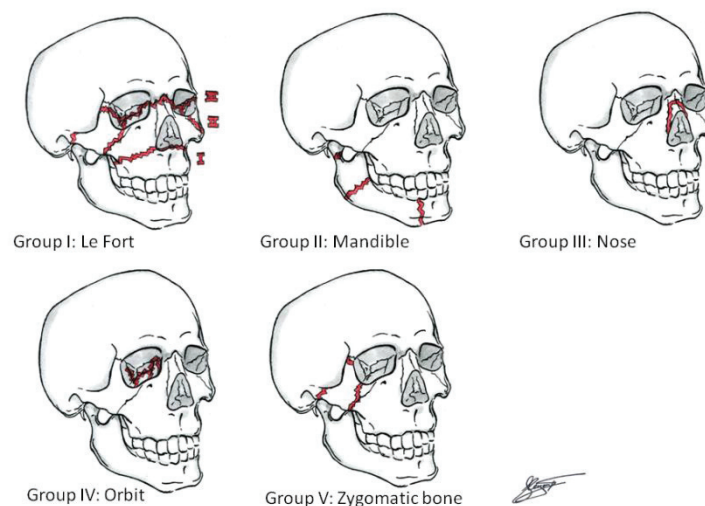


Figure 1. Used facial fracture classifications according to the localization of the fracture (red mark). Drawings done by one co-author Dr Hergen Friedrich (signature at the bottom)

In the present study we aimed to investigate whether trauma restricted to different parts of the maxillo-facial skeleton of the face are associated to different degrees of olfactory impairments. The rationale behind was twofold: It is speculated that patients with fractures of the face may absorb more energy from the trauma which is not presented to the brain. The maxillo-facial structures (nose, sinuses, mandible, etc.) would thus act as a kind of crumple zone preventing the brain to be damaged. Second, we wanted to investigate a well-defined group of trauma patients, rather than the usually reported posttraumatic patients that consist of a huge variety of trauma and injury types [3, 13-16]. Given the impact of sensory impairments on quality of life [17], it is of great importance to better define the typology of this consequence in order to provide better management for patients. Finally, in order to determine whether trauma type effects on olfaction are specific to this sensory modality or could be extended to another chemosensory function, we further examined gustatory function in the same patients.

Patients and Methods

Participants

Patients with maxillo-facial trauma that caused bone fractures were included into the study. They were admitted or presented themselves to Emergency Department of the University Hospital of Geneva and taken care by the maxillo-facial surgeon specialists. For quality of care reasons patients were offered an olfactory and gustatory examination together with the usual clinical workup in patients with maxillo-facial trauma and fractures. These exams usually comprise ENT and maxillo-facial examinations, radiological and photographic documentation as well as ophthalmological and neurosurgical workup for cases with orbital and intracranial involvement. The present study consisted of a retrospective data extraction for all patients where olfactory and gustatory examination has been done. The study was approved by the Institutional review board of the University of Geneva Hospitals (N° CE 13-161).

Inclusion criteria: only patients who had fractures related to the maxillo-facial trauma and who had done the entire olfactory testing were included. This testing was done whenever the patient was able and willing to perform it. For certain patients who had longer intensive care unit stays the testing was done with sometimes several weeks after the trauma. For patients who required emergency surgery due to their fractures, the testing was usually done after full postoperative recovery.

Exclusion criteria: (i) Trauma with fractures elsewhere than the maxillo-facial region (temporal bone, isolated skull fracture, etc), (ii) Maxillo-facial traumata without fractures, (iii) patients who had a positive history for preexisting olfactory dysfunction prior to the trauma.

Information about age of the trauma, type of fracture, fracture side and presence/absence of polyps were collected for patients who were eligible to be enrolled in the study (see Results section).

Five groups were defined according to the fracture type (*Figure 1*): (I) Le Fort type I-III (this group also included two isolated frontal sinus and four centro-facial fractures); (II) Mandible fractures; (III) Isolated nose fractures; (IV) Orbit fractures, and (V) Zygomatic bone (this group also included two isolated maxillary sinus fractures).

Output measurements

Olfactory (tested ortho- and retronasally) and gustatory functions were assessed using standardized, reliable and validated psychophysical tests detailed below. This was completed with a structured questionnaire to collect self-reported smell and taste perception of patients, as well as evaluation of nasal obstruction and rhinorrhea.

