THESE de DOCTORAT EN COTUTELLE DE L'UNIVERSITE CLAUDE BERNARD LYON 1 ET DE L'UNIVERSITE DE COPENHAGUE

Ecole Doctorale N° 205
Ecole Doctorale Interdisciplinaire Sciences Santé

Discipline : Santé Publique

Soutenue publiquement/à huis clos le 16/01/2024, par :
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Oral Somatosensory Perception of Cancer Patients:
Variability and Influence on Eating Experience

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Preface

This doctoral thesis is submitted in fulfilment of the requirements of the PhD degree at Interdisciplinary Doctoral School Health Sciences (EDISS), University Claude Bernard Lyon 1 with a double degree programme in collaboration with the Department of Food Science, Faculty of Science, University of Copenhagen. Most of the work was conducted in Institut Lyfe (formerly known as Institut Paul Bocuse) Research Center following the CIFRE agreement. The work was funded by the Association Nationale de la Recherche et de la Technologie (ANRT), Danone Nutricia Research, and La Ligue contre le Cancer. The overall theme of this doctoral thesis is understanding the oral somatosensory perception of cancer patients and how it influences their eating experience. The thesis is structured based on articles and the key messages are presented at the end of Chapters 3 to 8 to facilitate chapter transition.

"Life teaches us through our mistakes.

When you make a mistake,

simply ask yourself what you were meant to learn from it.

When we accept such lessons with humility and gratitude,

we grow that much more."

- ***Haemin Sunim***

Abstract (EN)

Malnutrition is common among cancer patients, particularly those with head and neck cancer (HNC), attributed to changes in their food perception namely taste and smell. Food perception is not only limited to taste and smell but also somatosensation (texture, temperature, and chemesthetic sensations such as spiciness of chilli), which very limited studies have investigated. We aimed to investigate the somatosensory perception of cancer patients and its influence on their eating behavior.

Study 1 compared HNC patients to healthy controls found that HNC patients had lower salivary function and reduced sensitivity to food texture, temperature, and chemesthetic sensations. Subjective measurements showed that sensory alterations and oral symptoms were associated with decreased food preference and difficulties in eating. Study 2 extended the investigation on the subjective perception of various cancer patients. It revealed similar findings that sensory alterations and oral symptoms predicted sensory-related food preferences and eating behavior. Study 3 focused on designing food concepts adapted to the perception and preference of cancer patients.

Overall, this thesis provided evidence that somatosensory alterations and oral symptoms are experienced by cancer patients, which can influence their food preferences and eating behavior. It highlights the importance of considering not only taste and smell but also somatosensory and oral comfort when designing food solutions for cancer patients.

Keywords: Oral somatosensory; cancer; food perception; food preference; eating behaviour; nutrition.

Résumé (FR)

La malnutrition est fréquente chez les patients atteints de cancer, en particulier ceux qui souffrent d'un cancer des voies aérodigestives supérieures (ORL), en raison de changements dans leur perception des aliments, le goût et l'odorat. La perception des aliments ne se limite pas au goût et à l'odorat, mais aussi à la somatosensation (texture, température, et sensations chemesthétiques), qui n'a fait l'objet que de très peu d'études. Nous avons étudié la perception somatosensorielle des patients atteints de cancer et son influence sur leur comportement alimentaire.

L'étude 1 a révélé que les patients atteints de cancer ORL avaient une fonction salivaire plus faible et une sensibilité réduite à la texture, à la température et aux sensations chemesthétiques. Des mesures subjectives ont montré que les altérations sensorielles et les symptômes bucco-dentaires étaient associés à une diminution des préférences et à des difficultés à s'alimenter. L'étude 2 s'est intéressé à la perception subjective de divers patients atteints de cancer. Elle a révélé des résultats similaires : les altérations sensorielles et les symptômes bucco-dentaires permettaient de prédire les préférences et le comportement alimentaire. L'étude 3 s'est concentrée sur la conception d'aliments adaptés à la perception des patients.

Cette thèse a démontré que les patients atteints de cancer subissent des altérations somatosensorielles et des symptômes bucco-dentaires qui peuvent influencer leurs préférences et leur comportement alimentaires. Elle souligne l'importance de prendre en compte non seulement le goût et l'odeur, mais aussi le somatosensoriel et confort oral lors de la conception de solutions alimentaires pour les patients atteints de cancer.

Mots-clés : Somatosensoriel oral ; cancer ; perception alimentaire ; préférence alimentaire ; comportement alimentaire ; nutrition.

Extended summary (EN)

Malnutrition is prevalent among cancer patients, especially in cancer sites related to food ingestion such as head and neck cancer (HNC). Among HNC patients, 74% were estimated to be malnourished. Malnutrition is a multifactorial condition, however, in this project, we focused on their eating experience. Cancer patients reported changes in their food perception due to sensory alteration. Numerous studies have documented alterations in smell and taste perception. However, food perception is not only limited to taste and smell but also somatosensation, which very limited studies have investigated. Somatosensation comprises perception towards texture, temperature, and chemesthetic sensations (e.g. spiciness of chilli) processed by the trigeminal system. Therefore, this project aims to investigate the somatosensory perception of cancer patients and their influence on food behaviour.

A cross-sectional study (Study 1) was conducted to compare HNC patients (n=30) with healthy controls (n=30). The objective measurements carried out in this study encompassed salivary function, point-pressure tactile sensitivity, whole-mouth chemesthetic stimulation, food texture discrimination, and temperature discrimination. The subjective measurements were collected through self-reported questionnaires. The questionnaires cover aspects of food perception, oral symptoms, food preference, and eating behaviour.

The findings from Study 1 can be divided into two main parts: objective measurements and subjective measurements. The somatosensory perception of HNC patients differed from control in several aspects. First, HNC patients showed lower textural sensitivity compared to control in terms of roughness ($p = 0.003$) and firmness ($p = 0.003$) but not on thickness ($p=0.587$) perception. Chemesthetic sensitivity was also significantly lower in HNC patients compared to the control for the medium and high concentrations of both menthol and capsaicin solutions. Patients were also less sensitive in terms of thermal sensitivity ($p = 0.038$). For tactile sensitivity, no significant differences were observed between the two groups although there was a tendency of lower sensitivity in the HNC group. The salivary function of HNC patients was significantly lower compared to the control ($p= 0.001$).

For the subjective measurements, hierarchical clustering analysis was performed to categorise patients based on their perceived sensory alteration which resulted in two distinct profiles of patients: no alteration (n=14) vs alteration (n=16) group. The alteration group displayed a reduced preference for various sensory modalities, particularly in the somatosensory domain. More patients in the alteration group agreed to negatively connotated eating behaviour statements (e.g. having food aversion, eating smaller portions). Furthermore, most patients reported experiencing several oral symptoms, of which related to salivary dysfunction. These symptoms were found to be correlated with their sensory preferences and eating behaviour. Patients who experience sensory alterations and oral symptoms are also more likely to experience greater difficulties in eating.

The investigation of the subjective oral somatosensory perception was extended to not only include HNC patients but also various other cancer populations. An anonymous online survey (Study 2) was distributed across France, Denmark, and the United Kingdom targeting all types of cancer patients (n=100). The survey included the same sets of questionnaires utilised in Study 1. More than 30% of cancer patients experienced changes in their somatosensory perception. This was also linked to changes in their food preferences. Hierarchical clustering identified three different clusters of patients based on their perception, the no alteration group (n=48) and the alteration group, with subclusters of generally increased perception (n=44) and generally decreased perception (n=8). It was demonstrated that sensory alterations contributed to changes in sensory-related food preferences. In addition, oral symptoms also contributed to these changes, which altogether impacted their eating habits.

The findings obtained from the two studies were integrated to create direction for Study 3 which aims to design food adapted to the food perception and preference of cancer patients. Six different food concepts were developed in collaboration with the culinary chefs. Following this, the food concepts were tasted and evaluated in a focus group discussion with cancer patients (n=4); two concepts were approved. The hedonic acceptance of the approved food concepts will be tested in a consumer test with cancer patients and the conception of the study design is described.

In conclusion, this doctoral thesis demonstrated evidence that somatosensory alterations and oral discomfort were experienced by HNC patients. These could influence their food preference and eating behaviour. In addition, it was indicated that these phenomena are not exclusive to HNC patients but were also experienced by patients across various cancer types. The studies provided some guidelines on food adjustments that are needed to adapt to the needs of cancer patients. Tailored food solutions should not only consider the taste and smell aspects but also the somatosensory and oral comfort.

Keywords: Oral somatosensory; cancer; food perception; food preference; eating behaviour; nutrition.

Résumé substantiel

La malnutrition est prévalente chez les patients atteints de cancer, en particulier pour les tumeurs localisées sur les sites d'ingestion d'aliments, comme le cancer de voies aérodigestives supérieures (ORL). Parmi les patients atteints d'un cancer ORL, on estime que 74% souffrent de malnutrition. La malnutrition est d'origine multifactorielle mais, dans ce projet, nous avons mis l'accent sur l'expérience alimentaire. Les patients atteints de cancer ont signalé des changements dans leur perception des aliments, comprenant une altération sensorielle. De nombreuses études ont mis en évidence des altérations de la perception de l'odorat et du goût. Cependant, la perception de la nourriture ne se limite pas au goût et à l'odorat, mais aussi à la somatosensation, qui n'a fait l'objet que de très peu d'études. La somatosensation comprend la perception de la texture, de la température et des sensations chemesthétiques (par exemple, le piquant du chili, la rafraichissant de la menthe) traitées par le système trigéminal. L'objectif de ce projet est donc d'étudier la perception somatosensorielle des patients atteints de cancer et son influence sur le comportement alimentaire.

Une étude transversale (étude 1) a été menée pour comparer des patients atteints de cancer ORL (n=30) à des témoins sains appariés en termes de sexe et d'âge (n=30). Les mesures objectives effectuées dans le cadre de cette étude comprenaient la fonction salivaire, la sensibilité tactile à la pression ponctuelle, la stimulation chemesthétique de la bouche entière, la discrimination de la texture des aliments et la discrimination de la température. Les mesures subjectives ont été recueillies à l'aide de questionnaire auto-déclaré. Les questionnaires portent sur la perception des aliments, les symptômes bucco-dentaires, les préférences alimentaires et le comportement alimentaire.

Les résultats de l'étude 1 peuvent être divisés en deux parties principales : les mesures objectives et les mesures subjectives. La perception somatosensorielle des patients atteints de cancer ORL diffère de celle des témoins à plusieurs égards. Tout d'abord, les patients atteints de cancer ORL ont montré une sensibilité texturale plus faible que les témoins : rugosité ($p = 0{,}003$) et fermeté ($p = 0{,}003$), consistance ($p = 0{,}587$). La sensibilité chemesthétique était également plus faible chez les patients atteints de cancer d'ORL que chez les témoins pour les solutions de menthol et de capsaïcine. Les patients étaient moins sensibles en termes de sensibilité thermique ($p = 0{,}038$). Pour la sensibilité tactile, aucune différence significative n'a été observée entre les deux groupes, bien qu'il y ait eu une tendance à une sensibilité plus faible dans le groupe de cancer ORL. La fonction salivaire des patients atteint de cancer ORL était significativement plus faible que celle du groupe témoin ($p = 0{,}001$).

Pour les mesures subjectives, une classification hiérarchique a été réalisée pour classer les patients en fonction de leur profil sensoriel, ce qui a permis de dégager deux profils distincts de patients : le groupe sans altération (n=14) et le groupe avec altération (n=16). Le groupe avec altération a montré une préférence réduite pour diverses modalités sensorielles, en particulier dans le domaine somatosensoriel. En ce qui concerne le comportement alimentaire, davantage de patients du groupe « avec altération » ont accepté les affirmations à connotation négative (par exemple, aversion pour certains aliments, manger de plus petites portions). En outre, la plupart des patients ont déclaré présenter plusieurs symptômes bucco-dentaires, dont certains étaient liés à un dysfonctionnement salivaire. Ces symptômes se sont révélés être en corrélation avec leurs préférences sensorielles et leurs habitudes alimentaires. Les patients qui présentent des altérations sensorielles et des symptômes bucco-dentaires sont également plus susceptibles d'éprouver de plus grandes difficultés à s'alimenter.

L'étude de la perception somatosensorielle orale subjective a été étendue non seulement aux patients atteints de cancer du sein, mais aussi à d'autres populations cancéreuses. Une enquête anonyme en ligne (étude 2) a été distribuée en France, au Danemark et au Royaume-Uni, ciblant tous les types de patients atteints de cancer (n=100). L'enquête comprenait les mêmes séries de questionnaires que ceux utilisés dans l'étude 1. Plus de 30 % des patients atteints de cancer ont ressenti des changements dans leur perception somatosensorielle. Ces changements étaient également liés à des modifications de leurs préférences alimentaires. Le La classification hiérarchique a permis d'identifier trois groupes différents de patients en fonction de leur perception sensorielle : le groupe sans altération (n=48) et le groupe avec altération, avec des sous-groupes de perception généralement accrue (n=44) et de perception généralement diminuée (n=8). Il a été démontré que les altérations sensorielles contribuaient à modifier les préférences alimentaires liées à la perception sensorielle. Par ailleurs, les symptômes bucco-dentaires ont également contribué à ces changements, ce qui a eu un impact sur les habitudes alimentaires.

Les résultats des deux études ont été intégrés pour orienter l'étude 3, qui vise à concevoir des aliments adaptés à la perception et aux préférences alimentaires des patients atteints de cancer. 6 concepts alimentaires différents ont été développés en collaboration avec les chefs culinaires. Ensuite, les concepts alimentaires ont été dégustés et évalués dans le cadre d'une discussion de groupe avec des patients atteints de cancer (n=4) ; deux concepts ont été approuvés. L'acceptation hédonique des concepts approuvés sera testée dans le cadre d'un test de consommation avec des patients atteints de cancer et la conception de l'étude est décrite.

En conclusion, cette thèse de doctorat a démontré que les patients atteints de cancer de la tête et du cou ressentaient des altérations somatosensorielles et une gêne buccale. Ces phénomènes peuvent influencer leur comportement alimentaire. De plus, il a été indiqué que ces phénomènes n'étaient pas l'apanage des patients atteints d'ORL, mais qu'ils étaient également ressentis par des patients atteints de divers types de cancer. Les études ont fourni quelques indications sur les ajustements alimentaires nécessaires pour s'adapter aux besoins des patients atteints de cancer. Les solutions alimentaires personnalisées ne doivent pas seulement prendre en compte les aspects gustatifs et olfactifs, mais aussi le confort somatosensoriel et oral.

Mots-clés : Somatosensoriel oral ; cancer ; perception alimentaire ; préférence alimentaire ; comportement alimentaire ; nutrition.

Resumé (DA)

Underernæring er et udbredt problem blandt kræftpatienter, især på kræftområder, der er relateret til fødeindtagelse, såsom hoved-halskræft. Blandt hoved-halskræft-patienter blev 74 % anslået til at være underernærede. Underernæring er en multifaktoriel tilstand, men i dette projekt lagde vi vægt på deres spiseoplevelse. Kræftpatienter rapporterede om ændringer i deres madopfattelse, og undersøgelser har vist, at nogle af bivirkningerne ved de forskellige kræftbehandlinger omfatter sensoriske ændringer. Det har negative konsekvenser for spiseadfærden og den generelle livskvalitet. Ændrede sanseopfattelser er forbundet med nedsat spiselyst, appetitløshed og ændringer i madvalg. Talrige undersøgelser har dokumenteret ændringer i lugte- og smagsopfattelsen. Sanseopfattelse er dog ikke kun begrænset til smag og lugt, men også somatosensation, som meget begrænsede studier har undersøgt. Somatosensation omfatter opfattelsen af tekstur, temperatur og kemestesi fornemmelser (f.eks. chiliens skarphed, pebermyntens kølende fornemmelse), som behandles af trigeminussystemet. Derfor har dette projekt til formål at undersøge kræftpatienters somatosensoriske perception og deres indflydelse på madadfærd.

Et tværsnitsstudie (Studie 1) blev udført for at sammenligne hoved-halskræft - patienter (n=30) med raske kontrolpersoner, der matchede med hensyn til køn og alder (n=30). De objektive målinger, der blev udført i denne undersøgelse, omfattede spytfunktion, taktil følsomhed ved punkttryk, kemestesi stimulering af hele munden, diskrimination af madtekstur og temperaturdiskrimination. De subjektive målinger blev indsamlet via spørgeskemaer, der blev udviklet specifikt til undersøgelsen og tilpasset fra forskellige eksisterende spørgeskemaer. Spørgeskemaerne var opdelt i to hoveddele: 1) sensorisk perception og orale symptomer; 2) madadfærd, herunder sensorisk præference, madforbrug og smag af mad.

Resultaterne fra Studie 1 kan opdeles i to hoveddele: objektive målinger og subjektive målinger. Den somatosensoriske perception hos hoved-halskræft-patienter adskilte sig fra kontrolgruppen på flere områder. For det første udviste hoved-halskræft-patienter lavere teksturfølsomhed sammenlignet med kontrolgruppen med hensyn til ruhed ($p = 0{,}003$) og fasthed ($p = 0{,}003$), men ikke med hensyn til tykkelsesopfattelse ($p = 0{,}587$). Kemestesi sensitivitet var også lavere hos hoved-halskræft-patienter sammenlignet med kontrolgruppen for både mentol- og capsaicinopløsninger, men kun på suprathreshold-niveau. Patienterne var mindre følsomme med hensyn til termisk følsomhed ($p = 0{,}038$). For taktil sensitivitet blev der ikke observeret nogen signifikante forskelle mellem de to grupper, selvom der var en tendens

til lavere sensitivitet i hoved-halskræft-gruppen. Spytfunktionen hos hoved-halskræft -patienter var signifikant lavere sammenlignet med kontrolgruppen (p = 0,001), især for de kvantitative parametre for spytfunktioner, herunder visuelt hydreringsniveau, spytkonsistens og stimuleret spytflow.

For de subjektive målinger blev der udført en hierarkisk clusteranalyse for at kategorisere patienterne baseret på deres sensoriske profil, hvilket resulterede i to forskellige profiler af patienter: ingen ændring (n=14) vs. ændring (n=16). Ændringsgruppen viste en reduceret præference for forskellige sensoriske modaliteter, især i det somatosensoriske domæne. Flere patienter i ændringsgruppenvar enige i negativt konnoterede udsagn om spiseadfærd (f.eks. at have madaversion, spise mindre portioner). Desuden rapporterede de fleste patienter, at de oplevede flere orale symptomer, hvoraf nogle var relateret til spytdysfunktion. Disse symptomer viste sig at være korreleret med deres sensoriske præferencer og spiseadfærd. Patienter, der oplever sensoriske ændringer og orale symptomer, er også mere tilbøjelige til at opleve større vanskeligheder med at spise.

Undersøgelsen af den subjektive orale somatosensoriske perception blev udvidet til ikke kun at omfatte hoved-halskræft-patienter, men også forskellige andre kræftpopulationer. En anonym online-undersøgelse (Studie 2) blev distribueret i Frankrig, Danmark og Storbritannien og var målrettet alle typer kræftpatienter (n=100). Undersøgelsen omfattede de samme sæt spørgeskemaer, som blev brugt i Studie 1. Mere end 30 % af kræftpatienterne oplevede ændringer i deres somatosensoriske perception. Dette var også forbundet med ændringer i deres madpræferencer. Hierarkisk gruppering identificerede tre forskellige grupper af patienter baseret på deres sensoriske perception, gruppen uden ændringer (n=48) og gruppen med ændringer, med undergrupper af generelt øget sensitivitet (n=44) og generelt nedsat sensitivitet (n=8). Det blev påvist, at sensoriske ændringer bidrog til ændringer i sensorisk relaterede fødevarepræferencer. Derudover bidrog orale symptomer også til disse ændringer, som samlet set påvirkede deres spisevaner.

Resultaterne fra de to undersøgelser blev integreret for at skabe retning for Studie 3, som har til formål at designe mad, der er tilpasset kræftpatienters madopfattelse og -præferencer. Seks forskellige madkoncepter blev udviklet i samarbejde med de kulinariske kokke. Herefter blev madkoncepterne smagt og evalueret i en fokusgruppediskussion med kræftpatienter (n=4); to koncepter blev godkendt. Den hedoniske accept af de godkendte madkoncepter vil blive testet i en forbrugertest med kræftpatienter, og udformningen af undersøgelsesdesignet er beskrevet.

Som konklusion viste denne ph.d.-afhandling, at HHK-patienter oplevede somatosensoriske ændringer og ubehag i munden. Disse kunne påvirke deres madadfærd. Derudover blev det indikeret, at disse fænomener ikke er eksklusive for HHK-patienter, men også opleves af patienter på tværs af forskellige kræfttyper. Undersøgelserne gav nogle retningslinjer for madjusteringer, der er nødvendige for at tilpasse sig kræftpatienters behov. Skræddersyede madløsninger bør ikke kun tage hensyn til smags- og lugteaspekter, men også til den somatosensoriske og orale komfort. Yderligere undersøgelser bør evaluere effektiviteten af denne tilgang og dykke ned i den underliggende mekanisme for somatosensoriske ændringer.

Abbreviations

BMI	Body Mass Index
(C)RT	Radiotherapy with or without chemotherapy
CRT	Chemoradiotherapy
CT	Chemotherapy
DEG/ENaC	Degenerin/Epithelial Sodium Channel
ESPEN	European Society for Clinical Nutrition and Metabolism
FGD	Focus Group Discussion
GLIM	Global Leadership Initiative on malnutrition
gLMS	generalised Labelled Magnitude Scale
HNC	Head and neck cancer
MUST	Malnutrition Universal Screening Tool
MST	Malnutrition Screening Tool
OR	Odds ratio
QoL	Quality of life
RT	Radiotherapy
TRP	Transient Receptor Potential
VAS	Visual Analogue Scale

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Chapter 1

General Introduction

1.1. Introduction

The prevalence of cancer has increased globally, affecting millions of people every year. In 2020, it was estimated that there were 18 million new cases worldwide (World Health Organisation, 2020). Among cancer patients, malnutrition negatively affects their treatment outcome and quality of life, and increases mortality rates (Oh *et al*., 2020). Findings from several countries reported the prevalence of malnutrition in cancer patients ranged between 25% and 70% (Muscaritoli *et al*., 2017).

Malnutrition is a common problem among cancer patients which negatively affects treatment outcome and quality of life. Overall, 39% of the cancer patients in a French cohort (n=1903) was reported to be malnourished. Analysis of malnutrition based on disease site was as follows: pancreas 66.7%; oesophagus and/or stomach 60.2%; head and neck 48.9%; lung 45.3%; ovaries/uterus 44.8%; colon/rectum 39.3%; leukaemia/lymphoma 34.0%; breast 20.5%; and prostate 13.9% (Hébuterne *et al*., 2014). The study revealed that patients whose cancer sites are related to food ingestion, digestion, and metabolism are at higher risk of malnutrition. This is in accordance with the findings from another multicenter study in France (n=1545) which demonstrated an increased risk of malnutrition among patients with upper digestive cancers (OR, 4.4; 95% CI, 2.6 – 7.7) and head and neck cancer (OR, 3.7; CI 95%, 2.4 – 5.8) (Pressoir *et al*., 2010). A study in Taiwan (n=3221) showed that patients with head and neck cancer lost the most weight (1.16 kg/mo), followed by those with upper gastrointestinal (-0.92 kg/mo) and gynaecological cancers (-0.38 kg/mo) during a 6-month follow-up study (Yang *et al*., 2019).

1.1.1. Malnutrition in head and neck cancer

Head and neck cancer (HNC) is "cancer that arises from epithelial cells and occurs in the oral cavity, pharynx, and larynx" (Machiels *et al*., 2020). It is the seventh most common type of cancer corresponding to 890,000 incidents and 507,000 deaths worldwide in 2018 (Global Burden of Disease Cancer Collaboration, 2019). Exposure to alcohol and tobacco is estimated to contribute to 75 -85% of HNC cases. The remaining 15 – 25% is estimated to be attributed to the human papillomavirus, the majority of these patients are in the lower age range with a favourable prognosis (Kaidar-Person *et al*., 2018; Machiels *et al*., 2020).

Malnutrition in HNC patients ranges between 9-100% (van den Berg *et al*., 2014; Citak *et al*., 2019; Hammerlid *et al*., 1998; Jager-Wittenaar *et al*., 2007; Lees, 1999; Mulasi *et al*., 2020; Neoh *et al*., 2020; Righini *et al*., 2013; Steer *et al*., 2020). This variation principally resulted from the different criteria of assessment, tumour site, type of treatment, and time of observation (before, during, or after treatment). **Table 1.1** summarises the studies investigating nutritional deterioration among HNC patients.

Table 1.1. Studies evaluating the nutritional status of HNC patients

Study	Population	Study design	Assessment criteria for malnutrition	Prevalence of malnutrition
van den Berg *et al*. 2013	n=32, Netherlands	Cross-sectional; nutritional assessment 14-68mo after CRT	MUST; BMI < 20.0 and/or > 5 % involuntary weight loss during the last 3–6 months	19% were at risk for malnutrition (13% moderate, 6% severe), 50% experienced weight loss
Righini *et al*. 2013	n = 169, France	Cross-sectional; nutritional assessment upon cancer diagnosis	Nutrition risk index	48.5% were malnourished (31% moderate and 17.8% severe)
Lees, 1999	n=100, UK	Cross-sectional, nutritional assessment before RT	Critical weight loss	54% had unintended weight loss
Jager-Wittenaar *et al*. 2007	n=447, Netherlands	Cross-sectional; nutritional assessment upon cancer diagnosis	Critical weight loss	19% of patients had critical weight loss
Neoh *et al* 2020	n= 50, Malaysia	Cohort; nutritional assessment pre-(C)RT, middle of (C)RT, end of (C)RT	Patient-Generated Subjective Global Assessment	• Pre-(C)RT 56% were malnourished (36% moderate, 20% severe) • End of (C)RT: all patients were malnourished (32% moderate, 68% severe)
Citak *et al*. 2019	n=61, Turkey	Cohort; nutritional assessment at pre-RT, end of RT, 1mo post-RT, 3mo post-RT	Patient-Generated Subjective Global Assessment	• Pre-RT: 9%; • End of RT: 74%, • 1 mo post-RT: 9% • 3mo post-RT 2%
Mulasi *et al*. 2020	n=19, US	Cohort; nutritional assessment at pre CRT, 1mo post CRT, 3mo post CRT	Patient-Generated Subjective Global Assessment	• Pre-CRT: 68%; • 1 mo post CRT:100% • 3 mo post CRT: 92%
Hammerlid *et al*. 1998	n= 48, Sweden	Most received RT with 27% combined with CT and/or surgery (59%)	Weight loss, anthropometry, weight index, BMI, serum albumin	51% of the patients were categorised as malnourished
Steer *et al*. 2020	n= 188, Australia	Various treatments	MST and GLIM	Based on MST 42%; based on GLIM 22%

BMI: Body Mass Index; (C)RT: radiotherapy with or without chemotherapy, CRT: chemoradiotherapy; CT: chemotherapy; GLIM: Global Leadership Initiative on malnutrition; MUST: Malnutrition Universal Screening Tool; MST: Malnutrition screening tool –

Various assessment criteria and tools are used to determine malnutrition: Malnutrition Universal Screening Tool (MUST), Nutrition risk index, Patient-Generated Subjective Global Assessment, critical weight loss, Malnutrition screening tool (MST), and Global leadership Initiative on malnutrition (GLIM) criteria. The prevalence of malnutrition differed depending on the assessment tool, using MST and GLIM criteria (Steer *et al*., 2020). Two studies highlighted that the prevalence of malnutrition among HNC patients varies depending on the tumour location, with the highest risk found among patients with cancer in the hypopharynx, followed by oropharynx/oral cavity and larynx (Jager-Wittenaar *et al*., 2007; Righini *et al*., 2013). Malnourished patients are more likely to report symptoms such as fatigue, loss of appetite, sticky saliva, chewing and swallowing difficulties, and dry mouth (Lees, 1999; Mulasi *et al*., 2020; van den Berg *et al*., 2006). Consequently, malnourished patients have significantly lower 2-year survival rates (35% for malnourished, 64% for well-nourished) (Hammerlid *et al*., 1998).

In addition to the tumour itself, HNC treatments lead to several side effects that significantly impact their nutritional status through reduced food intake (Talwar, 2010; Wang *et al*., 2021). A prospective study investigating the effect of radiotherapy among patients with different types of cancer (n=207) reported that before the radiotherapy 26% of cancer patients were already malnourished and this number almost doubled to 43% during the post-RT observation. Further, it was revealed that HNC patients were the most severely affected by radiotherapy (pre-RT: 24%, post-RT: 88%) indicating the relationship between malnutrition and cancer/radiation location (Unsal *et al*., 2006). A study among HNC patients also demonstrated that the percentage of patients who were malnourished doubled from 56% to 100% after the (chemo)radiotherapy treatment (Neoh *et al*., 2020). Two longitudinal studies demonstrated an increased prevalence of malnutrition during and up to 1 month after the treatment, however, the prevalence decreased at 3 months after treatment (Citak *et al*., 2019; Mulasi *et al*., 2020).

Malnutrition is a multifactor condition which requires a multidisciplinary approach. The factors contributing to malnutrition among HNC patients include dysphagia, loss of smell and taste, dumping syndrome, changes in body composition, poor dietary habits, excessive alcohol consumption, depression and anxiety, and limited support networks. Using exploratory factor analysis, the nutrition impact symptoms can be categorised into three different clusters: 1) radiotherapy-specific symptoms include pain, difficulty swallowing, oral mucositis, thick saliva, difficulty chewing, and dry mouth; 2) gastrointestinal symptoms include nausea, loss of appetite, fullness, and taste alteration which are closely related to chemotherapy; 3) psychological status include depression, anxiety, and lack of energy (Talwar, 2010). Compared to the other symptom clusters, radiotherapy-specific symptoms had a more straightforward and significant effect on nutritional status. The authors suggest that this may be due to the high prevalence and severity of these symptoms and their direct influence on swallowing and eating capacity (Wang *et al*., 2021).

The current treatment for HNC includes surgery, chemotherapy, and radiotherapy. Single modality therapy, such as surgery or radiotherapy, is usually recommended for early-stage tumours (stages I and II). Surgery is often the standard treatment for tumours in the oral cavity or early-stage larynx cancer while radiation therapy is often used for other regions in the head and neck. Locally advanced HNC (stages III and IV) usually requires multimodal treatment combining surgery, chemotherapy, and radiotherapy (Kaidar-Person *et al*., 2018). In general, the treatment approach of HNC depends on the characteristics of the primary site of the tumour. Treatment strategies also need to consider patient factors (smoking status, age, sex, and comorbidity), patient preference, and the experience of the clinical institution (Kaidar-Person *et al*., 2018; Machiels *et al*., 2020; Radosevich, 2013). Treatments for HNC continue to pose a major challenge as they are often associated with debilitating side effects that may influence food intake (**Table 1.2**).

Table 1.2. Summary of the most common treatments and associated side effects observed in patients with HNC (Sroussi *et al*., 2017; Talwar, 2010)

Treatments	Side effects
Surgery	Smell and taste dysfunction; nerve injury; dysphagia; oral, nasal, and gastric reflux; dumping syndrome; poor wound healing; risk of wound infection and aspiration
Radiotherapy	Taste and smell alterations; mucositis; xerostomia; mucosal infections; mucosal pain, dysphagia; trismus; impaired wound healing; susceptibility to dental caries; osteoradionecrosis,
Chemotherapy	Smell and taste alterations; mucositis; nausea and vomiting; anorexia; diarrhoea; renal impairment; metabolic abnormalities

1.1.2. Strategies to address cancer malnutrition

Pharmacological and nutritional interventions are the most common approach to address malnutrition among cancer patients. The pharmacological approach includes therapy using megestrol acetate, ghrelin, and steroids as well as hormonal therapy to increase appetite, the nutritional intervention includes active nutritional assessment followed by adjustment of diet type (food consistency, enteral, parenteral), provision of dietary and oral nutritional supplement, and personalised dietary counselling (Gorenc *et al*., 2015). The effect of the pharmacological approach on malnutrition was outlined in a systematic review of 20 RCTs, it shows promising effects of pharmacological agents (appetite stimulants, cytokine modulators, anabolic agents, and combination of treatments) on the management of cancer malnutrition (Advani *et al*., 2018).

The impact of different nutritional interventions on nutrition status, quality of life, and mortality among HNC patients were outlined in a systematic review of 10 RCTs. It was suggested that personalised dietary counselling had significant benefits on nutrition status and overall quality of life. The effect of enteral feeding is less conclusive. Oral nutritional supplement (ONS) was shown to increase energy and protein intake in 2 out of the 3 included studies, however, the long-term benefit was not investigated (Langius *et al*., 2013).

ONS is often used as a nutritional first aid. Enteral feeding was tolerated differently among patients (some patients reported positive effects while others completely tried to avoid it). The participants expressed the challenge of customising their meals to their physiological ability due to the absence of nutritional support from dietitians (Sandmæl *et al*., 2019). A randomised controlled trial demonstrated that personalised nutrition counselling is more effective than general nutrition advice by doctors or nurses (Qiu *et al*., 2020). Personalised nutrition counselling is most effective in increasing energy consumption during treatment among patients whose cancer sites were related to food ingestion, digestion, and metabolism. The study recommended that at least 3 counselling sessions are needed to produce a meaningful result (Yang *et al*., 2019). In addition, a study showed that better nutritional outcomes would be achieved by providing ONS in addition to nutrition counselling. The group receiving nutrition counselling and ONS had smaller weight loss, higher food intake, and higher quality of life compared to those only receiving nutrition counselling (Cereda *et al*., 2018; Ferreira *et al*., 2020).

The ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines on nutrition in cancer patients have suggested that nutritional intake is ideally achieved through regular food consumption but in some cases, this can be challenging, therefore ONS become necessary in addition to counselling sessions (Arends *et al*., 2017). Long-term observation has shown benefits in the nutritional intake and QoL of malnourished cancer patients (Baldwin *et al*., 2012). Despite the benefits, there are indications of poor compliance to ONS consumption due to low sensory acceptance (Methven *et al*., 2010; Neoh *et al*., 2020). ONS are initially well accepted by patients but eventually become difficult to consume over long period of time. ONS need to be consumed for several weeks to improve nutrition, however, most studies evaluated ONS acceptance using the single sip method (Enriquez-Fernández *et al*., 2019). The studies that assessed acceptance using the multi-sip method showed that negative attributes build up over multiple sips, which would not be detected using the single-sip method. Further, two studies investigated compliance to ONS over 21 days and 60 days, the authors concluded that initial dislike of taste and flavour fatigue were the main reasons for the decline in compliance. The study also highlighted that the flavour preference of cancer patients differs from that of the healthy population.

Therefore, in addition to the existing pharmacological and nutritional interventions, understanding patient's food perception and eating enjoyment through a sensory approach may offer added benefits, especially when considering the long-term quality of life. Consequences of sensory changes may play an important role in the aetiology of malnutrition through complex interaction of reduced food pleasure, development of food aversion, changes in food preference and dietary habits, loss of appetite, and reduced food intake. Moreover, sensory changes also induce stress, depression, and anxiety among patients subsequently leading to an overall reduction in quality of life (Brisbois *et al*., 2006; Kenza Drareni *et al*., 2019).

1.1.3. The loss of eating pleasure among cancer patients

A common side effect of all the different cancer treatments is sensory alteration, such as taste and smell alterations (**Table 1.1**). These alterations can contribute to malnutrition through changes in food intake. Although there is little direct evidence establishing the connection, several studies provided data related to the effects of sensory alteration on food intake. Sensory alterations directly influence food perception, leading to altered eating (Watson *et al*., 2018; Rolls, 1999). Furthermore, sensory alterations have been associated with reduced appetite, diminished food appreciation, and changed patterns of food selection or intake (Boltong & Campbell, 2013; Dalton *et al*., 2022; Ganzer *et al*., 2015) consequently leading to lower nutrient intake and more weight loss in cancer patients (Brisbois *et al*., 2011; Hutton *et al*., 2007; Snchez-Lara *et al*., 2010). A proposed hypothesis about how sensory alteration could influence nutritional status is illustrated in **Figure 1.1**.

Beyond the physical consequences, the psychological burden of impaired eating experience should not be underestimated. Food commonly provides comfort and the social interaction surrounding mealtimes increases overall wellbeing. It has been shown that altered eating leads to altered food relationships (Watson *et al*., 2018; Ganzer *et al*., 2015) and rituals and social activities linked to mealtimes (Boltong *et al*., 2012; Dalton *et al*., 2022). These can provoke feelings of frustration, sadness, and isolation.

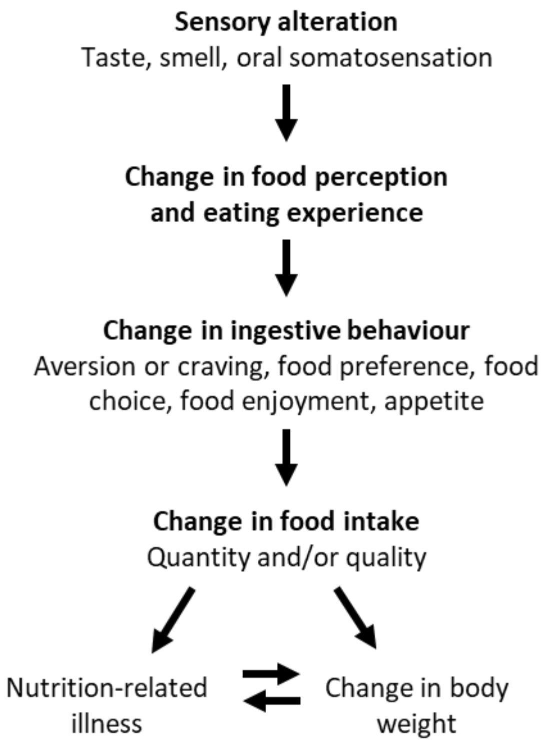

Figure 1.1. Hypothetical pathway through which sensory alteration may contribute to malnutrition (adapted from Rolls 1999)

Sensory alterations are prevalent side effects of cancer and its treatments but are often overlooked, as the primary focus is the disease itself and its treatment (Ganzer *et al*., 2015). Some patients admitted that they were not aware that food-related sensory alteration would be one of the side effects following the different treatments (Crowder *et al*., 2020). It is estimated to affect 16-70% of cancer patients undergoing chemotherapy and 50-90% of advanced cancer patients not undergoing active treatment (Bernhardson *et al*., 2009; Brisbois *et al*., 2006; Spotten *et al*., 2017; Zabernigg *et al*., 2010). A systematic review of taste alteration showed that the prevalence of taste alteration among HNC patients was 56.3% in groups receiving radiotherapy and 76% in groups receiving combined chemoradiotherapy (Hovan *et al*., 2010).

The prevalence of sensory alterations can vary based not only on the type of treatment but also the evaluation method (objective or subjective measurements) used. For instance, a study among colorectal cancer patients found a weak correlation between objective and subjective smell evaluations but no correlation between objective and subjective taste evaluations (Postma *et al*., 2020). It is important to note that sensory changes are not only attributed to physiological changes but also involve hedonic changes and/or individual subjective perception in a way that the taste of food has not changed but is no longer considered pleasant (Bernhardson *et al*., 2009).

The duration of sensory alterations also varies, with some studies reporting short-term (recovery as early as 8 weeks post-RT) to long-term (> 1-year post-RT) (Spotten *et al*., 2017). However, it was suggested that sensory alterations were more persistent among HNC compared to other types of cancer (Cancer Council Australia, 2015). Irradiated taste buds, disruption in the renewal cycle of sensory receptors, nerve damage in the head and neck area, micronutrient deficiencies, medications, infections, hyposalivation, and mucositis are some of the reasons for taste and smell alterations among HNC patients (Brisbois *et al*., 2006).

Different profiles of taste and smell alterations were reported: no alterations, increased sensitivity, decreased sensitivity, and mixed sensations (Kenza Drareni *et al*., 2019). This can be due to the heterogeneity of the cancer population under investigation and the method of assessment. Nevertheless, alterations in taste and/or smell may negatively impact food preferences and intake (Drareni *et al*., 2019; Nolden *et al*., 2019). To address the change in perception, studies have attempted to compensate for the reduced taste and smell sensitivity by offering food with enhanced taste and smell which improved their liking and nutritional outcome (Drareni *et al*., 2023; Schiffman *et al*., 2007).

Although sensory perception is a multimodal processing involving the three sensory systems: gustatory, olfactory, and somatosensory/trigeminal, the majority of the existing studies have only assessed gustatory and olfactory alterations. Limited research has been conducted to understand somatosensory alterations among cancer patients, therefore it is unclear whether somatosensory alteration is a phenomenon experienced by cancer patients. Although the findings from qualitative studies suggest that patients experienced sensory alterations beyond just taste and smell changes (Watson *et al*., 2018; Crowder *et al*., 2020), there is a paucity of quantitative research supporting these findings.

Addressing the link between sensory alterations, including oral somatosensory perception, and malnutrition in cancer patients is essential for optimal care. Healthcare professionals can develop tailored interventions to improve appetite and restore nutritional balance, by understanding patients' sensory perception and the impact on eating enjoyment. Such strategies may include developing guides or tailored food products to enhance the overall eating experience.

1.2.1. Understanding oral somatosensory perception: from sensation to perception

Somatosensory perception refers to mechanoreception (pressure, texture, form); nociception (noxious stimuli); and thermoreception (Hollins, 2010; Lundström *et al*., 2011).

The mechanism of sensory perception can be conceptually divided into three stages: stimulation, transduction, and interpretation. 1) Sensory stimulus stimulates various sensory receptors; this process of detecting sensory stimuli is also known as sensation. 2) The stimulus is then transduced by various channels into action potentials and conveyed to the central nervous system via the nerves. 3) Finally, this leads to an encoding process of interpreting the action potential into perception (Chen, 2014). **Figure 1.2** shows a graphical summary of the mechanism involved in somatosensory perception.

Table 1.3. Summary of oral somatosensory perception process

Somatosensory stimuli	Receptor	Channel
Touch, pressure, form, vibration	Mechanoreceptors (Meissner corpuscles, Merkel cells, Ruffini endings)	TRP channels; voltage-gated Na+, K+ and Ca2+ channels; DEG/ENaC superfamily; and Piezo 2 channels
Thermal difference	Thermoreceptor (free-nerve ending)	TRPA1 (garlic, noxious cold), TRPM8 (menthol, cool), TRPV1 (capsaicin, noxious heat), TRPV2 (noxious heat), TRPV3 (thymol, warm), TRPV4 (warm)
Chemesthetic compound	Nociceptor (free-nerve ending)	

DEG/ENaC: Degenerin/Epithelial Sodium Channel; TRP: Transcient Receptor Potential; TRPA: TRP ankyrin; TRPM: TRP melastatin; TRPV: TRP vanilloid.

Stimulation

Food perception is initiated when various sensory stimuli are detected by different receptors, creating a sensation. Texture, in the form of tactile stimulation such as pressure, vibration, slip, and movement, is primarily perceived by mechanoreceptors spread over superficial structures (hard and soft palate, tongue, and gums), periodontal membrane, muscles, and tendons (Kutter *et al*., 2011). These receptors are Aβ myelinated fibers which detect and transmit tactile information in the oral cavity necessary for texture perception and bolus manipulation (Engelen, 2012; Jacobs, 2011). The texture of soft and semisolid food is primarily perceived by the mechanoreceptors on the tongue and palate, whereas solid and hard foods are predominantly perceived by periodontal mechanoreceptors around the teeth (Engelen, 2012). Specialised end-organ structures associated with mechanoreceptors identified in the oral cavity are Meissner corpuscles (rapidly adapting mechanoreceptors) and Merkel cells (slowly adapting mechanoreceptors) in the hard palate and Meissner corpuscles in the fungiform papillae (Moayedi *et al*., 2021). Pacinian corpuscles (rapidly adapting mechanoreceptors) are found on the cutaneous membrane but have not been identified in the oral cavity (Moayedi *et al*., 2021; Trulsson & Essick, 2010).

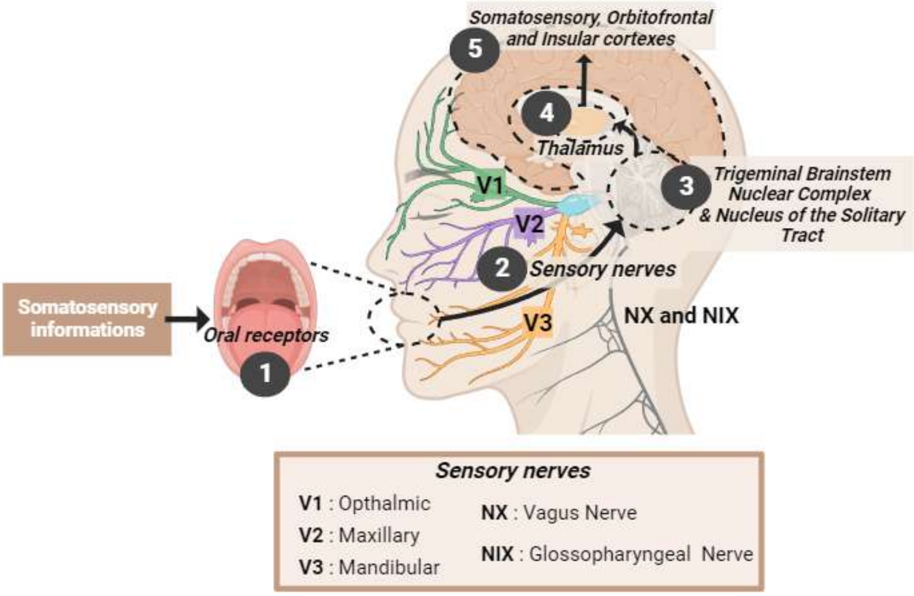

Figure 1.2. Graphical illustration of oral somatosensory perception, Valenti 2023
1) Mechanical, thermal, and nociceptive receptors present throughout the oral epithelium detect somatosensory information which consists of tactile (including for texture perception), temperature, and chemesthetic stimuli. 2) These stimuli are relayed via the trigeminal nerve (cranial nerve V) to the central nervous system but also by the vagus nerve (cranial nerve X) and the glossopharyngeal nerve (cranial nerve IX). 3-4) The information is then relayed by the trigeminal brainstem nuclear complex and by the nucleus of the solitary tract to the thalamus. 5) The somatosensory cortex processes the signals and integrates them with gustatory, olfactory, and somatosensory information. The insula and orbitofrontal cortex further contribute to the integration of sensory information, forming a complete perception of food.