Psychophysical measurements

Orthonasal olfactory performance was assessed using the Sniffin' Sticks test battery that evaluates olfactory threshold, discrimination, and identification scores [18]. Odor threshold (OT) was determined for (the rose-like) phenyl ethyl alcohol (PEA) with 16 stepwise dilutions starting at a 4% solution (dilution ratio 1:2 in propylene glycol). OT was measured using the single-staircase technique based on a three-alternative forced-choice task (3AFC) (score range from 1 to 16). Odor discrimination (OD) was assessed over 16 trials. For each individual discrimination task three pens were presented, two containing the same odor and the third containing the target odor. As OT, a 3AFC task was used for OD. Odor identification (OI) was assessed using 16 common odors with lists of four verbal descriptors each in a multiple forced-choice format (three distractors and one item describing the target odor). The interval between odor presentations was 20–30 s. A total score (OT–OD–OI: TDI) was calculated: a score as ≥ 30.5 , <30.5 and ≤ 16.5 indicated respectively normosmia, hyposmia and functional anosmia (« functional anosmia » will be referred to as « anosmia » throughout the manuscript) [18].

Retro-nasal olfaction of patients was examined with a modified version of the “smell powder test”. This test comprised 10 powdered foods with different flavors that are placed on

the middle of the tongue while the patients keep the nose closed. Then, the patients open the nose and have to identify the flavor from a list of 4 verbal descriptors. Before each trial the mouth is rinsed with fresh water [19]. All powders had food related flavors, are edible and used in the food industry [20]. The scores range from 0-10.

Taste function was evaluated using the Taste Sprays. The “Taste Sprays” are a rapid screening test for the four basic tastes, applied to the oral cavity at supra-threshold concentrations. Subjects have to identify the taste from a list with 4 items (sweet, sour, salty, bitter). The total score ranges from 0 to 4.

Self-reported taste and smell perception

Participants reported self-perception of their smell and gustatory abilities using Visual Analogue Scales (VAS; length 10 cm) ranging from 0 “*no olfactory/gustatory function*” (left hand end) to 10 “*excellent olfactory function*” (right hand end). They also self-reported rhinorrhea and nasal obstruction using VAS ranging from 0 “*no rhinorrhea/ nasal obstruction*” to 10” *rhinorrhea/ nasal obstruction*”. Finally, two additional questions related to food and taste alterations since the trauma were also administered: (i) “did your perception of food change since the trauma, possible answers: yes/no), (ii) “do you have a different or permanently altered taste perception since the trauma like metallic, bitter, etc. taste?”.

Statistical analysis

The TDI scores of the five groups were compared using a Kruskal-Wallis test, followed by a Dunn-test with Bonferroni correction. The dependency between fracture types and olfactory status was tested with Pearson’s Chi-square test. Correlations between psychophysical olfactory and gustatory results and participants’ self-report were examined. For all calculations, a *p*-value <0.05 was considered statistically significant. All analyses were performed using the R software (R project for statistical computing: www.r-project.org).

Results

A total of 124 patients with maxillo-facial traumata were included for the analysis (72.5% men and 27.5% women). The mean age of the group was 49.3 ± 18.1 years; the period of time between the accident and test session was variable in each group, ranging from 76 days in the mandibular fracture group to 134 days in the zygomatic bone fracture group (table 1). The distribution in the five groups of fracture types was unbalanced: most participants (34%)

presented with a fracture of the orbit. Demographic data and classification of patients according to the fracture type are summarized in *table 1*.

Table 1. Demographic and clinical characteristics of participants

	% (n) Male (n) Female (n)	Age [years] (mean ± SD)	Time between trauma and chemosensory tests [days] (mean ± SD)
All participants	100% (124) M (90) F (34)	49.3 ± 18.1	104.22 ± 74.28
(I) Le fort	13% (16) M (15) F (1)	46.1 ± 14.1	125.5 ± 65.27
(II) Mandible	20% (25) M (18) F (7)	40.8 ± 11.2	76.84 ± 68.8
(III) Nose	14.5% (17) M (12) F (5)	51.4 ± 20.9	84.29 ± 49.57
(IV) Orbit	34% (42) M (28) F (14)	45.9 ± 19.5	103.21 ± 84.02
(V) Zygomatic bone	18.5% (24) M (17) F (7)	44.5 ± 19.5	134.41 ± 72.04

Orthonasal olfaction

OT (a), OD (b), OI (c), and TDI scores (d) of participants in each group are depicted in *Figure 2*. The mean TDI score of the four groups was 29.3 ± 7.7 . Overall, patients with Le Fort fractures had significantly lower olfactory capabilities compared to other fracture types, reflected by lower OT, OD and OI scores, and, hence, also a lower TDI score (all detailed statistics are mentioned in the legend of *Figure 2*). OT was significantly lower (i.e. decrease in odor sensitivity in our case) in patients with Le Fort and Zygomatic bone fracture compared to

mandibular bone fracture ($p < 0.001$). We also observed that patients with Le Fort fractures tended to have a lower OT score than patients with orbit fracture ($p = 0.058$), and patients with orbit fracture tend to have lower OT than patients with mandible fracture ($p = 0.069$). No significant difference was observed in OD score between fracture type groups ($p > .05$). Concerning OI score, Le Fort fracture group scored significantly lower compared to mandible fracture group ($p = 0.01$). The global TDI score was lower in the Le Fort fracture group compared to mandible group ($p = 0.01$). No other significant difference was observed between groups.