Nociceptors are high-threshold receptors with free nerve endings. They respond to various noxious stimuli including thermal, chemical, and mechanical stimuli. Many nociceptors are polymodal neurons and are divided into three major classes: Aδ mechanical fibers, Aδ thermal fibers, and C-fibers (Engelen, 2012). Nociceptors are crucial for recognising and avoiding harmful situations, such as biting the tongue while eating, burning the oral cavity, and ingesting poisonous substances. During eating, a multitude of other stimuli are detected by nociceptors, such as the spiciness of chilli and the cooling of mint (Simons *et al*., 2019). These kinds of sensations are often referred to as chemesthetic or trigeminal sensations. Some of these stimuli are considered pleasant in low concentrations but could potentially cause damage to the tissues at high concentrations, such as capsaicin (chilli), eugenol (cloves), and menthol (Simons *et al*., 2019).

Thermoreceptors are responsible for detecting temperature differences (Engelen, 2012). Thermoreceptors have free nerve endings which are activated over a specific temperature range. The cold receptors are either thinly myelinated Aδ fibers or unmyelinated C-fibers activated at temperatures between 17 and 40ºC while warm receptors are C-fibers activated at temperatures between 30 and 48ºC. Generally, both warm and cold receptors are active at moderate temperatures such as 35ºC but stop firing altogether at a noxious temperature range (< 5 ºC and > 50 ºC) (Engelen, 2012).

Transduction

Tactile information (touch, pressure, form, vibration) detected by the mechanoreceptors are transduced into biological signals which result in the generation of action potentials in the peripheral nervous system. This transduction process is initiated by various mechanosensitive ion channels which include some Transient Receptor Potential (TRP) channels; voltage-gated Na+, K+ and Ca2+ channels; Degenerin/Epithelial Sodium Channel (DEG/ENaC) superfamily; and Piezo 2 channels (Fang *et al*., 2021; García-Mesa *et al*., 2017; Ranade *et al*., 2014). It is important to consider that most of the mechanosensitive ion channels, particularly the TRP channel, are also activated by chemical and temperature/heat stimulations (Engelen & de Wijk, 2012).

Thermal stimuli are transduced into action potentials by various TRP channels, specifically TRP vanilloid (TRPV), TRP melastatin (TRPM), and TRP ankyrin (TRPA). Cool temperatures (< 26 ºC) activate the TRPM8 ion channel while warm temperatures activate TRPV3 (> 33 ºC) or TRPV4 (> 27 ºC) (Güler *et al*., 2002; Xu *et al*., 2006). In the range of noxious temperatures, the TRPA1 channel activates at temperatures below 17 ºC whereas TRPV1 and TRPV2 activate at temperatures above 43 ºC (Schepers & Ringkamp, 2010). Thermoreception and nociception have been proposed as integrated modalities, which seem to have polymodal aspects and to be strongly interrelated (Engelen, 2012). An example of this is the responsiveness of the same transduction receptors TRPV1 to heat and capsaicin as well as TRPM8 to thermal cooling and chemical cooling of menthol (Simons *et al*., 2019).

Interpretation

The action potentials carrying various somatosensory information are then conveyed to the central nervous system predominantly via the trigeminal nerve and partly via the facial (via chorda tympani), vagus, and glossopharyngeal nerves, which also carry taste information (Simons & Carstens, 2008). The trigeminal nerve enters the trigeminal ganglion and then the trigeminal brainstem complex, which has two major components: the principal nucleus, responsible for processing mechanosensory stimuli and the spinal nucleus, responsible for processing thermal and painful stimuli (Jos, 2012). Somatic sensory information is then relayed to the ventral posterior medial of the thalamus through the trigeminal lemniscus and ascends to the somatosensory cortex. The representations from each sensory modality (taste, smell, somatosensation) are integrated into the multimodal regions, such as the orbitofrontal cortex, to form a complete picture, the perception (Engelen & de Wijk, 2012; Spence, 2016).

Haggard & de Boer (2014) highlighted that somatosensory perception refers to processing several sensory inputs to form a percept of a specific stimulus. A crucial feature of perception is integrating and combining information from different receptor types and regions. Gustatory, olfactory, and oral somatosensory inputs are first integrated into the anterior ventral insula (Small, 2012). Perception is a processed opinion, based on received sensation and is therefore influenced by physiological (ingestive and appetitive systems), psychological, and cultural factors (Chen, 2014).

1.2. Aim and Research Questions

As food-related sensory alterations have been frequently documented among cancer patients, we seek to explore whether their alterations were also contributed by alterations in their somatosensory perception or only limited to taste and smell perceptions. In the present project, somatosensory perception comprises texture, temperature, and chemesthetic perception. The overarching goal of the project is to explore the somatosensory perception of cancer patients and design food adapted to their senses.

The first part of the project aimed to investigate somatosensory perception specifically in the population of head and neck cancer patients through a clinical study. Both objective measurements, through sensory tests and subjective measurements, through questionnaires, were used. The second study aimed to extend our knowledge of somatosensory perception among various cancer populations using an online survey. This knowledge facilitated the creation of food designs that are adapted to the perception of cancer patients in Study 3.

Research question 1: Are there indications of oral somatosensory alterations among head and neck cancer patients, and what are the possible causes?

Research question 2: How is oral somatosensory perception assessed?

Research question 3: How does the somatosensory perception of HNC patients differ from the general population? and how does it influence their eating behaviour?

Research question 4: How is the somatosensory perception of various cancer patients?

Research question 5: How to design food adapted to the somatosensory perception of cancer patients?

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Chapter 2

Methodological Approaches

2.1. Methodological Approach

As discussed in Chapter 1, there have been numerous investigations on taste and smell alterations among cancer populations. It should be noted that the term "taste" has been frequently used by both patients and researchers to encompass flavour perception (Boltong *et al*., 2012), which actually involves not only taste and smell but also somatosensory perception(Small, 2012; Spence, 2016). However, our understanding of somatosensory perception in relation to food perception is relatively limited.

To address these knowledge gaps, the thesis project started with 2 narrative reviews. The first review (Chapter 3) aims to explore the state-of-the-art of oral somatosensory perception in cancer patients. Existing studies on this topic, on one hand, suggest that sensory alterations among cancer patients extend beyond taste and smell, based on subjective measurements (questionnaires) and qualitative approaches, but it remains unclear whether these alterations originated from peripheral or central processing. On the other hand, clinical studies employing objective measurements (sensory tests) have only examined certain aspects of somatosensory perception, such as tactile and thermal sensitivity (to a certain extent texture sensitivity), but their implications for food perception remain unclear. Information derived from both types of measurements are equally important. Objective measurements provide quantitative data that can be standardised and replicated, allowing for more precise comparisons between different groups. This type of measurement helps determine whether the changes observed among the patients are solely related to their central and psychological perception, or if there are also physiological and peripheral changes involved. Meanwhile, subjective measurements are needed to capture patients' personal experiences and perceptions.

In order to get an accurate depiction of their perception, it is important to select the right tools and methods. The second review (Chapter 4) describes and evaluates the existing assessment methods of oral somatosensory perception. The knowledge gathered from these two reviews was used as guidance to design a clinical study to investigate the oral somatosensory perception of HNC patients (Study 1). Study 1, discussed in Chapters 5 and 6, combined subjective and objective measurements, including the assessment of chemesthetic sensitivity and the use of real food to assess texture sensitivity.

Chapter 5 focuses on the objective measurements of somatosensory perception and salivary function in HNC patients compared to a control group. Meanwhile, Chapter 6 explores the subjective measurements of somatosensory perception, oral symptoms, and their influence on eating behaviour. In Study 2, discussed in Chapter 7, we expanded our investigations to explore subjective sensory perception not only among HNC patients but also among various other cancer populations. Knowledge gained from the two studies was used as guidance for Study 3, which aimed to design food adapted to the senses of cancer patients. Starting with culinary development sessions to create food concepts, which were then evaluated in a focus group discussion with a group of cancer patients (Chapter 8).

2.1.1. Study 1: Clinical study with head and neck cancer patients

Aiming to comprehensively understand HNC patients' somatosensory perception, the objective measurements (tactile, texture, chemesthetic, and thermal sensitivity) were complemented with subjective measurements of self-reported questionnaires. **Figure 2.1** presents the overview of the study.

2.1.1.1. Participants

As the cancer population is very heterogeneous, we aimed to limit the possible confounding factors associated with the cancer type. Therefore, we limited our investigations to HNC as this subpopulation of cancer patients is susceptible to somatosensory alterations due to the tumour and treatment location (Cancer Council Australia, 2015; Talwar, 2010; Wang *et al.*, 2021). As radiotherapy in that area was shown to be associated with somatosensory alterations and salivary dysfunction (Elfring *et al.*, 2012; Farhangfar *et al.*, 2014; Loewen *et al.*, 2010; Wang *et al.*, 2021), one of the inclusion criteria is to have received radiotherapy. Controls were healthy individuals matched in sex and age (±5 years old) to minimise the potential difference due to sex and age effect. Additionally, we restricted the age range to individuals under 70 years old to reduce the potential impact of age-related degeneration.

<u>Inclusion criteria</u>

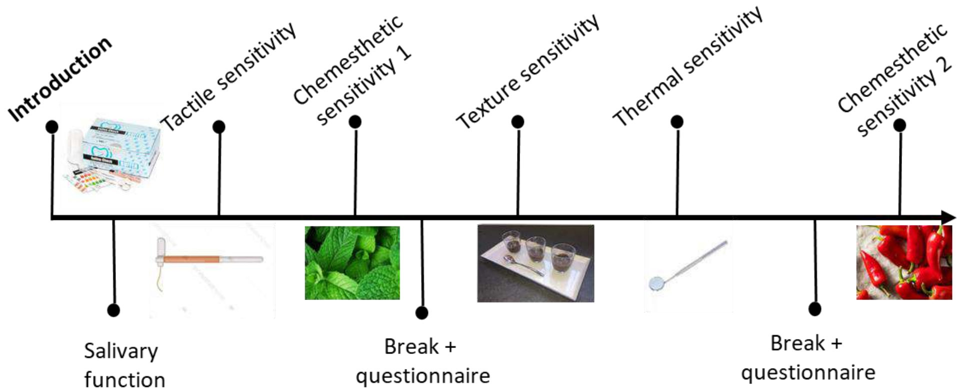
- All subjects:
- Persons between 18 and 70 years of age.
- Person affiliated with a French social security scheme.
- A person who is able to visit the Institut Lyfe or the Croix Rousse Hospital/ Lyon Sud Hospital.
- Patients:
- Patient diagnosed with a tumour of the upper aerodigestive tract (including oral cavity, pharynx, larynx), salivary glands, maxillary sinuses or nasopharynx with the following treatment regimen: Surgery + radiotherapy or radiotherapy.
- The patient may or may not have received chemotherapy.
- Recurrent patients may be included if they have not been treated with radiotherapy in the area concerned during previous treatment.
- Controls:
- Healthy individual aged ±5 years in relation to the patient to whom he/she is matched.

- Volunteer of the same sex as the patient to whom they are matched.
- Volunteer who has not had cancer within 5 years at the time of inclusion.

Exclusion criteria

- All subjects:
- Individuals with a known food allergy/intolerance (lactose or milk protein) or unable to consume dairy or semi-solid products (e.g. chocolate milk pudding, chocolate jelly).
- Individuals with a known allergy to chilli (or capsaicin).
- Individuals with diagnosed total ageusia.
- Individuals with diagnosed total anosmia.
- A pregnant or breastfeeding woman.
- Individuals with trismus (reduced opening of the jaws or limited range of movement of the jaws).
- Individuals unable to extend their tongue.
- Individuals who have undergone surgery on the tongue mobile and/or base of the tongue.
- Individuals unable to swallow soft foods.
- Patients:
- Patients receiving immunotherapy.
- Patients treated solely by surgery.

2.1.1.2. Methods



Measurement	Brief description
Salivary function	Direct diagnostic tool Saliva Check BUFFER kit
Tactile sensitivity	Point-pressure test with von Frey filaments
Chemesthetic sensitivity 1	Whole-mouth stimulation (sip-and -spit) with menthol solutions
Questionnaire part 1	Self-reported food perception and oral symptoms
Texture sensitivity	Ranking and intensity-rating of chocolate puddings
Thermal sensitivity	Temperature-discrimination test with dental mirrors
Questionnaire part 2	Self-reported food preference and eating behaviour
Chemesthetic sensitivity 2	Whole-mouth stimulation (sip-and -spit) with capsaicin solutions

Figure 2.1. Overview of the study visit, including the order of the tests

Objective measurements (Chapter 5)

The different sensory tests used to measure oral somatosensory perception were selected from existing methods (Chapter 4). The measurements carried out in this study encompassed point-pressure tactile sensitivity, whole-mouth chemesthetic stimulation, food texture discrimination, and temperature discrimination. Moreover, salivary functions namely hydration level, saliva consistency, saliva pH, stimulated saliva volume, and buffering capacity were also assessed. The subsequent section provides a concise summary of the methods employed in the included studies along with the rationale and the developmental work behind the selected method, whereas a more detailed description of the evaluation method for each test is described in Chapter 5.

Salivary functions: Saliva -check BUFFER kit

The saliva-check BUFFER kit is a direct diagnostic tool that evaluates the quantity (visual hydration, saliva consistency, and saliva pH) and quality (pH and buffering capacity) of saliva (Kubala *et al.*, 2018). It is often used as a diagnostic tool for healthcare professionals and has been used in previous clinical studies as an indicator of salivary function (Bechir *et al.*, 2022; Lin *et al.*, 2015). The whole procedure took less than 10 minutes for each participant and results were immediately available. This eliminates the need for biological storage and laboratory analysis.

Tactile sensitivity: point-pressure test with von Frey filaments.

The point pressure test using von Frey filament was selected to measure lingual tactile sensitivity. This method has been widely used both in the clinical and non-clinical populations (Appiani *et al.*, 2020; Cattaneo *et al.*, 2020; Greimel *et al.*, 2006; Loewen *et al.*, 2010).. The threshold procedure using the three smallest sizes available in the set was used, following previous studies (Cattaneo *et al.*, 2020; Liu *et al.*, 2021).

Figure 2.2. Illustration of tactile sensitivity test

Food texture sensitivity: texture discrimination test with real food samples.

To simulate a realistic eating experience, real food models were developed. Semi-solid food models in the form of chocolate pudding (**Figure.2)** were developed due to the chewing and swallowing difficulties that HNC patients often face with solid and liquid foods (Watson *et al.*, 2018; Crowder *et al.*, 2020). Geometrical attributes include surface properties, global shape, granularity, denseness, and homogeneity which represent the physical structure of the food. Mechanical attributes of food include properties such as hardness, adhesiveness, elasticity, and viscosity, related to food breakdown in the mouth (Bondu *et al.*, 2022; Szczesniak, 2002).

As texture perception is complex and multifaceted, three different textural dimensions were chosen to represent both the geometrical (roughness) and mechanical (firmness and thickness) texture attributes. Three different levels were developed for each textural attribute, thus nine different samples of chocolate pudding were developed (**Table 5.2**, Chapter 5).

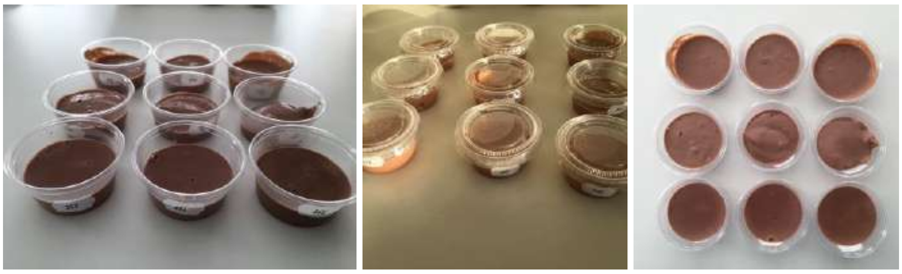


Figure 2.3. Chocolate pudding samples for texture sensitivity test

The development of food models was assisted by the culinary chef of the Institute Lyfe (ex. Institut Paul Bocuse) Research Center. Initially, three different hydrocolloids (agar, xanthan, and pectin) were used to create prototype samples. After consulting with the culinary team and prototyping to test the ease of modifying the texture and mouthfeel characteristics, agar was identified as the most appropriate hydrocolloid for the purpose. Xanthan produced a rather slimy mouthfeel whereas pectin were rather difficult to incorporate as specific pH was needed for the right gelification. Subsequently, the concentrations of agar were chosen through prototyping and internal tasting. To ensure the quality and appropriateness of the final recipe, it was internally tested by the supervisory team.

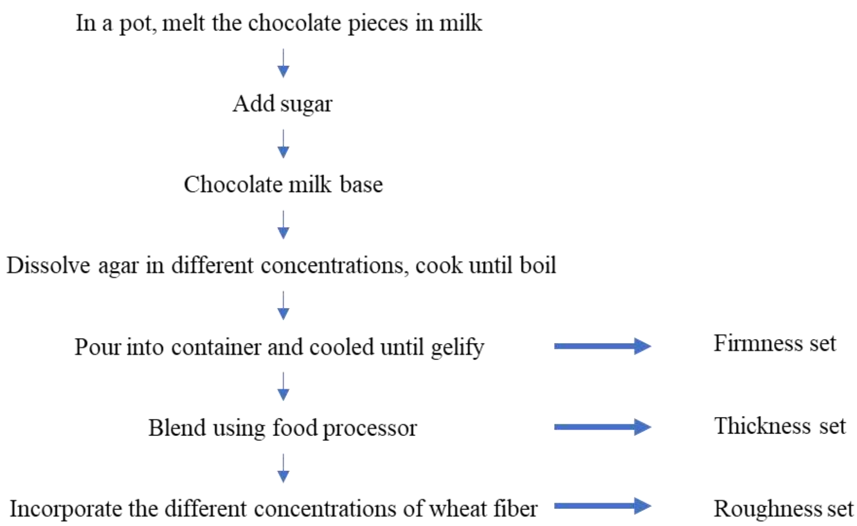


Figure 2.4. Flowchart of sample preparation

Characterisation of the samples was performed using sensory evaluation and instrumental analysis. This was done to ensure that the samples differed from each other specifically in terms of their evaluated textural aspect. A sensory evaluation using descriptive analysis was conducted to characterise the samples. It was conducted in December 2021 with 10 participants (8f, 2m) comprising students from the Neuroscience and Sensory Evaluation Master programme and internal colleagues. A 2h-training session was conducted to familiarise the participants with the samples and the attributes. Ballot training method was used with pre-determined attributes (**Table 2.1**) and scale calibration was done in consensus using examples, references, and samples. The evaluation was conducted in triplicates and data was collected using an online survey platform (Qualtrics).

Table 2.1. Attribute definition and anchor points used for sensory evaluation of samples.

Attributes	Definition	Anchor
Firm	Dense, hard; compress the sample between your tongue and palate and evaluate the force required to compress the sample	Not at all → extremely
Thick	Viscous; manipulate the sample with your tongue and palate, and evaluate the degree of resistance when you manipulate the sample	Not at all → extremely
Rough	Coarse, Presence of particles or bumps; rub the sample between your tongue against the roof of your mouth and evaluate the degree of abrasiveness of the sample's surface	Not at all → extremely

For the instrumental measurement, the firmness set was measured using texture profile analysis, the thickness set was measured using rheological analysis, and the roughness set was measured using particle size analysis. All measurements were done in triplicate.

Texture profile analysis was performed using a Texture Analyzer (Model TA-XT Plus, Stable Microsystem, Godalming, United Kingdom) equipped with a 5.0-kg load cell. The texture analysis was performed with double compression with a speed of 8.0 mm/second, 90% strain, and a trigger force of 3.0 g using an SMS P/25 probe (Riantiningtyas *et al.*, 2021). The hardness parameter presented was extracted using Exponent software (6.1.9.0 version) to represent the firmness of the sample.

Rheological measurement was characterised using a DHR-2 rheometer (TA Instruments, New Castle, USA) equipped with a geometric cone and plate (CP2/50, PL 65). The viscosity test was conducted in flow ramp mode with the shear rate increasing from 0.1 to 300 s^{-1}. The apparent viscosity presents the viscosity at a shear rate of 10 s^{-1} which corresponds to oral sensation and is indicative of the thickness of the sample (Mezger, 2020).

Particle size analysis was performed using Mastersizer 3000 (Mastersizer, Malvern Instruments, Worcestershire, UK) to measure particle size and particle size distribution of materials using laser diffraction technique. The particle size distribution of chocolate mousse was analyzed, and the volume-based parameters of D_{10}, D_{50}, and D_{90} were estimated. D_{10} is a particle size distribution parameter that represents the size at which 10% of the particles in the sample are smaller. It indicates the point where only a small fraction (10%) of the particles is finer or smaller, D_{50} represents the median diameter, and D_{90} represents the size at which 90% of the particles in the sample are smaller; the D_{90} value was correlated to the perception of graininess (Puleo *et al.*, 2020).

Table 2.2. Sample characteristics assessed using instrumental analysis and sensory evaluation

Set	Measurements	Low	Medium	High	p-value
Firmness set	Instrumental hardness (g)	358.9 ± 24.7	697.2 ± 6.6	1217.1 ± 9.3	< 0.001
	Perceived firmness (VAS)	11.1 ± 1.8	12.6 ± 1.8	13.9 ±1.0	< 0.001
Thickness set	Apparent viscosity (Pa.s)	1.0 ± 0.03	3.1 ± 0.14	5.8 ± 0.22	< 0.001
	Perceived thickness (VAS)	6.0 ± 2.9	7.3 ± 2.5	9.4 ± 2.8	<0.001
Roughness set	D_{90} value	104.0 ± 1.5	102.7 ± 1.2	105.7 ± 0.6	0.05
	Perceived roughness (VAS)	2.3 ± 1.7	6.9 ± 4.0	8.9 ± 3.8	<0.001

Table 2.2 presents the measurements of the samples using instrumental analysis and sensory evaluation. Both analysis were in agreement with each other and showed that the samples were significantly different from each other on its respective sensory attribute.