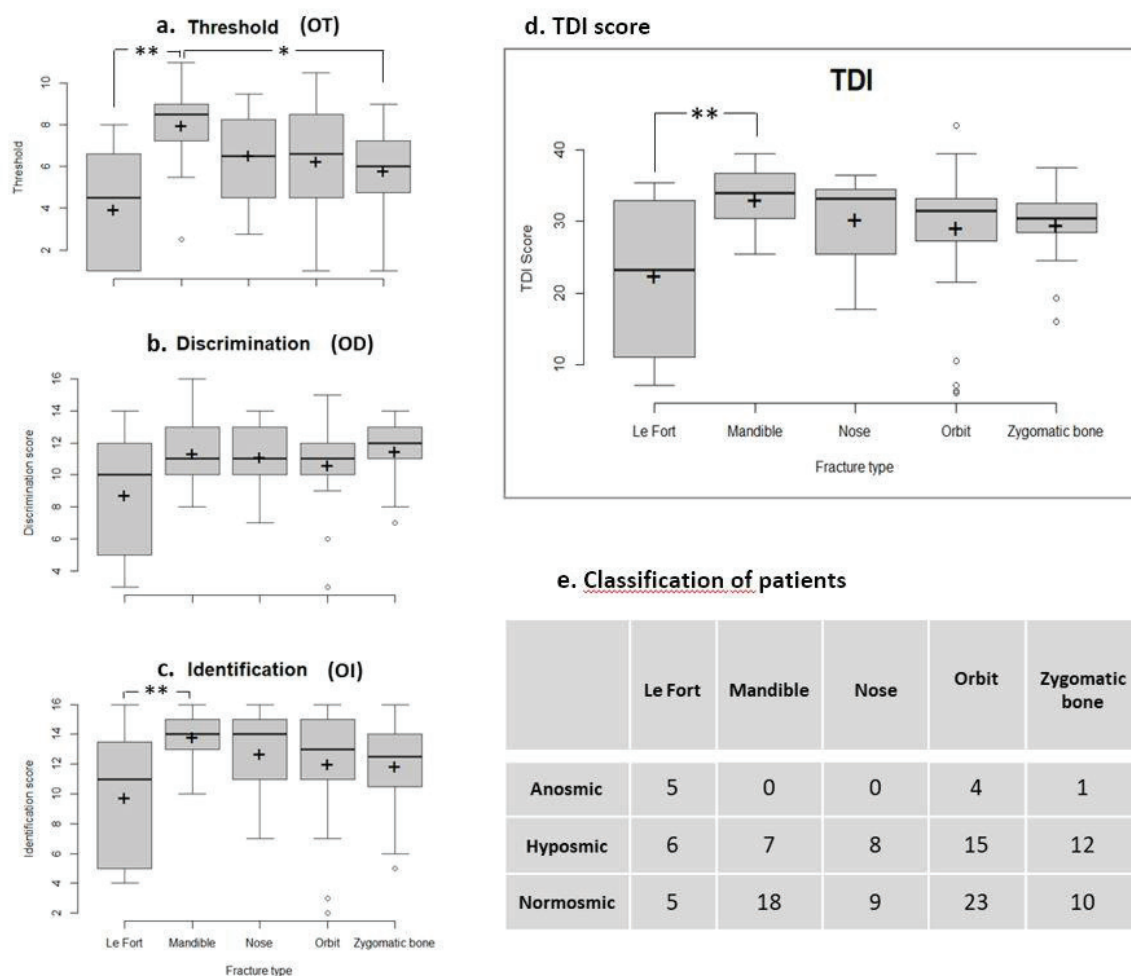


Figure 2. Threshold (a), Discrimination (b), Identification (c) and TDI score (d) of participants according to the fracture type. (+) refers to the mean values in each group. *: $p < 0.05$; **: $p < 0.01$. Mean comparison with Kruskal-Wallis test showed significant between group difference for threshold (Chi square = 24.6, $p < .001$, $df = 4$), identification score (Chi square = 11.8, $p = .001$, $df = 4$) and TDI score (Chi square = 14.6, $p = .005$, $df = 4$). Dunn-test (with Bonferroni correction) provided more details on the between group differences for each variable.

Retronasal olfaction

The results of retronasal olfactory function test are displayed in *table 2*. No significant difference between the 5 groups was found (Kruskal-Wallis chi-squared = 8.221, $p = 0.08$).

Gustation

The mean score of the gustatory spray test was 3.82 ± 0.4 across all participants, suggesting that the gustatory function of patients was not significantly altered by the maxillo-facial trauma (*table 2*). There was no difference in spray taste scores between the five groups ($p > .05$).

Table 2. Gustatory performances and self-reported nasal discomfort following the fracture type.

Fracture type	Taste spray score (<i>mean</i> ± <i>SD</i>)	Retronasal test score (<i>mean</i> ± <i>SD</i>)	Self-reported gustatory function (<i>mean</i> ± <i>SD</i>)	Self-reported nasal obstruction (<i>mean</i> ± <i>SD</i>)	Self-reported rhinorrhea (<i>mean</i> ± <i>SD</i>)
All types	3.82 ± 0.4	7.52 ± 1.95	7.7 ± 2.1	7.05 ± 2.55	2.49 ± 2.78
(I) Le Fort	3.56 ± 0.62	6.37 ± 2.86	7.18 ± 2.16	7.56 ± 2.58	2.50 ± 2.87
(II) Mandible	3.92 ± 0.27	8.36 ± 1.22	8.40 ± 1.50	7.16 ± 2.93	2.92 ± 3.13
(III) Nose	3.82 ± 0.39	7.43 ± 2.01	8.11 ± 1.57	6.70 ± 2.44	2.82 ± 2.96
(IV) Orbit	3.92 ± 0.26	7.47 ± 2.01	7.64 ± 2.27	7.30 ± 2.18	2.11 ± 2.66
(V) Zygomatic bone	3.72 ± 0.45	7.55 ± 1.9	7.33 ± 2.56	6.41 ± 2.85	2.45 ± 2.57
	$p > .05$	$p = .08$	$p > .05$	$p > .05$	$p > .05$

Means were compared with Kruskal-Wallis test and showed no between group differences

*pairwise comparison with Wilcoxon test showed no significant difference between the groups ($p > .05$).

Self-reported smell and taste abilities

Olfactory self-rating across the entire group was 6.88 (± 2.88). Patients in the Le Fort fracture group rated their olfactory abilities to be the lowest (3.75 ± 3.41), whereas patients with mandible

fracture indicated preserved olfactory abilities (8 ± 1.93) (all detailed statistics are mentioned in the legend of Figure 3). Nose, orbit, and zygomatic bone fracture groups also reported normal olfactory function (Figure 3).