Thermal sensitivity: temperature discrimination test with dental mirrors

The temperature discrimination test using dental mirrors was selected to assess thermal sensitivity (**Figure 2.5**). This test can be easily performed with a basic setup, and does not require a significant amount of time or cognitive effort from participants, to prevent fatigue. Despite its simplicity, previous studies were able to show significant differences between patients and controls (Elfring *et al.*, 2012; Loewen *et al.*, 2010). To improve the discrimination and resolution of the test, an additional middle temperature of 20°C was introduced alongside the extreme temperatures of 3°C and 55°C.

Chemesthetic sensitivity: whole-mouth stimulation with menthol and capsaicin solutions

The choice of using the whole-mouth stimulation test in this study was based on our objective to simulate the real eating experience. Menthol and capsaicin were used to evaluate the sensitivity towards pungency and cooling, respectively (Chapter 5). To minimise the number of samples the intensity rating procedure was used, with the generalized Labelled Magnitude Scale (gLMS). It has been shown that gLMS is a valid scale for comparing different study populations while still being easy to use (Bartoshuk *et al.*, 2004; Hayes *et al.*, 2013).

Figure 2.5. Illustration of thermal sensitivity test

Subjective measurements (Chapter 6)

Questionnaires were developed specifically for the study, adapted from various existing questionnaires. In the study visit, the questionnaires were divided into two parts: 1) food perception and oral symptoms; 2) food preference and eating behaviour to prevent fatigue (**Figure 2.1**). The questionnaires used in the study were specifically created for this project and were adapted from existing questionnaires (Amézaga *et al*., 2018; de Haan *et al*., 2021; Drareni *et al*., 2021; Hunot *et al*., 2016; Hutton *et al*., 2007; Singer *et al*., 2019). **Table 2.3** describes the different parts of the questionnaires.

Table 2.3. Summary of self-reported questionnaires

Questionnaire	Example question	Response options	Reference
Food perception	…I perceive that my sensitivity towards [salty/ sweet/ sour/ bitter/ smell of/ texture of/ cold/ hot/ pungent/ cooling/ astringent/ carbonated drinks/ alcoholic] product has…	Increased/ not changed/ decreased/ changed	(Amézaga *et al*., 2018; de Haan *et al*., 2021; Drareni *et al*., 2021; Hutton *et al*., 2007)
Oral symptoms	Frequency of experiencing 19 different oral symptoms (e.g. dry mouth, chewing difficulty, oral pain)	1=Never → 5= always	(Singer *et al*., 2019)
Food preference	… my preference towards [salty/ sweet/ sour/ bitter/ pungent/ cooling/ astringent/ carbonated drinks/ alcoholic] product has..”	Increased/ not changed/ decreased	(Amézaga *et al*., 2018; de Haan *et al*., 2021; Drareni *et al*., 2021; Hutton *et al*., 2007)
Eating behaviour	Items related to eating behaviour (e.g. eating a variety of food, trying novel food, eating smaller portions, losing pleasure from eating)	1= Disagree completely → 6= agree completely	(Hunot *et al*., 2016)

The questionnaire was initially developed in English and then translated into French. Native French speakers reviewed and confirmed the accuracy of the translations by comparing them with the original English questionnaire. To ensure clarity, the questionnaires were first tested with a group of healthy individuals (16 internal staff members of the Institut Lyfe Research Centre) and a small group of cancer patients (4 patients). Any feedback or comments provided by the testers were considered, and the final questionnaire was validated by the supervisory team.

Inspired by the work of (Laureati *et al*., 2020; Skouw *et al*., 2023) a visual questionnaire was additionally developed to further understand food preference on the somatosensory aspect (**Figure 2.6**). The visual questionnaire consists of food pairs contrasting on one somatosensory properties, including texture (hardness, thickness, particle size/roughness), chemesthetic sensations, and temperature (**Table 2.4**). The selection of food pairs was based on familiar food items, as well as an effort to maintain a balance between sweet and savoury options. Sixteen pairs of food pictures were taken and curated in Department of Food Science, University of Copenhagen and Institut Lyfe Research Center.

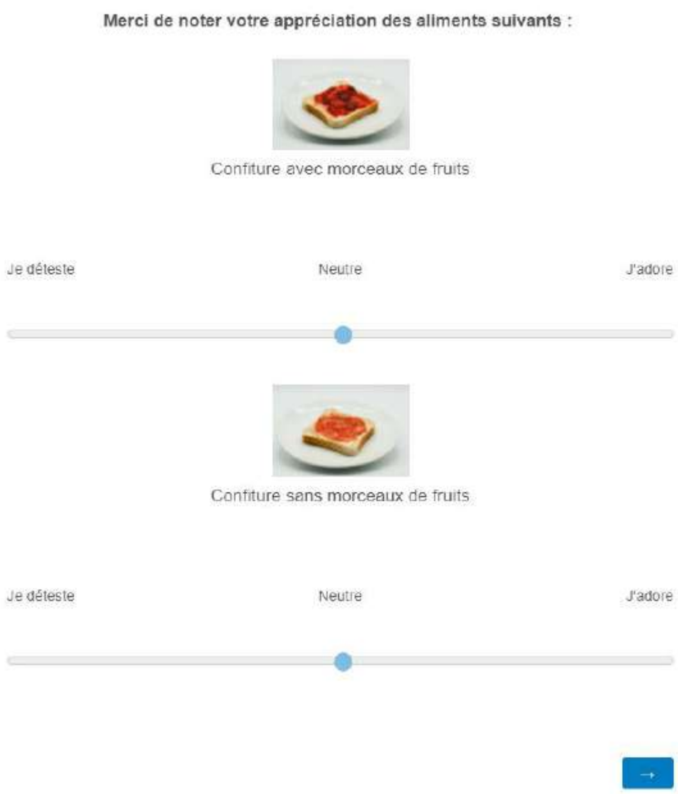


Figure 2.6. Example of a questionnaire to evaluate food preference

Table 2.4. Example of food pairs differing on somatoseosry properties

Sub modality	Pair A	Pair B
Texture (thickness)	Thin yogurt 	Thick yogurt 
Chemesthetic	Pasta without pepper 	Pasta with pepper 
Temperature	Warm soup (~40°C) 	Hot soup (> 60°C) 

2.1.1.3. Data analysis

For the objective measurements, comparison between the patient and control group were performed using an independent t-test, or chi-square test in case of categorical data (saliva parameters). For the subjective measurements, Two-way hierarchical clustering analysis was performed on patients' sensory perception to explore the different sensory profiles of patients. Subgroup analysis to compare the groups were performed using independent t-test or chi-square test, for nominal or ordinal data. Correlations were investigated between oral symptoms, sensory perception, and eating behaviour.

2.1.2. Study 2: Online survey with various cancer patients (Chapter 7)

As the overarching goal of this thesis is to understand somatosensory perception and eating behaviour of cancer patients, not limited to HNC, the investigations were extended to include various populations of cancer. Data collection consists of subjective measurement using self-reported questionnaires.

2.1.2.1. Participants

Various types of cancer patients and cancer survivors residing in France, Denmark, and the UK were eligible to participate. The following inclusion criteria were used: "1) individuals aged 18 or over, 2) had been diagnosed with cancer, 3) had received cancer treatment between 3 months and 5 years ago" (Chapter 7).

2.1.2.2. Methods

An anonymous online survey was distributed across France, Denmark, and the United Kingdom targeting all types of cancer patients. The survey included the same sets of questionnaires utilised in Study 1 (Chapter 6). The study was announced by the research partners, using diverse methods (online newsletters, mailing lists, and social networks of cancer organizations and support groups) to reach their national audiences.

2.1.2.3. Data analysis

To explore the different sensory profiles of patients, two-way hierarchical clustering analysis was performed on patients' sensory perception. Subgroup analysis to compare the groups were performed using one-way ANOVA, for continuous data, or chi-square test, for nominal or ordinal data. Multinomial logistic regression analysis was used to model the relationship between sensory-related food preference and independent predictors, whereas multiple linear regression was used to model the relationship between eating behaviour and independent predictors.

2.1.3. Study 3: Culinary development and focus group discussion (Chapter 8)

Integrating the findings of the first two studies, Study 3 aims to develop food concepts that are modified to address the sensory changes experienced by cancer patients. This study consists of three successive processes: 1) Culinary development of food concepts, 2) Focus group discussion (FGD), and 3) Consumer test on sensory-enhanced recipe. All of the process took place in Institut Lyfe Research Center, France.

2.1.3.1. Culinary development

These food concepts focused not only on taste and smell but also on the somatosensory aspects of food, including texture, chemesthesis, and temperature. The concepts were collaboratively developed during culinary session, integrating the findings of the studies as well as the creative input and ideas of the culinary chefs involved.

2.1.3.2. Focus group discussion

Following the development of the food concepts, a focus group discussion was conducted with a group of cancer patients. The aim of this discussion was to gather qualitative information regarding their sensory perception and food preferences. Additionally, the developed food concepts were evaluated by the patients during this session.

2.1.3.3. Consumer test

The food concepts were to be evaluated quantitatively in terms of hedonic acceptance among various cancer patients. Two food concepts were to be tested in a consumer study involving various cancer patients in which the protocol of the study is described in detail in Chapter 8.

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Chapter 3

Oral Somatosensory Alterations in Head and Neck Cancer Patients: An Overview of the Evidence and Causes

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Cancers. 2023, 15, 718. https://doi.org/10.3390/ cancers15030718

Abstract

Food-related sensory alterations are prevalent among cancer patients and negatively impact their relationship with food, quality of life, and overall health outcome. In addition to taste and smell, food perception is also influenced by somatosensation comprising tactile, thermal, and chemesthetic sensations; yet studies on oral somatosensory perception of cancer patients are lacking to provide patients with tailored nutritional solutions. The present review aimed to summarise findings on the oral somatosensory perception of head and neck cancer (HNC) patients and the potential aetiologies of somatosensory alterations among this population.

Subjective assessments demonstrated alterations in oral somatosensory perception such as sensitivity to certain textures, spices, and temperatures. Physiological changes in oral somatosensation have been observed through objective assessments of sensory function, showing reduced localised tactile function and thermal sensitivity. Changes in whole-mouth tactile sensation assessed using texture discrimination and stereognosis ability seem to be less evident. Available evidence indicated oral somatosensory alterations among HNC patients, which may affect their eating behaviour, but more studies with larger sample sizes and standardised assessment methods are needed.

Unlike other types of cancers, sensory alterations in HNC patients are not only caused by the treatments, but also by the cancer itself, although the exact mechanism is not fully understood. Prevalent oral complications, such as xerostomia, dysphagia, mucositis, and chemosensory alterations, further modify their oral condition and food perception. Oral somatosensory perception of cancer patients is an under-investigated topic, which constitutes an important avenue for future research due to its potential significance on eating behaviour and quality of life.

Keywords: sensory alterations; oral somatosensory perception; nutrition; eating behaviour; cancer treatment; quality of life

3.1. Introduction

Food-related sensory alterations are common side effects of head and neck cancer (HNC) and its treatments (Epstein *et al*., 2012; Sroussi *et al*., 2017; Talwar, 2010). It has adverse implications on nutritional outcomes and overall quality of life. In HNC patients, as well as in other types of cancers, sensory alterations are linked with reduced appetite and diminished food appreciation (Dalton *et al*., 2022; Hutton *et al*., 2007; Messing *et al*., 2021), altered food relationships (Watson *et al*., 2018; Ganzer *et al*., 2015), and changed patterns of food selection (Boltong *et al*., 2012; Ganzer *et al*., 2015). Sensory alterations have also been associated with reduced food intake (Brisbois *et al*., 2011; Hutton *et al*., 2007; Snchez-Lara *et al*., 2010), weight loss (Brisbois *et al*., 2011; Coa *et al*., 2015; Hutton *et al*., 2007; Jin *et al*., 2018) and declined quality of life (de Vries *et al*., 2018; Irune *et al*., 2014).

Taste and smell alterations are prevalent among HNC patients. Taste alterations were observed in 96% and 79% of radiated patients when assessed using subjective and objective methods, respectively (Gunn *et al*., 2021). Similarly, a greater prevalence of taste impairment was reflected by subjective measurements relative to objective measurements in a longitudinal study (Messing *et al*., 2021). Objective assessments of taste function involve measurement of sensitivity to basic taste (sweet, sour, salty, bitter, umami) solutions, whereas subjective assessments rely on self-reported questionnaires. In the latter, "taste" is often (inaccurately) used as a colloquial term to refer to food perception as a whole, although taste only represents the five basic taste aspects of food perception (Boltong & Campbell, 2013). The term taste is also often used to express the entire eating experience including the hedonic aspect (Boltong *et al*., 2012; Watson *et al*., 2018). On the other hand, smell alterations are underreported when measured using the subjective method (30–60%) compared to the objective method (0–100%) (Álvarez-Camacho *et al*., 2017). Therefore, the prevalent taste alterations experienced by cancer patients may not simply indicate alterations in the gustatory function but may encompass alterations in other dimensions of food perception.

Food perception is a complex sensation which involves a cross-modal interplay between gustation, olfaction, and somatosensation. In addition to taste molecules, various receptors in the oral cavity also detect somatosensory stimuli consisting of tactile, thermal, and nociceptive stimulations. These stimuli are relayed predominantly via the trigeminal nerve to the central nervous system where they are translated into the perception of texture, temperature, and chemesthesis (e.g., irritation or burning of chilli, cooling of peppermint, tingling of carbonated drinks). Taste and smell information is integrated with oral somatosensory information in the multimodal regions of the central nervous system to form a complete picture of food perception (Engelen, 2012; Simon *et al*., 2008; Spence, 2017). Research on multisensory perception provided ample evidence of the importance of oral-somatosensation in overall food perception and the interrelation of somatosensory with chemosensory processing (Engelen, 2012; Simon *et al*., 2008; Small, 2012; Spence, 2017). Hence, alterations in one of the sensory functions will modify the entire food perception and eating experience (Small, 2012).

Studies on sensory alterations among cancer patients predominantly revolve around taste and smell, yet knowledge about their oral-somatosensory perception is relatively unexplored. To define strategies for alleviating food-related issues of HNC patients, there is a need for a comprehensive understanding of their food perception. Qualitative studies observed that in addition to taste and smell alterations, patients also reported somatosensory-related complaints (Watson *et al*., 2018; McLaughlin & Mahon, 2014). However, it is unclear whether these alterations result from a perceptual origin related to the existing taste and/or smell alterations, or if there are physical and physiological changes in the somatosensory processing. The present paper aims to summarise the current evidence on the poorly understood oral somatosensory alterations in HNC patients and discuss some possible aetiologies.

3.2. Evidence of Oral Somatosensory Alterations in HNC Patients

Taste and smell alterations are well-documented symptoms experienced by HNC patients (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021; Messing *et al*., 2021). However, limited studies have investigated the oral somatosensory perception of HNC patients.

3.2.1. Subjective Perception of Oral Somatosensory Alterations in HNC Patients

Descriptive studies explored the eating behaviour of HNC patients using self-reported questionnaires and interviews; these studies not only explored their taste and smell perception, but also other aspects of food perception (Watson *et al*., 2018). HNC patients experienced various alterations related to oral somatosensory perception. A study on HNC survivors (n = 88) reported that they experienced higher sensitivity to spicy foods (27.3%), texture (27.3%), and temperature (2.3%), but 8% reported adding extra pepper and hot sauce to enhance the food (McLaughlin & Mahon, 2014). The majority of the participants (77.2%) were interviewed more than a year after their treatments, yet the sensory complaints continued to persist. Similar findings were also reported in a study in which patients complained about sticky mouthfeel, difficulties in consuming food with certain textures (dry and hard food), and altered sensitivity to spices due to oral pain (Watson *et al*., 2018). In a study through food-play workshops with HNC survivors, changes in chemesthetic-related experiences were also reported. Some patients developed an aversion while others developed a preference for spicy food (Crowder *et al*., 2020). These studies also highlighted that eating turned into an active and effortful activity due to oral pain and fear of choking, altogether leading to lowered quality of life.

Findings on subjective perception of oral somatosensory alteration in HNC patients provided valuable insights in defining the specific problems they faced, allowing potential optimisation of their meals. However, objective assessments of their oral somatosensory functions are necessary to characterise physiological changes and the causes of these changes. Thus, psychophysical methods have been used to gain insight into the changes in tactile and thermal sensations in HNC patients (**Table 2.1**). These objective assessment methods allow quantification of the relationship between physical stimuli and the perceptions they produce (Gabbiani & Cox, 2017).

3.2.2. Alteration of Tactile Functions in HNC Patients

The alteration of localised oral tactile sensation in HNC patients was studied by using a point-pressure test and a two-point discrimination test. Point-pressure test measures the lowest amount of pressure that can be detected, meanwhile the two-point discrimination test measures the minimum distance at which two points of contact can be perceived as two separate points. Studies employing these methods demonstrated lower localised tactile sensations in HNC patients receiving radiotherapy (Aviv *et al*., 1992; Bearelly *et al*., 2017) and surgery (Elfring *et al*., 2012) relative to the control group. In studies with HNC patients with hemiglossectomy, oral sensation on intact and reconstructed tongue regions were assessed and compared with a control group. It was revealed that the intact tongue region of patients had comparable tactile sensitivity with the control group; however, a significant difference was observed between the reconstructed tongue region and the control group (Loewen *et al*., 2010). Similar findings were shown by Kimata *et al*., revealing that patients who received adjunctive radiotherapy exhibited the greatest impairment in oral tactile sensitivity (Kimata *et al*., 1999).

In addition to the localised sensation, alteration of tactile functions was also observed using whole-mouth stimulation methods. One method is by measuring the ability to discriminate objects with different textures. HNC patients with hemiglossectomy showed a comparable texture discrimination ability with the control group (Loewen *et al*., 2010).

Table 3.1. Summary of psychophysical studies investigating oral somatosensory perception in HNC patients

Reference	Population	Tumour subsite, treatment	Sensory tests	Findings
(Aviv *et al*., 1992)	HNC patients 12-36 mo after RT (n=20), control (n=90). Cross-sectional	Tonsil or nasopharynx, RT	-Two-point discrimination (tongue and floor of mouth)	Radiated HNC patients were less sensitive in oral tactile acuity test than the control group
(Elfring *et al*., 2012)	HNC patients (n=30), control (n=30). Cross-sectional	Tongue, surgery with or without RT or CT	- Point pressure - Two-point discrimination - texture discrimination of resin - hot/cold discrimination with dental mirrors at 55 or 3 C - stereognosis	All patients with lingual nerve disruption exhibited significantly poorer outcomes in the point pressure test, 2-point discrimination test, and hot/cold discrimination test. No difference in texture discrimination, less conclusive for oral stereognosis
(Bearelly *et al*., 2017)	HNC patients (n=34), control (n=23). Cross-sectional	Oral cavity and oropharynx, RT	- Point pressure test (tongue, buccal mucosa, soft palate)	Elevated sensory threshold in patients compared to the control group
(Kimata *et al*., 1999)	HNC patients who received innervated (n=15) and noninnervated (n=13) free flaps reconstruction surgery. Cross-sectional study	Tongue, hemiglossectomy	- Point-pressure test - Two-point discrimination - Hot/cold discrimination with cotton swab	Sensory recovery was significantly better with innervated thigh flaps than noninnervated ones for all sensory modalities and better with innervated abdominis flaps than noninnervated ones for all modalities except thermal sensitivity.
(Loewen *et al*., 2010)	HNC patients with innervated free flap reconstruction surgery (n=8), control (n=8). Cross-sectional	Tongue, hemiglossectomy	- Point-pressure test - Two-point discrimination - Hot/cold discrimination with dental mirror - Texture discrimination with acrylic resin	Sensation of intact tongue tissue after reconstruction of the hemitongue did not differ from controls. Although some sensory ability was restored to patients' reconstructed tongue, differences existed between the patient group and controls. However, the texture discrimination ability was comparable with controls.
(Bodin *et al*., 2004)	HNC patients (n=27), control (n=20). Longitudinal (diagnosis, post-RT,6 mo post-surgery, 12mo post-surgery)	Oral or pharyngeal, RT and surgery	- Point pressure test - Hot/cold discrimination with metal rolls 44C and 28C	Deterioration of tactile and thermal sensitivity at 6mo after surgery
(Bodin *et al*., 1999)	HNC patients (n=31), control (n=20). Longitudinal (before RT, after RT, 6mo after surgery following RT, 12mo after surgery following RT)	Pharyngeal and oral cavity, surgery following RT	Stereognosis ability-hole size identification	The oral group did not show a decline in the hole size identification ability after radiotherapy but did 6mo after the surgery following RT. Deterioration was persistent for 1 year after. The pharyngeal group did not

				change performance in hole size identification at any time point.
(Bodin *et al.*, 2000)	HNC patients (n=30), control (n=20). Longitudinal (before RT, after RT, 6mo after surgery following RT, 12mo after surgery following RT)	Pharyngeal and oral cavity, surgery following RT	Stereognosis ability-shape identification	The mere existence of tumour did not affect shape-recognition abilities. RT caused some impairment of shape recognition while the combined effect of surgery following RT caused significant deterioration. No effect of tumour location was observed

RT: radiotherapy; CT: chemotherapy

Table 3.2. Overview of mechanisms in which cancer and its treatments alter oral somatosensation.

Mechanisms	Peripheral Level	Nerve Level
Cancerous Cells	Disruption of regeneration of sensory receptor cells Over-expression and sensitization of ion channels (e.g., TRPV1)	-
Tumour	Disruption of mucosal receptors on sites of tumour growth	Compression of sensory nerve on sites of tumour growth
Surgery	-	Impairment on sensory nerve
Radiotherapy	Damage to papillae and mucosal sensory receptors	-
Chemotherapy	Disruption of regeneration of sensory receptors	-

TRPV1: Transient receptor potential vanilloid type 1.

Similarly, only patients with lingual nerve cuts showed impairment in texture discrimination ability (Elfring *et al*., 2012). Texture perception requires innervation of the whole mouth; therefore, the intact tongue region can compensate for the impaired tongue region in providing the sensory feedback. The two studies also assessed oral stereognosis ability which is the ability to perceive and recognise the form of an object in the mouth using tactile cues, in the absence of visual information. It was shown that patients had compromised oral stereognosis ability compared to the control group (Loewen *et al*., 2010). Meanwhile, the study by Elfring *et al*. showed that impaired stereognosis ability was only observed in two subgroups of patients: the group with lingual nerve intact and the group with lingual nerve cable-grafted (Elfring *et al*., 2012). Although oral stereognosis is also considered to be a whole-mouth stimulation method, it was suggested that the assessment predominantly relies on sensory feedback from the tip of the tongue which is impaired in patients who underwent hemiglossectomy (Loewen *et al*., 2010).

The cross-sectional studies described above were conducted following cancer treatments; it is uncertain whether the alterations in tactile functions are caused as side effects of the treatments or if these alterations were present prior to the treatment. The longitudinal studies tend to show a trend of reduced tactile functions associated with treatments (Bodin *et al*., 1999, 2000, 2004). Localised tactile sensations of radiated patients were shown to decline 6 months after radiotherapy (Bodin *et al*., 2004). Similarly, stereognosis ability was not affected by cancer itself as demonstrated by the comparable performance in the shape-identification test between patient and control groups before treatments. Deteriorations were observed after radiotherapy, and further deteriorations were associated with the combined effect of surgery following radiotherapy in both oral and pharyngeal cancer groups (Bodin *et al*., 2000). Meanwhile, using a hole-size identification test, radiotherapy did not seem to affect stereognosis ability. Only the oral cancer group showed a decline in ability following radiotherapy and surgery (Bodin *et al*., 1999). It is possible that the two stereognosis methods (shape identification test and hole size identification test) may innervate different types or regions of mechanoreceptors and involve different mechanisms of tactile perception.

3.2.3. Alterations of Thermal Sensitivity in HNC Patients

Impaired thermal sensitivity was observed in HNC patients receiving surgery (Elfring *et al*., 2012). The intact tongue region of patients had comparable thermal sensitivity with the control group, however, a significant difference was observed between the reconstructed tongue region and the control group (Loewen *et al*., 2010). The two studies indicate that the impaired thermal sensitivity was associated with surgery however, it is not possible to confirm the causal effect of surgery due to the study design. In a longitudinal study, it was demonstrated that thermal sensitivity remain unchanged after radiotherapy but deteriorated 6 months after surgery following radiotherapy (Bodin *et al*., 2004). It could not be confirmed whether the impairment was due to the surgery itself or if it was a cumulative effect of radiotherapy and surgery.

Taken together, altered somatosensory perception is caused not only by perceptual changes, but also by physiological changes, as demonstrated by psychophysical studies. The studies showed altered thermal sensitivity and localised tactile functions, but findings for the whole-mouth tactile sensation (texture discrimination, stereognosis) are less conclusive. Altered sensitivity to chemesthetic sensations, such as spiciness (capsaicin), is not uncommon among HNC patients, but psychophysical studies using chemesthetic stimuli among cancer patients have not been reported. Therefore, it is not possible to ascertain whether the possible alterations in chemesthetic perception are attributed to physiological changes or merely a result of perceptual changes. More studies with larger sample sizes and standard assessment methods are needed to estimate the prevalence and the severity of somatosensory alterations. Studies associated the alterations with treatments rather than with the cancer itself, yet more longitudinal studies are needed to specify when exactly (and for how long) these alterations occur.

3.3. Aetiology of Oral Somatosensory Alterations in HNC

To understand the causes of oral somatosensory alterations in HNC, it is necessary to understand the physiology of sensory perception. The mechanism can be conceptually divided into three stages: stimulation, transduction, and interpretation. First, food (i.e., stimulus) that enters the mouth stimulates various sensory receptors. The stimulus is transduced into action potentials by ion-gated channels and conveyed to the central nervous system via the nerves. Finally, this leads to an encoding process of interpreting the action potential into ***perception*** which also involves integration of the different sensory modalities in the multimodal regions of the central nervous system (Chen, 2014). Altered somatosensory perception may occur if any of these processes are disrupted. Although the pathophysiology of oral somatosensory alterations is poorly understood, the following section outlines the evidence for a range of possible aetiologies. **Table 3.2** summarises the physical and physiological changes associated with cancer and its treatments on somatosensory perception.

3.3.1. Impact of Tumour and Cancer Inflammation on Oral Somatosensation in HNC Patients

The disease itself may alter oral somatosensory perception of HNC patients. As described in Section 2.2, the decline in tactile sensitivity appears to be associated with the treatments rather than the disease states, but there are possible mechanisms that the cancer itself may alter sensitivity to noxious stimuli. It can be a result of anatomical changes where the primary tumour compresses surrounding nerves responsible for conveying sensory information, or it damages the mucosal lining composed of sensory receptors (Togni *et al.*, 2021). It may also involve molecular changes, such as the activation of toll-like receptors and interferon during inflammation, which may disrupt normal regeneration of sensory receptor cells (H. Wang *et al.*, 2009).

Mechanistic studies using animal models have shown that HNC causes nociceptive and thermal sensitisation through various mechanisms. Oral squamous cell carcinoma can sensitise peripheral trigeminal nerve terminals via increased spontaneous firing of lingual fibres, which may result in altered sensitivity (Grayson *et al.*, 2019). Oral cancer may also alter sensitivity to capsaicin and noxious heat due to overexpression of protease-activated receptor-2, tumour necrosis factor-alpha, nerve growth factor, and adenosine triphosphate which can sensitise transient receptor potential vanilloid type 1 (TRPV1), an ion channel responsible for the transduction of capsaicin and noxious heat (Scheff *et al.*, 2022). Cancer cells also release a variety of pain mediators such as bradykinin, cytokines, chemokines, nerve growth factor, prostaglandins, and several vascular factors that can activate and sensitise nociceptive primary afferents, resulting in intense and spontaneous pain commonly experienced by HNC patients (Baral *et al.*, 2019; Lam & Schmidt, 2011; Sessle, 2006). These mechanistic studies provided indications of physiological changes that can contribute to altered chemesthetic sensitivity; however, there is insufficient published evidence to confirm this as there are no psychophysical studies on chemesthetic sensitivity in HNC patients.

3.3.2. Impact of Cancer Treatments on Oral Somatosensation in HNC Patients

In other types of cancer, it is suggested that the cancer in itself does not cause sensory alterations, but rather the cancer treatments are the cause (Boltong & Campbell, 2013). The treatments for HNC are surgery, radiotherapy, and chemotherapy. Each treatment has potential impacts on oral somatosensory perception of HNC patients through different mechanisms.

3.3.2.1. Impact of Surgery on Oral Somatosensation in HNC Patients

Surgery can result in anatomical changes; removal of cancerous tumours may include removal of key organs necessary for sensory perception such as partial or total removal of the tongue. If the surgery requires major tissue removal, such as jaw, skin, pharynx, or tongue, reconstructive surgery may be done to replace the missing tissue, however, it does not guarantee total restoration of oral sensations. Reduced localised tactile and thermal sensitivity have been observed following reconstructive surgery on the oral cavity or pharynx (Bodin *et al.*, 1999, 2000, 2004; Elfring *et al.*, 2012; Kimata *et al.*, 1999; Loewen *et al.*, 2010). This can be attributed to nerve impairment following the surgery, as patients who underwent reconstructive surgery with innervated flaps displayed greater sensory recovery compared with patients who received the non-innervated flaps (Kimata *et al.*, 1999). Similarly, patients with a cut lingual nerve demonstrated significantly lower tactile and thermal sensitivity, while those with an intact lingual nerve displayed comparable sensitivity to the control group (Bodin *et al.*, 1999, 2004; Elfring *et al.*, 2012). However, the texture discrimination ability, which requires whole mouth perception, was not affected (Elfring *et al.*, 2012; Loewen *et al.*, 2010).

Bartoshuk *et al*. summarised that anaesthesia or mild damage to chorda tympani resulted in elevated whole mouth sensitivity, both taste and somatosensation. This phenomenon is known as the *release of inhibition* or *disinhibitory effect* model which proposed that in normal conditions, the two sensory nerves (glossopharyngeal nerve and lingual nerve via chorda tympani) partially and mutually suppress one another. In the event of anaesthesia or mild damage to one of the nerves, the central suppression will be eliminated leading to a heightened sensitivity on the intact nerve, whereas extensive damage or damage to both nerves leads to diminished perception (Bartoshuk *et al.*, 2012).

3.3.2.2. Impact of Radiotherapy on Oral Somatosensation in HNC Patients

HNC patients receiving radiotherapy showed lower tactile sensitivity compared to controls (Aviv *et al.*, 1992; Bearelly *et al.*, 2017), however, the mechanism is unclear. A possible explanation is a reduction in the number of fungiform papillae which contain sensory receptors (Mirza *et al.*, 2008). In a longitudinal study, HNC patients showed reduced taste sensitivity 5 weeks after radiotherapy which improved in the 11th week (Yamashita *et al.*, 2006). The study also explored the underlying physiological mechanism using an animal model and showed that radiotherapy does not only damage the taste buds but also altered the papillae thickness. Another study lends credence to the theory of papillae damage as a pertinent factor in taste alterations following radiotherapy where it was found that the fungiform papillae of HNC patients with taste disorders have thicker epithelia compared with healthy subjects (Just *et al*., 2005). As fungiform papillae are also responsible for thermal and tactile perception (Mistretta & Bradley, 2021), it is likely that the damage will also influence somatosensory perception. The oral somatosensory decline can also be caused by radiotherapy-induced damage of mucosal sensory receptors located within the oral cavity and oropharynx (Bearelly *et al*., 2017).

3.3.2.3. Impact of Chemotherapy on Oral Somatosensation in HNC Patients

Studies investigating the effect of chemotherapy on oral somatosensory alterations among HNC patients have not been reported, since it is uncommon for HNC patients to receive chemotherapy as the only treatment. A popular hypothesis on the effect of chemotherapy on various cancers is that cytotoxic agents, such as cisplatin and doxorubicin, target rapidly dividing cancer cells by disrupting their proliferating activity, but it may also affect other rapidly dividing cells including sensory receptor cells (Togni *et al*., 2021; Zabernigg *et al*., 2010). Findings on the effect of chemotherapy on taste and smell alterations in various cancer patients are inconsistent and it is not possible to conclude whether the taste and/or smell changes following chemotherapy are attributed to perceptual or physiological changes (Boltong & Keast, 2012; Coa *et al*., 2015).

Another proposed mechanism is the inhibition of the hedgehog pathway, which regulates and restores taste buds (Murtaza *et al*., 2017). Inhibiting the hedgehog pathway using cancer drugs was shown to cause loss of taste buds, and consequently eliminating the relay of taste information to sensory nerves. It was expected that the inhibition will also affect somatosensory perception, however, it was shown that touch and temperature responses stayed intact (Mistretta & Kumari, 2017). This is because the hedgehog signal blocking only eliminates taste buds but leaves the soma and nerve fibres intact (Mistretta & Kumari, 2019).

3.3.3. Secondary Effects and Consequences of Treatment That Impact Oral Somatosensation in HNC Patients

There are several secondary effects and consequences that accompany cancer treatments. Some of these effects directly influence oral conditions and may impact the oral somatosensory perception. Xerostomia, dysphagia, mucositis, and chemosensory alterations influence different aspects of somatosensory perception.

3.3.3.1. Impact of Xerostomia on Oral Somatosensation in HNC Patients

Xerostomia, which refers to the perception of dry mouth, is a prevalent adverse effect reported by HNC patients. Damage to the salivary glands or the blood vessels and nerves supplying the glands causes a reduction in salivary flow. It usually occurs as a side effect of radiation and translates into sensations of dry mouth and thickened or stringy saliva (Logemann *et al*., 2003; Nascimento *et al*., 2019). It was reported that 64% of long-term HNC survivors and 91.7% of HNC patients receiving concurrent chemoradiotherapy experienced xerostomia (Dirix *et al*., 2006; Wang *et al*., 2021). Around 60% of patients developed xerostomia during radiotherapy which remained even after 2 years (Langius *et al*., 2010). Xerostomia is often accompanied by taste alterations, difficulty in speaking, increased risk of caries, oral pain, and burning sensation (Nascimento *et al*., 2019). Patients with xerostomia are also more likely to experience swallowing difficulties, food sticking in the mouth and/or throat, needing a water assist when swallowing, and a change in taste, which affects their overall sensory perception and food enjoyment (Logemann *et al*., 2003). Textural and mouthfeel sensations such as viscosity, stickiness, creaminess, and astringency were shown to be influenced by the amount, composition, and buffering capacity of saliva (Engelen & de Wijk, 2012). Therefore, it is expected that xerostomia will influence texture and mouthfeel perception of HNC patients.

3.3.3.2. Impact of Dysphagia on Oral Somatosensation in HNC Patients

HNC patients reported dysphagia or swallowing difficulty among the adverse effects. Dysphagia is a multifactorial condition which can be caused as a side effect of surgery and other cancer treatments (García-Peris *et al*., 2007). Cancer in the head and neck region may result in anatomical changes including reduction of pharyngeal or hypopharyngeal space, incontinence of oral cavity, and alteration of pharyngeal peristalsis. These collectively result in impaired swallowing function (Denaro *et al*., 2013). In addition, radiotherapy on the region was also shown to cause dysphagia. A longitudinal study reported that at the onset of the radiotherapy, 18% of patients developed dysphagia and this number increased to ~90% at the 5th week, which persisted after 2 years for ~20% of the patients (Langius *et al*., 2010). Another study reported that 78.7% of HNC patients receiving concurrent chemoradiotherapy developed dysphagia (Y. Wang *et al*., 2021). Dysphagia was associated with difficulties in eating certain food consistencies and difficulties in managing dry food, therefore a lot of these patients required texture-modified diets (García-Peris *et al*., 2007).

3.3.3.3. Impact of Mucositis on Oral Somatosensation in HNC Patients

Mucositis occurs in the majority of patients receiving radiotherapy on the oral and oropharyngeal mucosa. Mucositis is the lesion of oral mucosa specifically associated with cytotoxic cancer therapy (Shankar *et al*., 2017). In its mild form, mucositis presents as mucosal erythema accompanied by a feeling of a burning sensation but in its advanced stage, it presents as deep and painful ulcerations of oral mucosa. Mucositis occurs in the majority of patients receiving radiotherapy on the oral and oropharyngeal mucosa. It starts to develop 2 weeks following radiotherapy and by the 5th week, almost 90% of the patients had mucositis which persisted until 2 years in 60% of the patients (Langius *et al*., 2010). It could also be a side effect of chemotherapy via the proinflammatory cytokines (Shankar *et al*., 2017). Up to 74% of HNC patients receiving concurrent chemoradiotherapy developed mucositis (Wang *et al*., 2021). Patients with mucositis are more likely to be sensitive to spicy food and hot temperature (Sonis & Costa, 2003).

3.3.3.4. Impact of Chemosensory Alterations and Other Oral Complications on Oral Somatosensation in HNC Patients

Chemosensory alterations are common side effects experienced by HNC patients (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021). Taste and/or smell alterations may contribute to oral somatosensory alteration through the interrelation between the three modalities in the multimodal region of the central nervous system (Baral *et al*., 2019). A study showed that individuals with taste dysfunction also displayed lower tactile acuity, suggesting a possible alteration in their texture perception (Bogdanov *et al*., 2021). Other possible oral complications that may alter patients' somatosensory perception are summarised in **Table 3.3.**

Table 3.3. Summary of other oral complications influencing oral somatosensory perception.

Oral Manifestation	Description	Influence on Oral Perception
Osteoradio-necrosis (Aarup-Kristensen *et al*., 2019; Sroussi *et al*., 2017)	Condition of bone and mucosal breakdown after RT. Incidence rate is 4–37% in HNC patients. Mandible surgery and tooth extraction before RT, tobacco use, and treatment dose were associated with the development of ORN	Chronic oral pain and irritation
Temporo-mandibular disorder (Pauli *et al*., 2019)	A collective term to describe masticatory pain and dysfunction. A study showed that 68, 94, and 81% of HNC patients had TMD before, 6 mo after treatments, and 12 mo after treatments, respectively	Difficulty with certain textures, oral pain, and discomfort
Trismus (Loh *et al*., 2017)	Restricted mouth opening caused by radiation damage on the temporomandibular joint, resulting in scarring and fibrosis of pterygoid muscles and ligaments. Prevalence among HNC patients ranges from 5–86% depending on tumour location, treatment, and stage of treatment	Oral discomfort, difficulty chewing and swallowing certain food textures
Trigeminal Neuralgia (Jones *et al*., 2019)	A chronic syndrome is signified by recurrent facial pain in the dermatome of the trigeminal nerve (fifth cranial nerve). It is associated with nerve injury or lesion.	Heightened sensitivity to temperature and trigeminal sensation

Burning mouth syndrome	Constant burning sensation or discomfort. Multifactor, unclear aetiology may be caused by a damaged chorda tympani, nerve-stimulation phantoms	Intensified trigeminal sensations, sensitivity to hot temperature
Opportunistic infection (e.g., oral candidiasis) (Sroussi *et al.*, 2017; Villafuerte *et al.*, 2018)	Infection caused by fungi, bacterial, or viral due to disrupted homeostasis (RT, mucositis, hyposalivation) leading to dental caries (> 25% of patients receiving RT)	Mucosal pain, dysphagia, taste change, trigeminal sensitivity, sensation of coating in the mouth
Periodontal disease (Sroussi *et al.*, 2017)	Loss of tooth-supporting tissue and alveolar bones. Oral manifestation of RT through mucositis and changes in oral microbiome	Pain and infection in jaw bones, tooth loss, reduced sensitivity to particles (texture), chewing difficulty

Oral-somatosensory alterations in HNC patients are caused by the cancer itself and the various cancer treatments. Physical and physiological changes influence different levels of sensory processing. In relation to the secondary effects of cancer treatments, oral complications cause the oral cavity to be more sensitive to spices, noxious temperatures, and certain textures (e.g., dry and hard textures), consequently, limiting their food choices and food intake. To address these changes, it is beneficial to constantly monitor the oral hygiene of patients to prevent worsening oral conditions, provide saliva replacement or stimulants, and modify the sensory properties of meals based on their perception.

3.4. Conclusions and Future Perspectives

The current review focused on investigating oral somatosensory perceptions of HNC patients in relation to food perception. Causal relationships have not been established between sensory alterations and nutritional outcomes. However, mounting evidence has shown associations between sensory alterations on food perception and altered food intake. Sensory alterations, particularly taste and smell, have been associated with weight loss, reduced food intake, and diminished quality of life. HNC patients experience altered sensitivity to certain food textures, spices, and temperatures, but the experience varies between individuals. Objective assessments indicated reduced localised tactile function and thermal sensitivity, but findings on chemesthetic sensitivity and whole-mouth sensation are less conclusive. Collectively, it seems evident that altered food perception does not only constitute taste and smell aspects, but also the oral somatosensory aspect. However, more studies with larger sample sizes and standardised assessment methods are needed to estimate the prevalence of oral somatosensory alterations among HNC patients.

In the case of HNC, the cancer site may influence oral somatosensory perception through physiological changes due to its location directly involved in food intake. Mechanistic studies with murine models show indications that HNC triggers nociceptive sensitisation through various pathways. Additionally, cancer treatments influence sensory perception, including oral somatosensory perception, through disruption to the receptors and nerve impairment, but the exact mechanism is not fully understood. Oral complications following the disease and treatments, such as xerostomia, dysphagia, mucositis, and chemosensory alterations, result in altered oral conditions and perceptual changes which further influence patients' food perception.

Disorders of food perception are generally difficult to diagnose and treat as food perception is not only influenced by the physiological state of sensory systems, but also by the perceptual and hedonic aspects. Adding to the challenge, the multidimensionality of sensory perception makes it difficult to disentangle an eating experience into individual sensory modalities, yet the distinction is essential to address specific interventions. In addition to the aforementioned knowledge gaps, critical questions such as: the duration and severity of oral somatosensory alteration, its correlation with taste and smell alterations, as well as its significance on eating behaviour, remain to be investigated. Without enough knowledge in this area, there is a limited basis for developing appropriate assessment frameworks or potential interventions. The present review brings attention to the need for a multidisciplinary perspective, as food perception is one of the key drivers affecting eating behaviour. Food does not only carry physiological importance, but also conveys psychological and psychosocial values. Therefore, a comprehensive assessment of cancer patients' food perception will allow the development of personalised dietary interventions to provide a more pleasant eating experience and improve their quality of life.

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The current review focused on investigating oral somatosensory perceptions of HNC patients in relation to food perception. Sensory alteration in HNC patients does not only constitute taste and smell aspects, but also the oral somatosensory aspect. Further, oral complications following the disease and treatments contribute to modified eating experience.

From existing studies, two gaps in knowledge were identified. First, studies employing objective measurements were limited to tactile and thermal sensitivity. No studies were measuring chemesthetic sensitivity and measurements of texture sensitivity was assessed using non-edible tools. Second, studies either solely used subjective measurements or solely used objective psychophysical tests. However, it is important to understand that perception is a complex process that requires a combination of both objective and subjective measurements to fully comprehend the patients' experiences. To accurately investigate cancer patients' somatosensory perception, it is important to select the right tools and methodologies. The following chapter describes the existing methods to measure individual sub-modalities of somatosensory perception, including evaluation on their strengths and limitations.

Chapter 4

A Review of Assessment Methods for Measuring Individual Differences in Oral Somatosensory Perception

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Submitted

Abstract

While taste and smell perception have been thoroughly investigated, our understanding of oral somatosensory perception remains limited. Further, assessing and measuring individual differences in oral somatosensory perception pose notable challenges. This review aims to evaluate the existing methods to assess oral somatosensory perception by examining and comparing the strengths and limitations of each method. The review highlights the lack of standardized assessment methods and the various procedures within each method. Tactile sensitivity can be assessed using several methods, but each method measures different tactile dimensions. Also, further investigations are needed to confirm its correlation with texture sensitivity. In addition, measuring a single textural attribute may not provide an overall representation of texture sensitivity. Thermal sensitivity can be evaluated using thermal-change detection or temperature discrimination tests. The chemesthetic sensitivity tests involve either localised or whole-mouth stimulation tests.

The choice of an appropriate method for assessing oral somatosensory sensitivity depends on several factors, including the specific research objectives and the target population. Each individual method has its unique intended purpose, strengths, and limitations, so there is no universally superior approach. To overcome some of the limitations associated with certain methods, the review offers alternative or complementary approaches that could be considered. Researchers can enhance the comprehensive assessment of oral somatosensory sensitivity by carefully selecting and potentially combining methods. In addition, a standardised protocol remains necessary for each method and researchers are encouraged to document a clear and comprehensive protocol to allow for experiment replication and result comparison.