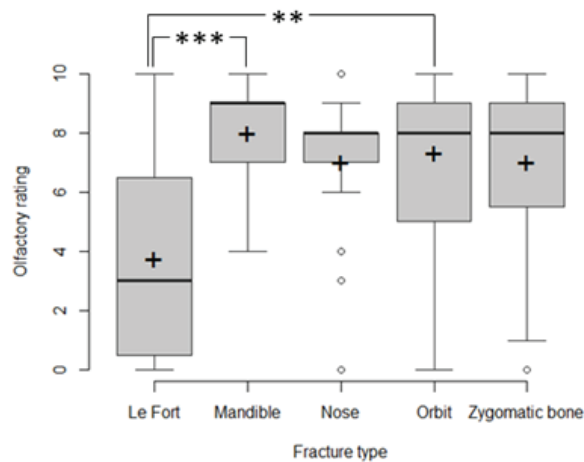


Figure 3. Self-reported olfactory abilities rated on VAS - scale. (+) refers to the mean values in each group. **: $p < 0.01$; ***: $p < 0.001$. Mean comparison with Kruskal-Wallis test showed significant between group difference in olfactory rating (Chi square = 17.9, $p = 0.001$, $df = 4$). Patients with Le Fort fractures rated their olfactory ability significantly lower than patients with mandible fracture (3.75 ± 3.41 vs. 8.0 ± 1.93 ; $p < .001$), and patients with orbit fracture (3.75 ± 3.41 vs. 7.3 ± 2.7 ; $p = 0.002$). No difference was found between other groups ($p > .05$).

Average gustatory self-ratings were 7.7 ± 2.1 . The subjective results are in line with the scores obtained with the spray taste, suggesting that the facial trauma had no major effect on participants' taste function. No difference was observed between the five groups for the ratings of gustatory abilities ($p > .05$).

Correlations between psychophysical tests and self-reports

Participants' TDI score was correlated with the self-ratings of their olfactory function ($r = 0.61$, $p < .001$) (Figure 4c). This correlation was strong in patients with zygomatic bone fracture ($r = 0.78$, $p < .001$) and almost non-existent ($r = 0.09$, $p = 0.64$) in patients with mandible fracture. Interestingly, 28 individuals with anosmia or hyposmia were discordant, and assigned a score greater than or equal to 7 when self-assessing their olfactory function on the VAS scale (1-10) (Figure 4a). As shown in Figure 4b, there was a variable proportion of discordant patients in each group (Le Fort: 13%, mandible: 20%, nose: 28%, orbit: 22%, zygomatic bone: 30%).

Rated gustatory function and measured taste scores did not correlate significantly ($r=0.14$, $p=0.12$), whereas self-ratings of olfaction and taste correlated significantly ($r=0.62$, $p<.001$)

Overall anosmia and hyposmia incidence

Out of the 124 included patients a total of ten (8%) were anosmic and 48 were hyposmic (38%). Half of the anosmia cases were recorded in the group of Le Fort fractures and another 4 cases in the orbit fracture group. The Le Fort fractures group not only had the highest percentage of anosmia (31%) but also the lowest percentage of patients with preserved, normal olfactory function (31%) amongst all trauma groups.