Keywords: Oral tactile; Texture; Temperature; Chemesthesis; Multisensory perception; Assessment methods

4.1. Introduction

Food perception is a complex process involving multimodal integration of the different sensory systems: gustatory, olfactory, and the somatosensory system (Small, 2012). While taste and smell perception have been extensively investigated as drivers of food liking, it is crucial to recognise the contributions of the somatosensory perception, such as texture, temperature, and chemesthesis, in shaping our preferences. Texture, for instance, plays a significant role in our perception and preference of food (Lukasewycz & Mennella, 2012; Tournier *et al*., 2007). Engelen and de Wijk (2012) suggest that individuals have specific expectations regarding the texture of different foods. When these expectations are met, there may be less emphasis on texture, yet a discrepancy between the anticipated and actual texture of the food will lead to rejection. Likewise, food temperature can significantly impact our overall perception (Foster *et al*., 2011; Steen *et al*., 2017). Additionally, chemesthesis, the perception of chemical or irritant sensations in the mouth, can also influence our preference. For example, the pungency of spicy foods can either enhance or deter our liking of certain foods (Byrnes & Hayes, 2015; Reinbach & Martinussen, 2010). These sensory perceptions become even more crucial in certain populations, such as in individuals with specific sensory impairments or eating difficulties.

Despite the significance of somatosensory perception in shaping our food preferences, it remains the least understood of the three sensory systems (Lundström *et al*., 2011). Somatosensation is composed of different sub-modalities (tactile involved in texture perception, thermal, and chemesthesis) and different methods have been developed to measure the individual sub-modalities: tactile and texture sensitivity, thermal sensitivity, and chemesthetic sensitivity. Unlike taste and smell perception, which have been extensively studied and for which standardized assessment methods have been established, there is currently no clear consensus on how to assess somatosensory responses. Assessing and measuring individual differences in oral somatosensory perception remains a challenging task for researchers aiming to understand and address issues related to oral somatosensory perception.

Appropriate assessment methods will not only contribute to the advancement of research on individual differences in oral somatosensation but also guide the development of new food products following the current trend of using sustainable alternative ingredients. Furthermore, it can help identify individuals who may experience difficulties with certain food textures, temperatures, or chemesthesis. This knowledge can guide nutrition interventions aimed at enhancing the overall food acceptance and quality of life for individuals with sensory-related challenges or eating difficulties. Therefore, the aim of this review is first to describe the various assessment methods used in the field, including the variations in procedures. Secondly, to evaluate the existing methods by examining their strengths and limitations.

4.2. Existing sensory methods to measure oral somatosensory perception

Various methods have been utilized to assess individual differences in the different sub modalities of oral somatosensory perception, each with their own distinct procedures. This section describes how these methods are employed to measure oral sensations related to food perception. In order to facilitate comparison and comprehension, a summary of the different methods and their variations in protocols is presented in **Table 4.1**. This compilation serves to underscore the heterogeneity of approaches and allows for an overview of the assessment methods currently employed in the field.

4.2.1. Tactile and texture sensitivity

Mechanoreceptors in the oral cavity play a crucial role in the perception of tactile sensations, which provide sensory feedback for important oral functions such as tongue positioning, chewing, manipulating food, and swallowing (Moayedi *et al*., 2021). Consequently, assessments of oral tactile function have been conducted in clinical studies to investigate physiological functioning of elderly or populations susceptible to eating difficulties (Elfring *et al*., 2012; Furukawa *et al*., 2019; Loewen *et al*., 2010). In addition, these mechanoreceptors are also responsible in the perception of food texture (Engelen *et al*., 2004; Kutter *et al*., 2011). Tactile and texture sensitivity can be measured using several different measures including point-pressure sensitivity, spatial acuity, stereognosis ability, and texture discrimination ability.

4.2.1.1 Point-pressure sensitivity

Oral tactile sensitivity can be assessed with the point-pressure test using von Frey filaments. These tools consist of a single filament which exerts light tactile stimulation at varying forces. Two existing procedures can be used for the test, the threshold procedure, and the signal detection procedure. In the threshold procedure, stimulus of different filament thickness is always presented until participant can detect the tactile stimulation. A thicker or thinner filament would be presented on the next stimulation, depending on the participant's ability to detect the touch. On the other hand, the signal detection procedure is based on the signal detection theory where true (signal) and false (noise) touch are presented. Using this procedure, participants are asked to indicate whether the stimulus is present or absent and their degree of certainty (certain/uncertain) (Cattaneo *et al*., 2020; Liu *et al*., 2021).

4.2.1.2. Spatial acuity

Spatial acuity measures an individual's ability to perceive a fine structure. Unlike the point-pressure sensitivity which assesses mechanical sensitivity on one point of the oral region, the spatial acuity involves a wider area of stimulation and a more complex innervation of several types of mechanoreceptors. It can be assessed using a two-point discrimination test, grating an orientation task, and a letter recognition task.

Two-point discrimination test

The two-point discrimination test is performed using an adjustable caliper or a specialized set of tools with two points that can be adjusted to varying distance (Furukawa *et al*., 2019). The test measures the minimum separations at which an individual can discern the two points of physical contact (Essick & Trulsson, 2008). Two different procedures can be used: the threshold procedure and the signal detection procedure. The threshold procedure involves adjusting the distance between the two points until the participant can certainly perceive them as two distinct points. Meanwhile, the signal detection procedure involves stimulating the tongue of blindfolded participant with either one or two points and they are asked to indicate how many points are perceived. Based on participant's response, the distance between the two points is adjusted on the next stimulation (Boliek *et al*., 2007; Fukunaga *et al*., 2005).

Grating orientation task

The grating orientation task uses a square grid engraved with evenly spaced ridges/grooves ranging from 1.25 mm to 0.20 mm (Appiani *et al*., 2020). The grids are applied on the tongue of blindfolded participant either vertically or horizontally. Participant is asked to indicate the orientation of the ridges and their degree of sureness.

2D- Letter recognition task

The letter recognition task involves the use of acrylic strips with a letter embossed on one side (A, I, J, L, O, T, U, or W) with different heights of 2-8 mm. The strips are applied on the tongue and participants are instructed to indicate the letter that they perceive. The presentation of sizes is adjusted based on participant's response.

Table 4.1. Summary of the different methods measuring oral somatosensory responses

Modalities	Assessment methods	Variation in methods	Application	Comments	Reference
Oral tactile	Point pressure test	- **Tools**: von Frey or Semmes Weinstein monofilament, aesthesiometer - **Procedures**: threshold, signal detection	**NC**: adults, children **C**: patients with HNC, BMS	Suitable for measuring nerve impairment; location of stimulation need to be specified	(Appiani *et al*., 2020; Bearelly *et al*., 2017; Bodin *et al*., 2004; Elfring *et al*., 2012; Kimata *et al*., 1999; Liu *et al*., 2021; Loewen *et al*., 2010; Santagiuliana *et al*., 2019)
	Two-point discrimination	- **Tools**: caliper, 2-Point discriminator wheel, tweezers, drawing compass - **Stimuli presentation:** static, moving - **Evaluation procedures**: threshold, signal detection;	**NC**: adults **C**: patients with HNC	Questionable validity on measuring spatial acuity, but may be a useful assessment tool of nerve impairment	(Aviv *et al*., 1992; Boliek *et al*., 2007; Elfring *et al*., 2012; Essick & Trulsson, 2008; Fukunaga *et al*., 2005; Furukawa *et al*., 2019; Kimata *et al*., 1999; Loewen *et al*., 2010)
	Grating orientation task	-**Tools**: grating size	**NC**: adults, children **C**: none	Suitable for measuring spatial tactile acuity but still underutilised	(Appiani *et al*., 2020; Lee *et al*., 2022)
	Letter recognition	**- Tools:** acrylic resins with different letters, modified version uses different shapes instead of letters	**NC**: adults, children **C**: patients with taste dysfunction	There are some disagreements about whether the task measures tactile spatial acuity or stereognosis ability	(Bangcuyo & Simons, 2017; Bogdanov *et al*., 2021; Essick *et al*., 1999; Lukasewycz & Mennella, 2012; Shupe *et al*., 2018)
	Stereognosis test	- **Tools**: confectionary alphabets, steel spheres of different sizes, acrylic resins with different shapes, discs with different hole sizes	**NC**: adults, children **C**: patients with HNC	Suitable for measuring sensitivity to whole-mouth oral sensation	(Bodin *et al*., 2000; Elfring *et al*., 2012; L. Engelen *et al*., 2004; Shupe *et al*., 2019)
Oral texture	Discrimination test- non-edible stimuli	- **Tools**: acrylic resin, metal bars	**NC**: adults **C**: patients with HNC	Suitable for investigating sensitivity to oral roughness	(Boliek *et al*., 2007; Linne & Simons, 2017)
	Discrimination test- edible stimuli	- **Dimensions of texture**: hardness, particle size, thickness - **Food models**: edible hydrogels, cream, quark, cream cheese, chocolate	**NC**: adults **C**: none	Suitable for investigating specific texture sensitivity, but results may not be easily interpolated to other aspects of texture	(Breen *et al*., 2019; Furukawa *et al*., 2019; Puleo *et al*., 2020; Santagiuliana *et al*., 2019)
Chemesthesis	Localised testing	- **Tools**: cotton swabs, filter paper, pipette - **Stimuli**: capsaicin, menthol	**NC**: adults (including elderly) **C**: none	Suitable for investigating thermal threshold sensitivity	(Fukunaga *et al*., 2005)

	Whole-mouth testing	- **Stimuli**: capsaicin, piperine, menthol; either as aqueous solution or mixed in food models - **Stimuli presentation:** sip-and-spit, sip-and-swallow - **Evaluation procedures**: detection threshold, difference testing, intensity rating	**NC**: adults (including elderly) **C**: none	A simple and rapid method to screen for severe impairment in oral sensation.	(Roukka *et al*., 2021; Yang *et al*., 2022)
Temperature	Thermal-change detection test	- **Tools**: temperature-controlled thermodes	**NC**: adults **C**: patients with BMS, oro-facial pain	Suitable for investigating regional variation in case of localised damage in oral sensation	(Baad-Hansen *et al*., 2015; Rolke *et al*., 2006)
	Temperature discrimination	- **Tools**: dental or pharyngeal mirror, test tube, water, metal rolls - **Temperatures**: 10 and 50ºC; 3 and 55ºC; 28 and 44ºC	**NC**: adults **C**: patients with HNC	Suitable for investigating food perception during normal eating/drinking	(Bodin *et al*., 2004; Boliek *et al*., 2007)

BMS: burning mouth syndrome; C: clinical population; HNC: head and neck cancer; NC: non-clinical population

4.2.1.3. Stereognosis ability

Stereognosis is the ability to perceive and recognize the form (shape, size) of an object in the mouth using tactile cues, in the absence of visual and auditory information. It measures the tactile function of the entire oral cavity rather than the tongue alone (Sivapathasundharam & Biswas, 2020). The stereognosis ability can be assessed using different tools of three-dimensional objects, varying in shapes, sizes, and materials. Edible stimuli such as confectionary alphabets and non-edible stimuli such as acrylic with different shapes, steel spheres with different sizes, and acrylic discs with different hole sizes have been used (Bodin *et al*., 1999, 2000; L. Engelen *et al*., 2004; Shupe *et al*., 2019). Participants are presented with the tool and are instructed to indicate the shape or size. These studies measured stereognosis ability in healthy adults, children, and cancer patients.

4.2.1.4. Texture discrimination ability

Studies focused on understanding how individuals perceive and respond to certain textures in relation to eating behavior often directly assess the individual texture discrimination ability. This assessment involves providing stimuli varied in one textural dimension, for example stimuli with different levels of hardness, thickness, or particle size. Several different forms of stimuli have been documented, examples include physical tools such as spheres of textured resin attached to small rods (Boliek *et al*., 2007); as well as edible stimuli such as hydrogels made of agar or xanthan solution (Furukawa *et al*., 2019); model food such as cocoa-based cream (Puleo *et al*., 2020), quark and cream cheese (Santagiuliana *et al*., 2019), and chocolate (Breen *et al*., 2019). The evaluation procedure used in the studies include intensity scaling procedure (i.e. evaluating intensity of the given sensory attribute on a visual scale) and paired comparison procedure (i.e. identification which of the pairs have higher intensity of the given sensory attribute).

4.2.2. Chemesthetic sensitivity

Chemesthetic sensitivity is a sensory sensitivity to direct chemical irritants and have been assessed using chemesthetic compounds that elicit pungency or cooling sensation such as capsaicin and menthol, respectively (Cardello & Wise, 2008; Rentmeister-Bryant & Green, 1997; Roukka *et al*., 2021). Oral chemesthetic sensitivity can be assessed using the localized test and the whole-mouth test. Localized test involves stimulation on a distinct part of the tongue either with a filter paper disk or cotton swabs impregnated with a chemesthetic compound (Cliff & Green, 1996). Another procedure is to apply chemesthetic solutions on distinct part of the tongue using pipette (Epstein *et al*., 2019).

The whole-mouth test involves participants sipping aqueous solutions and holding it in their mouth for a few seconds, then they are instructed either to expectorate (sip and spit procedure) or swallow depending on the study design (B. G. Green & McAuliffe, 2000). Commonly used evaluation procedures are the detection threshold procedure (i.e. identifying the lowest concentration for which the participant reported the existence of stimuli); the difference testing procedure (i.e. comparing stimuli with control); and the rating procedure (Fukunaga *et al*., 2005; Roukka *et al*., 2021; Yang *et al*., 2022).

4.2.3. Thermal sensitivity

The methods to assess thermal sensitivity are the thermal-change detection and the temperature discrimination method. The thermal-change detection test is part of the Quantitative Sensory Testing (QST), a standardized protocol to assess somatosensory function in a clinical setting (Rolke *et al*., 2006) developed by the German Research Network on Neuropathic Pain. In the thermal-change detection test, a temperature-controlled thermode is used to stimulate the tongue. The surface temperature of the tongue can be transiently increased or decreased with a square Peltier thermode. The test starts with a neutral temperature and then increased or decreased until the participant perceives a noticeable change in temperature (Rolke *et al*., 2006).

The temperature discrimination method involves the use of tools submerged in two different temperatures of water (hot or cold). The tool is applied on the tongue and blindfolded participants are instructed to discriminate whether the stimulus is hot or cold. The tools used can be metal rolls, test tubes, and dental mirrors; and the water temperatures used in previous studies are reported to be 55-60°C for hot and 3-4°C for cold (Bodin *et al*., 2004; Boliek *et al*., 2007).

4.3. Choosing the right assessment method for measuring oral somatosensory perception

When selecting an assessment method to measure oral somatosensory perception, several factors should be considered. The method should demonstrate good validity to accurately measure the intended objective or specific research question. The differences in procedure among the various methods should be considered, as this may impact the reliability and feasibility of the assessment. Furthermore, it is important to consider the characteristics of the target population, as some methods may be more suitable for certain age groups or specific populations. The following section compares the different methods and procedures to provide guidance on choosing the most appropriate assessment method by considering the aforementioned factors.

4.3.1. Tactile and texture sensitivity

Overall, the methods to measure oral tactile sensitivity are generally practical as the tools are reusable and do not require complex set up; they do not demand laborious preparation and are affordable for routine use. It is important to note that each of these methods measures different aspects of oral tactile sensitivity. The point-pressure test and the two-point discrimination test only stimulate one distinct point so does not represent whole-mouth sensation. They are associated to the slowly adapting superficial mechanoreceptor (SA1, Merkel cells) (Tong *et al*., 2013).

The point-pressure test is among the most widely used methods to measure tactile sensitivity and has been tested with healthy adults and children (Appiani *et al*., 2020; Bearelly *et al*., 2017; Cattaneo *et al*., 2020), as well as in clinical investigations among cancer patients to measure orosensory reinnervation following surgical reconstruction of the tongue or the oral cavity (Bodin *et al*., 2004; Elfring *et al*., 2012; Kimata *et al*., 1999; Loewen *et al*., 2010). Regarding the choice of procedure, a study using the threshold procedure observed a floor effect even with the thinnest available monofilament of 0.008 g (Santagiuliana *et al*., 2019). This suggests that the procedure may not accurately represent the absolute detection threshold, which is the lowest magnitude that the participant can detect. To overcome the limitation, an aesthesiometer can be used, which can provide forces as low as 0.0044 g (Liu *et al*., 2022). Alternatively, the signal detection procedure can be used as R-index is calculated to estimate the probability of a participant identifying correctly a real signal against the noise (Appiani *et al*., 2020; O'Mahony, 1992).

The two-point discrimination test has been used in adults and in clinical investigations with cancer patients to assess sensory innervation (Aviv *et al*., 1992; Elfring *et al*., 2012; Kimata *et al*., 1999; Loewen *et al*., 2010). However, the threshold procedure of this method has been scrutinized in terms of test-retest reliability due to inconsistencies over repeated testing on the same individuals (Craig & Johnson, 2000). Furthermore, investigations on cutaneous sensations observed that the signal detection procedure induced nonspatial cues that enable participants to discriminate between one and two points. For example, one can easily distinguish one point from two points as the former feels sharper. Hence, it is posited that the two-point discrimination test is not a valid measure of spatial acuity and advised alternative method such as the grating orientation task (Craig & Johnson, 2000).

The grating orientation task activates both rapid and slowly adapting mechanoreceptors over a wider area (Appiani *et al*., 2020; Lee *et al*., 2022). To date, there are few reported studies utilizing the grating orientation task to assess spatial acuity in the oral region (Appiani *et al*., 2020; Lee *et al*., 2022) and its use in clinical populations has not been reported. The grating orientation task addresses the limitations of the two-point discrimination test by using stimuli with identical spatial structures, thus avoiding the possible nonspatial cues (Craig & Johnson, 2000). However, it is argued that lateral scanning and exploratory movements are necessary to assist participants in extracting relevant spatial cues, yet this method limits these actions and rely on static evaluation (i.e. participants are not allowed to move the tongue) (Essick *et al*., 1999). An alternative method to address this limitation is by using the 2D-letter recognition task, where participants are encouraged to dynamically examine the stimuli.

The 2D-letter recognition task has been used to assess spatial acuity of healthy adults, children, and patients with taste dysfunction (Bangcuyo & Simons, 2017; Bogdanov *et al*., 2021; Essick *et al*., 1999; Lukasewycz & Mennella, 2012). Nonetheless, issues were raised that 2D-letter recognition task may be unsuitable for those who are unfamiliar with Latin alphabet (Liu *et al*., 2022). Moreover, it was argued that not all letters would be equally identifiable, for instance letter 'I' would be relatively easier to identify than 'W' (Lukasewycz & Mennella, 2012). An adaptation using 2D-geometrical shapes instead of letters may potentially address these limitations and has been tested among healthy adults and elderly (Shupe *et al*., 2018).

While the aforementioned methods are useful measures for indicators of physiological function, they may not be suitable for measuring tactile sensitivity as a proxy measure of food texture sensitivity. Texture perception involves innervation of the entire oral cavity, whereas the stimulated area of these methods is isolated on the tongue. The stereognosis test can potentially reflect texture sensitivity as it innervates the entire oral cavity. It has been tested among healthy adults, children, and cancer patients (Bodin *et al*., 1999, 2000; L. Engelen *et al*., 2004; Shupe *et al*., 2019). However, there has not been conclusive evidence to support the correlation between stereognosis ability and food texture sensitivity. Moreover, the heterogeneity of tools used in different studies lead to varying results (Bodin *et al*., 1999, 2000). Furthermore, age and dental status have significant effects on oral stereognosis ability and should be considered as confounding factors (R. Jacobs *et al*., 1998).

The most valid method that may reflect texture sensitivity is to directly measure the texture discrimination ability. However, the use of texture discrimination test with inedible stimuli is relatively rare and limited only to roughness sensitivity (Elfring *et al*., 2012; Loewen *et al*., 2010). It is unclear whether the measurements using these inedible stimuli are representative of food roughness sensitivity, l*et al*one other dimensions of food texture sensitivity. However, the use of inedible stimuli has its own advantages, namely its practicality and ease of use for routine assessments as the tools can be reused and do not require additional preparation. The use of the texture discrimination test with edible stimuli allows full manipulation of the stimuli, thus may be the closest representation of food texture perception and individual's food texture sensitivity. The versatility of the stimuli allows each experimenter to develop their own prototype of food models suited to their study objectives. However, this creates heterogeneity in study designs, thus there is no standardized stimuli for comparison between studies. Another limitation concerns the limited number of samples that can be tested due to fatigue and post-ingestive effects.

Unlike taste and smell perception which have been directly attributed to specific gustatory and olfactory receptors, the neurological principles of translating information detected by various mechanoreceptors into texture perception is considerably less understood (Lina Engelen & de Wijk, 2012). Texture perception involves a multifaceted nature and dynamic process integrating a multitude of neural inputs from the receptors spread over the entire oral cavity (Lina Engelen & de Wijk, 2012; Furukawa *et al*., 2019; Liu *et al*., 2022). Therefore, assessing a single dimension of tactile function or a single textural attribute may not fully represent overall food texture sensitivity. Combinations of the methods and assessment of several textural attributes should be done to obtain a comprehensive depiction. Measurement techniques, individual variability (sex, age, fungiform papillae density, physiological and pathological factors), and dimension of texture are the contributing factors to the variability in oral tactile sensitivity and its relation to texture perception and preference (Liu *et al*., 2022). To fully understand texture perception, measurements related to oral processing ability such as salivary function, chewing ability, and bite force should also be considered.

4.3.2. Chemesthetic sensitivity

There are no standardized chemical compounds and concentrations for the chemesthetic sensitivity tests. Moreover, the choice of methods largely depends on the study objectives. The use of localized testing would benefit studies whose objectives are to investigate regional variation of oral sensitivity and to screen possible neural damage. This method limits potential irritations to the stimulated area, but precise and consistent placement of stimuli is necessary for all participants, requiring experimenter training.

For studies aiming to mimic real eating or drinking experiences, whole mouth testing is recommended. Chemesthetic compounds have slow onset and decay (B. G. Green, 1991, therefore in studies where the chemesthetic compounds are dissolved in a food model (Lyu *et al*., 2021; Piochi *et al*., 2021), swallowing the stimuli may present a post-ingestive effect and difficulty in removing residual sensation. To limit these effects, the sip-and-spit procedure is preferable (B. Green, 2001). For the same reason, the choice of evaluation procedure is also crucial. The threshold and discrimination testing procedure would require several samples to be tested. Therefore, it should be conducted over multiple sessions. On the other hand, the intensity rating procedure does not require many samples to be evaluated but may require a precise instruction on the use of scale.

Temperature control is critical for testing with chemesthetic compound due to the overlap of TRP channels for temperature and chemesthesis (Christopher T. Simons *et al*., 2019), which may result in an interaction effect (B. G. Green, 1985). An ideal serving temperature of taste solutions should be 35 to 37°C (B. Green, 2001). In addition, it is necessary to provide sufficient rating time and interstimulus interval between different samples (B. G. Green, 1991). Both the localized and whole-mouth stimulation methods have been performed in healthy adults and elderly (Fukunaga *et al*., 2005; Roukka *et al*., 2021; Yang *et al*., 2022) but applications in the clinical setting have not been documented.