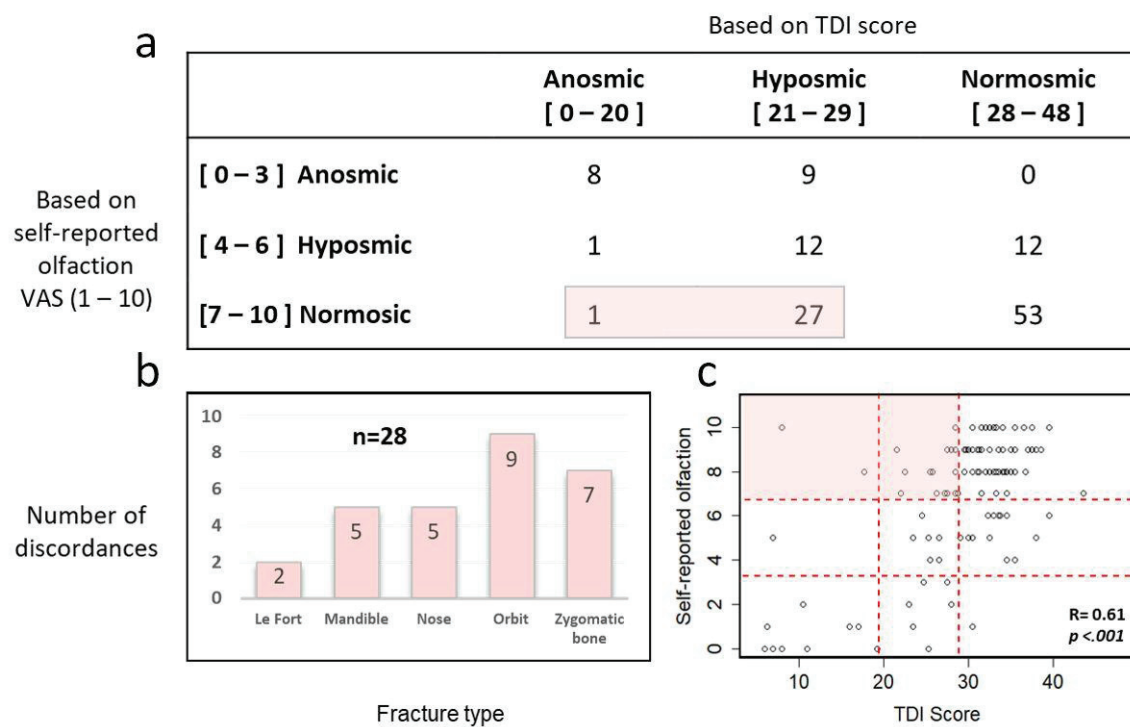


Figure 4. Correlation between TDI score and patients' self-rating of olfactory function ($r=0.61$, $p<.001$). **a**) The number of patients classified as anosmic, hyposmic or normosmic according to the TDI score (columns) and the corresponding self-rating the patients made about their olfactory ability (lines); ratings between 0 and 3 were considered to reflect self-reported anosmia, 4 to 6 hyposmia and above or equal 7 normosmia. The box represents the most discordant self-ratings and is detailed according to their trauma type in panel **b**) showing that the most olfactory affected group (Le Fort) tended to rate olfactory function more accurately than the other groups. **c**) Correlation between measured olfactory function and rated olfactory function. Overall self-rating seems accurate with an anchor effect for most anosmic patients.

Self-reported nasal obstruction, rhinorrhea and dysgeusia/food perceptual changes

Within the five groups the incidence and evaluation of nasal obstruction, rhinorrhea (table 2) and food perceptual changes did not differ (table 3). Seventeen patients reported an equivalent of dysgeusia with a distorted sense of taste. However, the distribution amongst the trauma groups was not significantly different (table 3).

Table 3. Percentage of patients with food perceptual changes in different fracture types.

Fracture type	Abnormal taste in mouth (%)	Food seems bland (%)	Food tastes different (%)	Food tastes bad (%)
All types	13.7	20	25	0.8
(I) Le Fort	25	37.5	37.5	0
(II) Mandible	20	8	12	0
(III) Nose	11.7	29.5	29.5	0
(IV) Orbit	9.5	16.7	23.8	2.4
(V) Zygomatic bone	8.3	20	29	0
	p>.05	p>.05	p>.05	p>.05

Proportions were compared with Fisher's exact test and showed no between group significant differences.

Discussion

This study examined a very homogenous and well defined type of head trauma: pure maxillo-facial trauma with an associated fracture of the face. The main results of the present study are a) an overall anosmia rate of 8 % in maxillo facial traumata, b) a significant association between fracture type and anosmia occurrence and c) the frequent mismatch between self awareness and measured olfactory status in many patients.

Taken all together the group of patients with maxillo facial traumata had rates of anosmia (8%) and hyposmia (39%) that were only slightly higher than what had been previously reported in large epidemiological studies [21-22]. In light of a rather young mean age of 49 years of the patients, this however indicates that maxillo-facial trauma has clear effect of olfactory function with consecutive impairment. On the other hand these data also suggest that maxillo-facial traumata, in contrast to neurosurgical head trauma [14, 23-24] probably less often lead to severely impaired olfactory deficits [10]. Although this study does not support that with clear data, this finding may open some speculation to which extent the facial skeleton and its

classical breaking points may act as crumple zone to prevent the brain from absorbing too much traumatic energy.