4.3.3. Thermal sensitivity

The thermal-change detection test is primarily used for cutaneous sensations and has limited application in oral sensations. Due to its constant yet subtle changes in temperature, it measures thermal sensitivity at a higher resolution, but the test requires constant level of participant concentration and higher level of cognitive processing. Depending on the duration of the test, this may cause fatigue for children, elderly or clinical populations. As there are no simple devices to conduct the test (Rolke *et al*., 2006), the thermode may not be affordable especially if it is not meant for a routine or repeated use.

On contrary, the temperature-discrimination test measures the supra-threshold level, therefore provides a lower resolution as only two extreme temperatures (hot/cold) are tested. The relevance of this test is to detect neural damage or severe disturbances in the oral sensations of patients with orofacial pain, head and neck cancer, or burning mouth syndrome (BMS) rather than comparing individual sensitivity in the general population. Compared to the thermal-change detection method, it is a rapid, simple, and affordable tool to screen clinical populations who have altered thermal sensitivity (Bodin *et al*., 2004). To improve the discrimination and resolution of the test, it is suggested to include more temperature intervals between the two extremes, rather than relying solely on the two temperatures. Both methods have been performed in the clinical setting in relation to assessing sensory re-innervation function following surgical procedures in the oral cavity.

4.4. Conclusion and perspectives

Research has been conducted to examine different sub-modalities of oral somatosensation, including tactile and texture sensitivity, chemesthetic sensitivity, and thermal sensitivity. However, there is a lack of standardised assessment methods and various procedures exist. Tactile sensitivity can be assessed using various methods, ranging from localised to whole-mouth stimulations, but each method clearly measures different dimensions of tactile function. Measuring a single textural attribute may not provide a comprehensive representation of overall texture sensitivity due to the multifaceted nature of texture perception. Thermal sensitivity can be evaluated using thermal-change detection or temperature discrimination tests. The chemesthetic sensitivity tests involve either localised or whole-mouth stimulation tests.

There is no best method for assessing oral somatosensory sensitivity, as each method has different intended purposes, strengths, and limitations. If the selected method has limitations, alternative or complementary methods suggested in the review can be considered to address the issues. By carefully considering these factors, researchers can choose the most appropriate assessment method for their specific research objectives and target population. Nevertheless, it remains a necessity for a standardised protocol for each method, or that researchers should document a concise and comprehensive protocol to enable replication of the experiment and facilitate comparison of the results among other researchers. In addition to these objective measurement methods, information on their subjective perception should be examined for a more comprehensive depiction of their food-related sensory perception in relation to eating behaviour.

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Various methods are available for measuring the different sub-modalities of somatosensory perception. However, there is no universally standardised assessment method and , and the different studies showed variation in procedures. Therefore, there is no definitive "best" method for evaluating oral somatosensory sensitivity, as each method has its own specific objectives, strengths, and limitations. The current review helped to assess and identify the most suitable methods to be employed in the subsequent clinical study involving HNC patients. The methods used in the following chapter include point-pressure test, texture discrimination test with edible sample, temperature discrimination test, and whole-mouth stimulation test.

Chapter 5

Oral Somatosensory Alterations and Salivary Dysfunction in Head and Neck Cancer Patients

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Support Care Cancer 31, 627 (2023).

Abstract

Purpose: Patients with head and neck cancer (HNC) are at high risk of malnutrition due to eating difficulties partly mediated by sensory alterations and salivary dysfunction. Clinical studies have mostly focused on taste and smell alterations, while changes in oral somatosensory perception are largely understudied. The study aimed to investigate oral somatosensory (tactile, texture, chemesthetic, and thermal) responses and salivary functions of HNC patients in comparison to healthy controls.

Methods: A cross-sectional study was conducted using psychophysical tests in HNC patients (n=30) and in age- and gender-matched control subjects (n=30). The tests included measurements of point-pressure tactile sensitivity, whole-mouth chemesthetic stimulation, food texture discrimination, and temperature discrimination. Salivary functions, including hydration, saliva consistency, pH, volume, and buffering capacity were also evaluated.

Results: HNC patients demonstrated significantly lower chemesthetic sensitivity (for medium and high concentrations, $p< 0.05$), thermal sensitivity ($p = 0.038$), and salivary functions (p=0.001). There were indications of lower tactile sensitivity in the patient group ($p = 0.101$). Patients were also less sensitive to differences in food roughness ($p = 0.003$) and firmness ($p = 0.025$).

Conclusion: This study provided evidence that sensory alterations in HNC patients extend beyond their taste and smell. The measurements demonstrated lower somatosensory responses, in part associated with their reduced salivary function. Oral somatosensory alterations and salivary dysfunction may consequently impart the eating experience of HNC patients. Thus, further investigations on food adjustments for this patient group seem warranted.

Keywords: Oral somatosensation; salivary function; head and neck cancer; oral tactile sensitivity; food texture sensitivity; thermal sensitivity; chemesthetic sensitivity

5.1. Introduction

An estimated 747,000 new cases of head and neck cancer (HNC) occurred worldwide in 2020 (Sung *et al*., 2021). Due to the cancer site, HNC patients are at higher risk of malnutrition, with the prevalence of malnutrition among this population estimated to be 74% (Citak *et al*., 2019). HNC patients experience physiological changes that contribute to eating difficulties such as food-related sensory alterations and salivary dysfunction (Farhangfar *et al*., 2014; Kathrine *et al*., 2021; Wang *et al*., 2021). These side effects were experienced by 70-90% of HNC patients undergoing radiotherapy and continued to persist in some of the patients 1-2 years post-treatment (Galaniha & Nolden, 2022; Langius *et al*., 2010; Wang *et al*., 2021). These altogether influenced their eating experience, resulting in weight loss and a negative impact on their quality of life (Brisbois *et al*., 2011; García-Peris *et al*., 2007; Hutton *et al*., 2007).

Altered sensory perceptions are associated with diminished eating pleasure, loss of appetite, and changes in food choices (Dalton *et al*., 2022; Ganzer *et al*., 2015; Hutton *et al*., 2007). Sensory perception is a multimodal process involving the gustatory/taste, olfactory/smell, and somatosensory systems (Small, 2012). The somatosensory system comprises multiple sub modalities detecting and translating mechanical, thermal, and nociceptive stimulations throughout the oral epithelium into the perception of texture, temperature, and chemesthesis (e.g. spiciness of chili, cooling of mint) (Chen, 2014; Hollins, 2010). In addition, saliva serves several functions that influence patients' eating experience including food flavour release and perception, facilitation of chewing and swallowing, lubrication, and cleansing of the oral cavity (Haahr *et al*., 2004; Pedersen *et al*., 2002).

Studies among HNC patients have focused on examining chemosensory alterations (i.e., taste and smell). The prevalence of taste alterations among radiated HNC patients was estimated to be 79%, with the prevalence of long-term alterations at 23-53% while smell alterations were reported by 30-60% of HNC patients (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021). These reported changes in taste and smell are clear indicators of orosensory changes and may also relate to changes in somatosensory perception and mouthfeel as they share similar oral tissues. A few studies have reported on one or two sub modalities of the somatosensory mechanisms (Bodin *et al*., 2004; de Groot *et al*., 2020; Loewen *et al*., 2010). Others reported on altered perceptions of food texture, temperature, and chemesthetic sensations and their influence on the eating behaviour of HNC patients using subjective measurements (Burges Watson *et al*., 2018; Crowder *et al*., 2018). The present study aimed to reveal the extent to which changes in oral somatosensory perception and salivary functions occur in HNC patients using a set of objective sensory measurements. These findings will provide further insights into the underlying mechanisms of altered food perception in this patient group.

5.2. Materials and methods

5.2.1. Study design and setting

The study was a part of a cross-sectional study (Somestalim) conducted in accordance with the Declaration of Helsinki, approved by the Personal Protection Committee of Ile-de-France (RCB N° 2021-A02961-40), and registered to the Clinical Trials Registry (NCT05272917). The patient group consisted of HNC patients recruited during their outpatient consultations at the Hospices Civils de Lyon (France) by clinical research associates or physicians. The control group consisted of healthy volunteers matched in terms of sex and age, recruited from Ecully (France) through advertisements via flyers and newsletter e-mails. Informed consent was obtained from all participants. The present paper was written in accordance with the STROBE guidelines (Supplementary Table S1).

5.2.2. Study participants

Patients were eligible if they fulfilled the following criteria: age between 18-70 years old, diagnosed with tumours of the upper aerodigestive tract (including oral cavity, pharynx, and larynx), salivary glands, maxillary sinuses, or nasopharynx, treated by radiotherapy alone in combination with systemic treatment, surgery, or both. The radiotherapy must have been completed between 4 months to 5 years ago. Controls were healthy volunteers matched in sex and age (±5y). For all participants, the exclusion criteria were as follows: pregnant or breastfeeding, known food allergy or intolerance, inability to swallow soft food, restricted mouth opening (trismus), and a lack of tongue mobility (unable to extend the tongue or large tongue resection).

5.2.3. Outcomes

The outcomes were comparisons of somatosensory responses (tactile, texture, chemesthetic, and thermal sensitivity) and salivary function between HNC patients and controls.

5.2.4. Study procedure

The study consisted of a single visit (~1.5h) which took place at Croix Rousse and Lyon-Sud hospitals (Lyon, France) for the patient group and at the Institute Paul Bocuse research centre (Ecully, France) for the control group, between May 2022 and April 2023. Participants were informed to refrain from eating, drinking, and smoking 1 hour before the visit. The visit commenced with a verification of the eligibility criteria followed by a detailed explanation of the procedure **(Figure 5.1)**. Then, participants were asked to complete their sociodemographic information and medical history. Participants performed the salivary function test, followed by the different psychophysical tests**.**

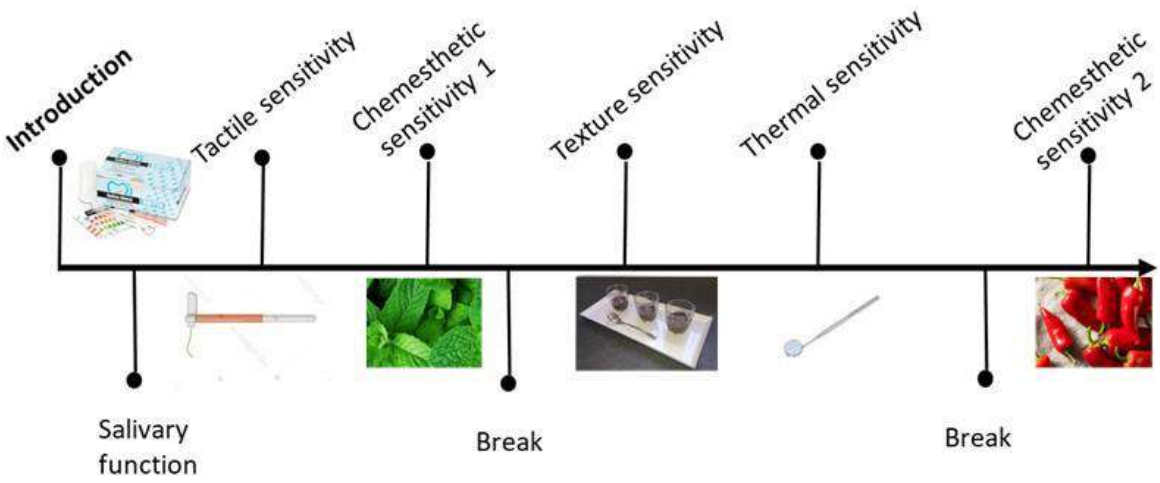

Figure 5.1. Overview of the study visit, including the order of tests.

5.2.4.1. Analysis of salivary function

The salivary function test was performed using Saliva-Check BUFFER kit (GC Europe, Sucy-en-Brie, France). The test aimed to measure hydration, saliva consistency, pH, volume, and buffering capacity. All tests were performed according to the instructions of the manufacturer. First, the unstimulated saliva was analysed. Hydration was assessed, after drying the labial mucosa with gauze and subsequent measuring of the time taken for new saliva droplets to appear (< 60s: normal, > 60s: low). The consistency was classified as clear/watery, frothy/bubbly, or sticky/frothy following visual observation of saliva at the back of the mouth. The pH of unstimulated saliva was determined using pH paper (pH 6.8-7.8: normal, 6.0-6.8: moderately acidic, 5.0-5.8: very acidic). Stimulated saliva was then analysed. Stimulated saliva flow corresponds to the volume of saliva collected for the 5 minutes during which patients chewed a paraffin tablet (> 5 ml: normal, 3.5-5 ml: low, < 3.5 ml: very low). The buffering capacity was determined by depositing stimulated saliva on a test strip provided in the kit.

5.2.4.2. Analysis of oral tactile sensitivity

The tactile sensitivity on the tongue was determined with a point-pressure test using Von Frey monofilaments (Aesthesio®, San Jose, USA). The test was performed with three different sizes of monofilaments representing forces of 0.008, 0.02, and 0.04 g (Cattaneo *et al*., 2020).

Participants were blindfolded and asked to respond to whether they could detect a touch on the tongue apex. A balanced number of true and false touch exposures (5 each) were randomly presented for each monofilament. In addition to identifying the tactile stimulus (present/absent), participants were asked to indicate the degree of certainty of their response (sure/unsure). R-index was calculated as an estimated probability of correctly identifying the target touch stimulus from the presentation of the blank stimulus (no touch), representing an index of their tactile sensitivity (Cattaneo *et al*., 2020).

5.2.4.3. Analysis of chemesthetic sensitivity

Preparation of menthol and capsaicin solutions

Menthol and capsaicin were selected to evaluate sensitivity to cooling and pungent sensations, respectively. The menthol and capsaicin solutions were made from single stock solutions. L-menthol (≥99%, Sigma-Aldrich, Steimheim, Germany) and natural capsaicin (#360376, Sigma-Aldrich, Steimheim, Germany) were first dissolved in 96% ethanol (EMSURE®, Sigma-Aldrich, Steimheim, Germany). These stocks were diluted with water to reach the final concentrations (**Table 5.1**) and supplemented with ethanol to standardise all stimuli to equal ethanol concentration of 0.5% (v/v) for menthol and 0.1% (v/v) for capsaicin, as ethanol may also elicit chemesthetic stimulation. The preparation procedure including the concentrations referred to a previous study (Nolden & Hayes, 2017) followed by a series of pilot tests.

Table 5.1. Sample series for chemesthetic sensitivity test with menthol and capsaicin solutions.

Chemesthetic modality	Chemical compound	Concentrations (ppm)		
		Low	Medium	High
Cooling	Menthol	7.8	31.3	125.0
Pungency	Capsaicin	0.1	1.0	10.0

Whole-mouth stimulation test

Whole-mouth stimulation tests using menthol and capsaicin solutions at varying concentrations were used to assess chemesthetic sensitivity. Using the sip-and-spit procedure, participants were asked to sip the entire solution (10 mL) and expectorate it after 10 seconds. After another delay of 10 seconds, participants rated the perceived intensity on a 100-mm general labelled magnitude scale (gLMS). The solutions were presented in increasing order of concentration and a break of 3-4 minutes was held between evaluations to avoid adaptation to the stimulus. The cooling and pungent sensations were evaluated at different sessions of the experimental procedure (**Figure 5.1**) to avoid cross-adaptation.

5.2.4.4. Analysis of food texture sensitivity

Preparation of food samples

Three sets of chocolate mousse with three different levels of firmness, thickness, or roughness were prepared to assess food texture sensitivity. First, a chocolate milk base was prepared with 800 g of whole-fat milk (UHT), 200 g of chocolate (Carraibe 66% cacao, Valrhona), and 100g of granulated sugar. These ingredients were mixed on medium heat until fully homogenised.

Firmness samples were produced by dissolving the respective amount of agar (Texturas gelification agar, Albert y Ferran Adria) as indicated in **Table 5.2** into the chocolate milk base, then mixing on medium heat until boiling. The mixtures were poured into containers and cooled into a gel consistency. The same procedures were followed to produce thickness samples but once gelified, samples were blended into puree using a food processor. The roughness samples were similarly produced by mixing the chocolate milk base with 0.5% (w/w) of agar and blended upon gelification. Then the respective amount of wheat fibre (Jelucel® WF 90, provided by Jeluwerk, Rosenberg, Germany) as indicated in **Table 5.2** was incorporated into the mixture. Wheat fibre is insoluble in water, therefore elicited a sensation of roughness when incorporated into the mousse.

Table 5.2. Sample series for food texture sensitivity test with chocolate mousse samples varying in firmness, thickness, or roughness.

Texture attribute	**Mechanical treatment**	**Added ingredient**	**Concentrations of added ingredients** (w/w)		
			Low	**Medium**	**High**
Firmness	Different concentrations of agar are added and allowed to gelify	Agar	0.50%	0.75%	1.0%
Thickness	Same procedure as firmness samples, but samples are blended upon gelification	Agar	0.50%	0.75%	1.0%
Roughness	Same procedure as low thickness sample, but wheat fibres were added	Wheat fibre	0%	2.0%	4.0%

Texture discrimination test

A texture discrimination test using the chocolate mousse samples was used to determine food texture sensitivity. Participants were first asked to taste the samples and rank them in increasing order, based on the texture attributes of the set (firm/thick/rough). The accuracy in ranking the samples was used to calculate the percentage of correct responses, in each attribute. Next, participants were asked to rate the intensity of the texture attributes on a 100-mm visual analogue scale anchored by the terms "not at all" and "extremely". The presentation order of the sets and samples was randomised for each participant.

5.2.4.5. Analysis of thermal sensitivity

A temperature discrimination test using metal dental mirrors immersed in water maintained at temperature of 3, 20, or 55°C was used to assess thermal sensitivity (Elfring *et al.*, 2012). The dental mirror The back of the dental mirror was placed in contact with the centre of the tongue for 1s. Blindfolded participants had to indicate the thermal sensation that was perceived (cold/neutral/hot), from which the percentage of correct responses was calculated. Each temperature was presented 3 times in a randomised order.

5.2.5. Statistical analyses

Sample size calculation was based on a previous study using tactile sensitivity as the outcome measure with an α risk of 0.05, power 1-β of 80%, effect size of 0.8, standard deviation of 0.7, and delta of 0.37 (Bearelly *et al.*, 2017) which lead to a minimum of 29 participants per group. SPSS Statistics 23 (IBM Corporation) was used to perform statistical analyses. Descriptive statistics are presented as mean ± SD or percentage. Comparisons between the patient and control group were analysed using an independent t-test (continuous) or chi-square test (categorical). Significant level was set at p= 0.05.

5.3. Results

5.3.1. Characteristics of the study population

In total, 30 patients and 30 controls participated in the study. Sex and age (±5y) were individually matched between the patient and control. All patients received radiotherapy, 70% of the patients had surgery, and 47% had systemic treatment. **Table 5.3** shows the characteristics of the participants in the patient and control groups.

Table 5.3. Demographic and clinical characteristics of patients and healthy controls, n (% [a])

Variable	Patient group (*n*=30)	Control (*n*=30)
Age (mean ± SD)	59.9 ± 7.5	59.7 ± 6.8
Sex		
Male	23 (77)	23 (77)
Female	7 (23)	7 (23)
Household		
Alone	6 (20)	7 (23)
Living with partner/ children	23 (7)	23 (7)
Other	1 (3)	0 (0)
Smoking status		
Current smoker	6 (20)	2 (7)
Former smoker	4 (13)	6 (20)
Clinical characteristics		
Primary tumour site		
Oropharynx	17 (57)	-
Hypopharynx	2 (7)	
Nasopharynx	2 (7)	-
Oral cavity	6 (20)	-
Larynx	3 (10)	-
Histologic type		
Squamous cell carcinoma	26 (87)	-
Other	4 (13)	-
Tumour stage		
I	0 (0)	-
II	3 (10)	-
III	13 (43)	-
Iva	9 (30)	-
IVb	2 (7)	-
N/a	3 (10)	-
Types of Treatment		
Radiation	2 (7)	-
Radiation + surgery	14 (47)	-
Radiation + surgery + systemic treatment	7 (23)	-
Radiation + systemic treatment	7 (23)	-
Duration since the end of radiotherapy		
< 1 year	11 (37)	-
> 1 year	19 (63)	-

[a] The sum of percentages may be dissimilar to 100% due to rounding.

5.3.2. Measurements of oral somatosensory responses

Somatosensory responses of the two groups are presented in **Table 5.4.** The tactile sensitivity in the patient group did not differ significantly compared to the control across all filament sizes 0.04 g (p=0.171), 0.02 g (p=0.329), and 0.008 g, (p=0.101).

Table 5.4. Somatosensory responses of HNC patients in comparison to controls

Somatosensory responses	**Patient group**	**Control**	***p*-value**
Oral tactile sensitivity (R-index)			
0.008 g filament	0.73 ± 0.22	0.79 ±0.15	0.171
0.02 g filament	0.81 ± 0.16	0.85 ± 0.20	0.329
0.04 g filament	0.85 ± 0.15	0.92 ± 0.14	0.101
Food texture sensitivity			
Roughness			
Discrimination task **(**% correct response**)**	66.7 ± 42.9	93.3 ± 20.3	**0.003**
Intensity scaling task (mm)			
Low roughness	17.9 ± 16.5	8.0 ± 6.9	**0.002**
Medium roughness	36.9 ± 22.6	27.9 ± 16.2	0.089
High roughness	55.3 ± 25.3	54.3 ± 21.8	0.853
Firmness			
Discrimination task **(**% correct response**)**	76.7 ± 34.1	93.3 ± 20.3	**0.025**
Intensity scaling task (mm)			
Low firmness	27.8 ±18.8	31.66 ± 21.4	0.266
Medium firmness	57.5 ± 20.2	63.21 ± 20.1	0.193
High firmness	68.0 ± 22.3	79.24 ± 11.9	**0.018**
Thickness			
Discrimination task **(**% correct response**)**	90.0 ± 26.5	93.3 ± 20.3	0.587
Intensity scaling task (mm)			
Low thickness	18.9 ± 14.6	15.6 ± 10.2	0.303
Medium thickness	41.5 ± 16.8	50.5 ± 16.8	**0.031**
High thickness	67.4 ± 16.0	66.6 ± 16.9	0.969
Chemesthetic sensitivity			
Cooling sensation/irritation (gLMS)			
Menthol low	5.0 ± 5.4	7.10 ± 6.0	0.169
Menthol medium	13.3 ± 9.7	19.57 ± 8.9	**0.011**
Menthol high	26.8 ± 13.5	34.37 ± 13.6	**0.034**
Heating sensation/irritation (gLMS)			
Capsaicin low	3.1 ± 4.4	2.8 ± 3.4	0.745
Capsaicin medium	17.2 ± 12.9	28.6 ± 13.7	**0.002**
Capsaicin high	54.2 ± 23.2	65.7 ± 19.2	**0.044**
Thermal sensitivity (% correct response)	94.1 ± 10.4	98.5 ± 4.8	**0.038**

Values are expressed as means ± SD, $p < 0.05$: significant difference on independent t-test.