However, one thing our data show is that the type of fracture within the maxillo-facial region is clearly relevant and associated to a higher or almost absent occurrence of olfactory disorders. Fractures with a very elevated incidence of anosmia were those associated to an involvement of the skull base and frontal sinus (31%) followed by orbital fractures to a much lower degree (9%). In contrast fractures of the nasal bones, mandible or zygomatic bone alone, virtually never showed total olfactory loss. These data fill a gap of knowledge about how likely anosmia occurs after a given fracture of the face. We have the feeling that this information might be of interest in medico-legal considerations. Still speculation, but these data also tend to support that trauma energy leading to fractures of bones more distal to the skull base or frontal skull may protect brain and especially olfactory parenchyma from harm. The anosmia rates for skull base /frontal sinus fractures are similar to those reported for neurosurgical traumata whereas the remaining fractures showed extremely little olfactory impairment [23]. A shortcoming of the present study is its cross-sectional character and uncertainty regarding patients recovering olfactory function on the long term. The patients were tested after a mean period of 3 months after the trauma and it is expected that pure congestion-related anosmia would have resolved by then [25]. However, although recovery rates after traumatic brain injury is low [26], it cannot totally be ruled out that some patients may improve gradually olfactory function [27]. This issue is currently investigated by a long term follow up of the concerned patients with brain imaging if necessary.

The literature shows only three studies that also exclusively investigated maxillo-facial traumata, [8, 28-29] that we would like to comment and compare to the present data. Whereas Renzi et al. [28] and Van Damme et al. [8] also investigated on all different kinds of maxillo-facial traumata, Hwang et al. [29], in a systematic review concentrated only on nasal fractures. The first two authors confirm our findings that Le Fort and nasofrontal fractures are clearly more often associated to olfactory impairment than other localizations. Hwang et al. [29] reports almost 30 % of patients with olfactory impairments after simple nasal fracture, which clearly contrasts with our findings. One explanation could be that all three studies simply asked about self-assessed olfactory performance rather than measuring smell function. It is well known, acknowledged and repeatedly shown that self-rated olfactory function is unreliable and often different from the measured olfactory function [30-32]. One reason is that humans confound

olfactory function and nasal congestion [30]. Consequently, any nasal condition (such as nasal fracture) inevitably increases the amount of people that state having an olfactory disturbance.

This brings us to the third main finding of our investigation: The mismatch between self-rated olfactory impairment and measured olfactory function. As stated before, self assessment is not reliable, a finding that goes in line with the fact that almost a fourth of severely affected patients did not consider themselves as hypo- or anosmic (Figure 4). Although a general awareness for impaired olfactory function was found with a positive and significant correlation between ratings and TDI scores, the self ratings remain not very precise. These results highly suggest that olfactory function should be measured instead of simply investigated by asking.

Besides olfactory function, taste was also investigated in our sample, without any major effect of the maxillo-facial trauma on gustatory function. A shortcoming for the taste testing was the rather screening character the spray method had, compared to more thorough taste testing such as taste strips [33]. Thus, it can only be stated, that rough taste screening seems to be normal in patients with maxillo facial fractures.

Besides the mentioned shortcomings of the study we would also like to underline the new elements for the literature and strengths the study has. First, it is one of the few studies with very well selected and thus homogenous sample of traumata. Second, its sample size with over 120 included patients is rather big and finally, it seems to be the first study to measure psychophysically olfactory and gustatory function in maxillo facial traumata.

In conclusion, in a group of 124 patients with facial trauma, olfactory impairment was prominent and found in almost half of the patients. Le Fort fractures are likely to have the most significant impact on patients' both objective and subjective olfactory perception whereas anosmia is rare in fractures of the zygomatic bone, the orbit, the nose, or the mandibula zones. Discrepancies between self-reports and psychophysical olfactory measurement were found in approximately one quarter of the cases, which underlines the importance of the two approaches in olfactory assessment. Gustatory function for its part is less disturbed by the facial trauma, and usually associated to olfactory impairments.

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Thesis Valorization

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Goût et Cancer : satisfaire les sens pour maintenir le plaisir de manger pendant la chimiothérapie

Le maintien du plaisir à s'alimenter durant un traitement par chimiothérapie est un enjeu majeur pour les patients, leurs familles et les professionnels de la restauration en hôpital afin de lutter contre la dénutrition. Or, les altérations sensorielles fréquemment observées chez les patients et exprimées différemment d'un patient à l'autre peuvent interférer avec le goût des aliments, impactant négativement le plaisir résultant de leur consommation.

L'objectif de ce travail est de contribuer à définir un modèle exhaustif de l'effet de la chimiothérapie pendant le cancer sur les capacités olfactives et gustatives des patients, et des conséquences que cela peut avoir sur leur comportement alimentaire.

Une première partie porte sur la compréhension de la variabilité des modifications sensorielles et de leurs conséquences sur le comportement alimentaire des patients. Nos résultats ont conclu à l'existence de divers profils sensoriels chez les patients sous chimiothérapie : les patients ne présentant pas d'altérations sensorielles, les patients présentant une hyposensibilité, et les patients présentant une hypersensibilité aux stimulations olfactives/gustatives. Les patients ayant des altérations des capacités olfactives/gustatives ont également montré des modifications du comportement alimentaire.

D'une part, la classification des patients sur la base de leurs capacités sensorielles auto-déclarées a mis en évidence l'impact négatif de l'hyposensibilité aux stimulations olfactives et gustatives sur la perception des aliments. D'autre part, une classification basée sur les capacités olfactives évaluées par des tests psychophysiques a montré une modification des habitudes de consommation chez les patients atteints d'hyposmie. Les deux approches ont conclu à une tendance générale à la baisse des capacités perceptives chez les patients atteints de cancer et traités par chimiothérapie. Une seconde partie plus opérationnelle a permis de tester l'enrichissement sensoriel comme stratégie de palliation des déficits sensoriels. Les résultats suggèrent qu'un enrichissement en saveur ou en arôme augmente l'appréciation de l'aliment pour le groupe de patients ayant reporté une baisse de la sensibilité olfactive/gustative, ainsi les patients n'ayant déclaré avoir de déficits sensoriels mais pas dans le groupe de sujets contrôles. Ces travaux mettent en évidence la diversité interindividuelle existante entre les patients et confirment l'implication des altérations olfactives/gustatives dans la modification du comportement alimentaire.

Nos résultats soulignent l'importance d'une prise en charge nutritionnelle personnalisée des patients selon leur profil d'altérations sensorielles.

Mots clés : Cancer, Chimiothérapie, Odorat, Goût, Comportement alimentaire, plaisir alimentaire

Taste and Cancer : satisfy the senses to maintain food enjoyment during chemotherapy

Maintaining the pleasure of eating during a chemotherapy treatment is a major challenge for patients, their families and hospital catering professionals to avoid malnutrition. However, the sensory alterations frequently observed in patients and expressed differently from one patient to another can interfere with the taste of food and reduce the pleasure resulting from food consumption.

The aim of this work is to contribute to define a model of the effect of chemotherapy during cancer on olfactory and gustatory abilities of patients, and the consequences that this may have on their eating behavior.

The first part of this work focuses on understanding the variability of sensory changes and their consequences on patients' eating behavior. Our results highlighted three main sensory profiles : patients with no sensory impairment, patients with hyposensitivity, and patients with hypersensitivity to olfactory / gustatory stimuli. Patients with impaired olfactory / gustatory abilities expressed also changes in their food behavior. The classification of patients on the basis of their self-reported sensory abilities highlighted the negative impact of hyposensitivity on food taste perception. The classification based on psychophysical assessment of olfactory abilities showed a change in consumption habits in patients with hyposmia. Both approaches found a general downward trend in perceptual abilities of cancer patients treated with chemotherapy. In the second part of this work we examined the effect of food sensory enhancement as a coping strategy to sensory alterations. The results suggest that taste or aroma enhancement increases food liking in patients with decreased olfactory / taste sensitivity, and patients who did not report taste and smell deficits but has no effect on the hedonic rating of food in the group of control subjects. This work highlights the interindividual diversity existing between patients and confirms the involvement of olfactory / taste alterations in patients food behavior modification.

Our results stresses the importance of personalized nutritional management of patients considering their sensory alteration profile.

Key words : Cancer, Chemotherapy, Smell, Taste, Food behavior, Food enjoyment