The texture sensitivity for the chocolate mousses differed between the two groups. The patient group was significantly less sensitive to the differences in roughness compared to the control (*p*=0.003). Patients rated the samples to be higher in roughness compared to controls, with 17% of patients perceiving the samples to be identical to each other. The patient group was also significantly less sensitive to the differences in firmness compared to the control group (*p*=0.025). Patients showed a tendency to perceive the samples to be less firm compared to controls, with 10% of patients reported perceiving the samples to be identical to each other. In terms of discrimination ability to thickness, no significant difference was observed between the two groups (*p*=0.587).

Patients perceived the chemesthetic solutions to be less intense compared to the control group (**Table 5.4**). Significant differences were observed in the medium and high concentrations for both menthol (*p*=0.011 and *p*=0.034) and capsaicin (*p*=0.002 and *p*=0.044) solutions. For both chemesthetics, the sensory threshold did not seem to be affected, however, in the range above sensory detection the dose-responses relationship showed a significant decline for the patient group. The thermal sensitivity measured as physical-induced sensation (cold/warm) demonstrated a lower accuracy for the patient group in discriminating these sensations (p=0.038), although they still showed a general good ability to discriminate cold/warm stimuli.

5.3.3. Measurements of salivary functions

Measurements of salivary functions between the two groups are presented in **Table 5.5**. Patients demonstrated significantly lower salivary function compared to the controls (*p*=0.001). Patients had lower scores for hydration (*p*=0.002) and stimulated salivary volume (*p*=0.001), while displaying higher values for saliva consistency (*p*=0.004). Most participants had an acidic salivary pH of 5.0-6.6 and a normal buffering capacity of 10.0-12.0, with no significant differences between the patient and control groups.

Among the patient group, those who were tested more than a year after their radiotherapy showed a higher salivary function compared to patients whose radiotherapy ended less than a year ago (*p*=0.031). The correlations between salivary functions and texture perceptions were not significant.

Table 5. Salivary functions of HNC patients in comparison to controls, n (% [a])

Salivary measurements	Patient group	Control	*p*-value
Salivary function score (mean ± SD)	10.6 ± 2.6	12.7 ± 2.0	**0.001**
Hydration			
Low	12 (40)	2 (7)	**0.002**
Normal	18 (60)	28 (93)	
Consistency			
Sticky and frothy	16 (53)	5 (17)	**0.004**
Frothy and bubbly	8 (27)	8 (27)	
Clear and watery	6 (20)	17 (57)	
Saliva pH			
Very acidic	5 (17)	2 (7)	0.329
Moderately acidic	15 (50)	20 (67)	
Normal	10 (53)	8 (27)	
Stimulated saliva volume			
Very low	12 (40)	3 (10)	**0.001**
Low	9 (30)	4 (13)	
Normal	9 (30)	23 (77)	
Buffering capacity			
Very low	3 (10)	2 (7)	0.610
Low	5 (17)	8 (27)	
Normal	22 (73)	20 (67)	

5.4. Discussion

In addition to confirming previous findings on tactile and thermal sensitivity of HNC patients (Bodin *et al*., 2004; de Groot *et al*., 2020; Loewen *et al*., 2010), our study investigated other sub modalities of somatosensory perception. We included measurements of chemesthetic sensitivity and texture sensitivity using real food samples. We also explored the link between salivary function and sensory perception, in particular food texture sensitivity.

5.4.1. Oral tactile and food texture sensitivity

The tactile sensitivity observed in the patient group is consistent with previous clinical studies employing point-pressure tests. For instance, HNC patients with hemi glossectomy were less sensitive than control but the difference is only significant when comparing the reconstructed tongue region vs. control, and not when comparing the intact tongue region vs. control (Loewen *et al*., 2010). Patients were less sensitive than the controls, yet the magnitude of the difference highly depends on the type of treatment and the moment at which the assessment was done (before or after treatment) (Bodin *et al*., 2004). Cancer patients with tumours located on the mandible and tongue/floor of mouth had a significant decrease in their tactile sensitivity following cancer treatments, but not in patients whose tumour site is on the maxillary region. The authors suggested the difference was due to the treatment site for maxillary tumours which did not involve the tongue (de Groot *et al*., 2020). These studies suggest that the lowered tactile sensitivity of HNC patients is attributed to the side effect of cancer treatments.

Tactile sensitivity measured using the point-pressure test is a contact-detection sensitivity which stimulates distinct parts of the slowly adapting superficial mechanoreceptors (Abraira & Ginty, 2013). These are linked to the perception of surface properties such as roughness, particle sizes, and grittiness (Engelen & Van Der Bilt, 2008). A reduced tactile sensitivity may translate to an altered perception of some aspects of food textures, as observed in the roughness discrimination test. A previous study demonstrated that participants with lower tactile sensitivity were shown to be less sensitive at discriminating the grittiness/roughness of chocolates (Breen *et al*., 2019). The reduced sensitivity to roughness in cancer patients could also be attributed to the lack of salivation in the patient group, resulting in reduced lubrication and increased friction thereby increasing the perception of roughness (De Wijk & Prinz, 2006).

Food firmness is perceived through the amount of force needed to fracture the foodstuff (Devezeaux de Lavergne *et al*., 2015), therefore physiological factors such as jaw muscle activity and tongue function may explain the underlying difference in the firmness perception of the two groups. Radiation-induced trismus, which is the restricted mouth opening due to fibrosis of muscles, is common among HNC patients (Abboud *et al*., 2020). Although in this study patients who have self-reported trismus are excluded, it is not unlikely that the patients have a certain level of impairment in their jaw muscle activity (Martins *et al*., 2020). Moreover, patients with cancer in the oral cavity demonstrated reduced tongue mobility and tongue force (de Groot *et al*., 2020), altogether influencing their perception of firmness. Additionally, as the samples were semi-solids that can be masticated without chewing, the incorporation of saliva during this stage plays major importance (Devezeaux de Lavergne *et al*., 2015; Engelen & de Wijk, 2012), thus the lack of saliva may influence the firmness perception of cancer patients.

The amount and viscosity of saliva can either dilute or intensify the perception of food thickness (Engelen *et al*., 2007). Thus, it was expected that cancer patients have altered sensitivity to thickness due to their reduced salivary function, however, no significant difference was observed in this study. This may be attributed to the visual bias, as the difference in visual texture was evident between the thickness samples. As sensory perception is a multidimensional process, visual appearance could also influence the judgement of textural properties (Spence, 2017).

5.4.2. Chemesthetic and thermal sensitivity

The lower chemesthetic sensitivity may be linked to the release of inflammation-associated factors released by cancer cells which can activate and sensitise nociceptors (Mantyh *et al*., 2002). The persistent activation may lead to chronic desensitisation of the receptors (Alsalem *et al*., 2016). Other possible explanation may include a more acute mechanism in which the difference between patients and controls may not necessarily originate from the perceived intensity per se but from the time-intensity profile. Application or consumption of capsaicin and menthol either leads to sensitisation or desensitisation depending on the temporal delay (Cliff & Green, 1996). The procedure established to evaluate the chemesthetic solutions, including the 10 seconds delay before evaluating the samples and the 3-4 minutes interstimulus interval period, was based on healthy individuals (Green, 1991). It is possible that the 10 seconds delay was insufficient for patients to fully perceive the sensation, or that the 3-4 minutes interval was too short that it caused adaptation while evaluating the proceeding samples.

Patients also demonstrated lower thermal sensitivity, consistent with previous findings (de Groot *et al*., 2020; Loewen *et al*., 2010). The authors explained that it could be attributed to the late side effects from the surgery and/or the radiotherapy which resulted in an impairment of the sensory function in the oral cavity. Medications such as NSAIDS, corticosteroids, and opioids used to treat cancer pain may also desensitise nociceptive afferents (Mantyh *et al*., 2002).

5.4.3. Salivary function

The observed reduction in salivary function of cancer patients is consistent with previous findings (Barbosa da Silva *et al*., 2019; Li *et al*., 2007; Lin *et al*., 2015; Murdoch-Kinch *et al*., 2008; Sim *et al*., 2018). Radiotherapy causes tissue damage in the radiation field. In the case of HNC this includes severe, and sometimes permanent, damage to the salivary gland which influenced the amount and composition of saliva production (Lin *et al*., 2015; Sim *et al*., 2018). A reduction in parotid and submandibular glands volumes was observed 3 months after radiotherapy in the oral cavity (Sim *et al*., 2018), therefore reducing the salivary quantity. In addition, chemotherapeutic agents such as 5-fluorouracil and doxorubicin used by the patients also induced hyposalivation (Jensen *et al*., 2003).

Quantity, but not quality (pH and buffering capacity) of saliva, was significantly different between the two groups. In addition to having less saliva production, cancer patients also produced thicker saliva. This may be attributed to the radiosensitivity of the different salivary glands. Parotid glands, responsible for producing most of the watery saliva, were shown to be more affected by radiation compared to submandibular glands which produce more viscous and mucin-rich saliva (Deasy *et al*., 2010; Li *et al*., 2007; Murdoch-Kinch *et al*., 2008).

In terms of salivary quality, most of the patients were assessed more than 1 year after radiotherapy (**Table 5.3**) and had acidic saliva (pH <6.8). Patients who were observed more than 1 year after the end of their radiotherapy showed higher salivary functions compared to those observed less than a year after the end of their radiotherapy. This is consistent with previous studies, which demonstrated a significant decrease in salivary pH after radiation but began to increase between 6 months to 2 years post-radiation, although it didn't recover to the initial pH of 7.0 (Lin *et al*., 2015; Sim *et al*., 2018). These two longitudinal studies also showed that buffering capacity decreased upon radiation but recovered to normal at 6 months post-radiotherapy (Lin *et al*., 2015; Sim *et al*., 2018), which also supported our findings.

In terms of food perception, saliva is an essential component influencing the perception of taste, smell, texture, astringency and temperature (De Wijk & Prinz, 2006; Kubala *et al*., 2018; Lester *et al*., 2021). The lubricating property of saliva is necessary for mastication, bolus formation, and swallowing, so the lack of it may lead to eating problems (Galaniha & Nolden, 2022). The correlations between salivary function and the perception of texture was observed in a previous study (Engelen *et al*., 2007) but in the present study, the correlations were not evident.

5.4.4. Limitations of the study

This study presents some limitations, for instance, the cross-sectional design does not permit to infer causality. A longitudinal study following patients across different treatments and time points would have allowed observations on the progression of their somatosensory perception. The study involved a rather heterogenous population regarding the treatment type and duration since treatment, therefore unable to discern whether the changes were caused by certain treatments or the disease itself. Further, as the test was conducted at different times of the day and periods of the year, it may influence the measurements of salivary function. Different testing locations for the two groups could potentially introduce contextual influence on perception. In addition, patients treated with radiotherapy have an enlarged periodontal ligament, which is a valuable indicator of proprioception and texture. It would therefore be interesting to study the contribution of the periodontal ligament to texture in HNC patients.

5.5. Conclusion

The present study assessed oral somatosensory perceptions and salivary function of HNC patients, which are largely understudied relative to the taste and smell perceptions. The findings indicated that oral somatosensory alterations and salivary dysfunction are symptoms experienced by HNC patients, and the need to further explore the field. These symptoms should be carefully assessed and considered when providing nutritional support.

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The present study indicates that HNC patients experience changes in their somatosensory perception. Particularly, compared to the matched control, HNC patients demonstrated lower thermal sensitivity and chemesthetic sensitivity. Patients also differed from control in terms of roughness and firmness perception. In addition, patients showed reduced salivary function, which may mediate the difference in perception. The next chapter is part of the same clinical study; however, it focuses more on the subjective measurements and their relation to eating behaviour.

Chapter 6

Influence of Oral Somatosensory Perception and Oral Symptoms on Eating Behaviour of Head and Neck Cancer Patients

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Abstract

Purpose: Altered eating experience due to sensory alteration is prevalent among head and neck cancer (HNC) patients. While taste and smell alterations have been thoroughly investigated, studies on their oral somatosensory perception remain limited. This study aimed to examine the sensory perception, including somatosensation and oral symptoms, in HNC patients and evaluate their impact on food behavior.

Methods: A cross-sectional study was conducted using self-reported questionnaires on sensory perception, food preference, food consumption, food liking, and eating behaviour among HNC patients (*n*=30). Hierarchical clustering analysis was performed to categorise patients based on their sensory profile. Comparisons between the sensory profile groups and correlations between oral symptoms and eating behaviour were explored.

Results: Two distinct profiles of patients were identified: no alteration (n=14) vs alteration (n=16) group regarding sensory perception. The alteration group showed decreased preference towards several sensory modalities, especially the somatosensory. Concerning eating behaviour, more patients in the alteration group agreed to negatively connotated statements (e.g. having food aversion, eating smaller portions). In addition, several oral symptoms were reported by the majority of patients related to salivary dysfunction. These oral symptoms were correlated with sensory perception, sensory-related food preference, and eating habits.

Conclusion: This study presented evidence demonstrating that sensory alterations in HNC patients are not limited solely to taste and smell but cover somatosensory perception and are linked to various aspects of food behavior. Moreover, patients reported experiencing several oral symptoms. Those with sensory alterations and oral symptoms were more vulnerable to eating difficulties.

Keywords: Oral Somatosensory Perception; Oral Symptoms; Head and Neck Cancer; Questionnaire; Eating Behaviour.

6.1. Introduction

Altered eating, or "losing the ability to eat well", is a problem among cancer patients, including and especially among head and neck cancer (HNC) patients due to the cancer location being in the food ingestion site (Watson *et al*., 2018; Citak *et al*., 2019; Muscaritoli *et al*., 2017). Several side effects were reported prior to and following cancer treatments that interfere with their eating ability. These oral symptoms include dry mouth, mucositis, and difficulty chewing/swallowing (Farhangfar *et al*., 2014; Wang *et al*., 2021). Altered eating caused reduced food intake that may contribute to a decline in nutritional status, for instance, 51-74% of HNC patients were malnourished (Citak *et al*., 2019; Muscaritoli *et al*., 2019). It also adds a psychological burden as patients lose pleasure from eating and the social interactions surrounding mealtimes (Dornan *et al*., 2022). Consequently, this leads to a lowered quality of life (Hutton *et al*., 2007).

Another aspect that contributed to altered eating experience was the sensory aspect. Altered sensory perception plays a crucial role in cancer patients' eating behaviour. Eating behaviour is a broad and complex term encompassing aspects of eating behaviour that can influence individuals' nutritional choices; this includes food preferences, food intake, and eating behaviour (Nolden *et al*., 2019). It was shown that sensory dysfunction was correlated to lower energy intake and higher weight loss, contributing to declined nutritional status and quality of life (Hutton *et al*., 2007; van Elst *et al*., 2022). Yet several studies have investigated sensory alterations focusing on alterations in smell and taste perception, with prevalence ranging from 60 to 86% % (de Haan *et al*., 2021; Hutton *et al*., 2007). However, sensory perception is not only limited to taste and smell but also somatosensation, which few studies have investigated. Somatosensation comprises perception towards texture, temperature, and chemesthetic sensations (e.g. spiciness of chilli, cooling sensation of peppermint) processed by the trigeminal system (Lundström *et al*., 2011). Therefore, the present study aimed to investigate sensory perception, including somatosensation and oral symptoms of HNC patients and their influence on eating behaviour. It is hypothesised that perceived sensory alterations will be related to modified food preferenceand eating behaviour.

6.2. Materials and methods

6.2.1. Study design

This questionnaire-based study was a part of the cross-sectional study (Somestalim) registered to the Clinical Trials Registry (NCT05272917), conducted in accordance with the

Declaration of Helsinki. The protocol and study design were approved by the Ethics Personal Protection Committee of Ile-de-France (RCB N° 2021-A02961-40). Informed consent was obtained from all participants. The Somestalim study is a cross-sectional study comparing HNC patients and matched control. The study consisted of objective measurements of salivary function and somatosensory sensitivity, as well as subjective measurements through self-reported questionnaires. The first part of the study, which focused on the objective measurements of the somatosensory perception of HNC patients in comparison with matched control, was reported in (Riantiningtyas *et al*., 2023). The present paper explores the subjective perception of HNC patients and its relationship with eating behaviour.

6.2.2. Participants

Participants were HNC patients recruited by clinical research associates or physicians during their outpatient consultations at the Hospices Civils de Lyon (France). Thirty HNC patients were recruited; the sample size calculation is presented in Chapter 5 (Riantiningtyas *et al*., 2023). "Patients were eligible if they fulfilled the following criteria: age between 18-70 years old; diagnosed with tumours of the upper aerodigestive tract (including oral cavity, pharynx, and larynx), salivary glands, maxillary sinuses, or nasopharynx; treated by radiotherapy alone in combination with surgery, systemic treatment, or both. The radiotherapy must have been completed between 4 months to 5 years ago. Exclusion criteria were being currently pregnant or breastfeeding, having known food allergy or intolerance, being unable to swallow soft food, experiencing trismus (restricted mouth opening), having difficulties extending the tongue and having large tongue resection" (Riantiningtyas *et al*., 2023)

6.2.3. Procedure

The study visit lasted 1.5h and was conducted at Croix Rousse and Lyon-Sud hospitals in May 2022 – April 2023 (between 10.00 and 14.00). The exact time and location depend on the participant's availability. Participants completed the questionnaires in between the objective measurements described in **section 6.2.1.** using a tablet via an online platform, Qualtrics (Provo, US). The questionnaire took approximately 20 minutes to complete. The questionnaire is provided in **Appendix 2.A**.

The self-reported questionnaires were developed specifically for the study and adapted from existing questionnaires (Amézaga *et al*., 2018; de Haan *et al*., 2021; K. Drareni *et al*., 2021; Hunot *et al*., 2016; Hutton *et al*., 2007; Singer *et al*., 2019). The questionnaire was developed in English and translated into French. Native speakers checked and verified the translations with the English questionnaire. The questionnaires were pilot-tested with healthy individuals (internal staff of the Institut Lyfe Research & Innovation Centre) (n=16) and cancer patients (n=4) to ensure clarity. Following this step, the comments of the testers were considered, and the final questionnaire was validated by the supervisory team.

The questionnaire included questions on sociodemographic (sex, age, country of residence). Furthermore, questions on sensory perception and sensory-related food preference (Amézaga *et al*., 2018; de Haan *et al*., 2021; Drareni *et al*., 2021; Hutton *et al*., 2007), oral symptoms (Singer *et al*., 2019), and eating behaviour (Hunot *et al*., 2016) were included. The different parts of the questionnaires were as follows:

1) Sensory perception: 13 items covering 5 subsections covering the basic tastes, smell, texture, temperature, and chemesthetic sensations (represented by questions on spiciness, cooling sensation, astringency, carbonation, and alcohol). Questions for sensory perception were phrased as follows "Compared to the situation before cancer treatment, I perceive that my *sensitivity* towards [salty/ sweet/ sour/ bitter/ smell of/ texture of/ cold/ hot/ pungent/ cooling/ astringent/ carbonated drinks/ alcoholic] food/drink has…". The response options for both questions were: "has decreased/ remains unchanged/ has increased", except for texture in which the response options were "changed/ remains unchanged".
2) Oral symptoms: 19 different oral symptoms with response options ranging from "1= Never" to "5=Always".
3) Sensory-related food preference: Similar to the questions on sensory perception, the 9 questions for sensory preference were phrased "In comparison with the situation before cancer treatment, my *preference* towards [sensory modality] food/ drink has..". The response options were: "has decreased/ remains unchanged/ has increased", except for texture in which the response options were "changed/ remains unchanged".
4) Eating behaviour: 15 different statements related to eating behaviour with response options of "1= disagree completely" to "6= agree completely".

6.2.4. Data analysis

Descriptive statistics were used to describe the sociodemographic and clinical information of the participants. In order to explore the various sensory profiles of the patients, a clustering analysis was conducted based on their responses to sensory perception. The analysis involved two-way hierarchical clustering using Ward's method, and the resulting heatmap was created using the pheatmap package in R studio. To compare the groups, independent t-test was used for continuous data and the chi-square test was used for nominal or ordinal data.

To investigate the relationship between oral symptoms and other variables, the scores for each of the 19 individual oral symptoms were added to create an oral symptom score. Sensory-related food preference was treated as a categorical variable with three different levels: decreased preference, no change, and increased preference. Correlations between oral symptoms score, sensory perception, sensory-related food preference, and eating behaviour were assessed using Spearman correlations. A p-value of ≤ 0.05 was considered significant SPSS. Statistics 23 (IBM Corporation) was used for statistical analyses.

6.3. Results

6.3.1. Characteristics of the study population

The complete demographic and clinical characteristics of patients are presented in **Table 6.1**. In total, 30 patients (23 males and 7 females, mean age 59.9 ± 7.5) diagnosed with tumour on the oropharynx, hypopharynx, nasopharynx, larynx, or oral cavity participated in the study. All patients received radiotherapy; 70% had surgery, and 47% had chemotherapy.

Table 6.1. Demographic and clinical characteristics of patients (Riantiningtyas *et al*., 2023)

Variable	**Patient (*n*=30)**
Age (mean ± SD)	59.9 ± 7.5
Sex	
Male	23 (77)
Female	7 (23)
Household	
Alone	6 (20)
Living with partner/ children	23 (7)
Other	1 (3)
Smoking status	
Current smoker	6 (20)
Former smoker	4 (13)
Non-smoker	20 (67)
Clinical characteristics	
Primary tumour site	
Oropharynx	17 (57)
Hypopharynx	2 (7)
Nasopharynx	2 (7)
Oral cavity	6 (20)
Larynx	3 (10)
Histologic type	
Squamous cell carcinoma	26 (87)
Other	4 (13)
Tumour stage	
I	0 (0)
II	3 (10)

III	13 (43)
Iva	9 (30)
IVb	2 (7)
N/a	3 (10)
Types of Treatment	
Radiation	2 (7)
Radiation + surgery	14 (47)
Radiation + surgery + systemic treatment	7 (23)
Radiation + systemic treatment	7 (23)
Duration since the end of radiotherapy	
< 1 year	11 (37)
> 1 year	19 (63)

*The sum of percentages may be dissimilar to 100% due to rounding.

6.3.2. Sensory alterations among head and neck cancer patients

6.3.2.1. Patient clustering based on perceived sensory alterations.

The hierarchical clustering allows the classification of patients into groups based on their response to sensory perception (**Figure 6.1**). Two distinct clusters were identified: 1) group of patients with little to no perceived alteration (n=14), hereafter mentioned as "*no alteration group*"; 2) groups of patients with perceived alteration in several aspects of their sensory perception (n=16), hereafter mentioned as "*alteration group*".

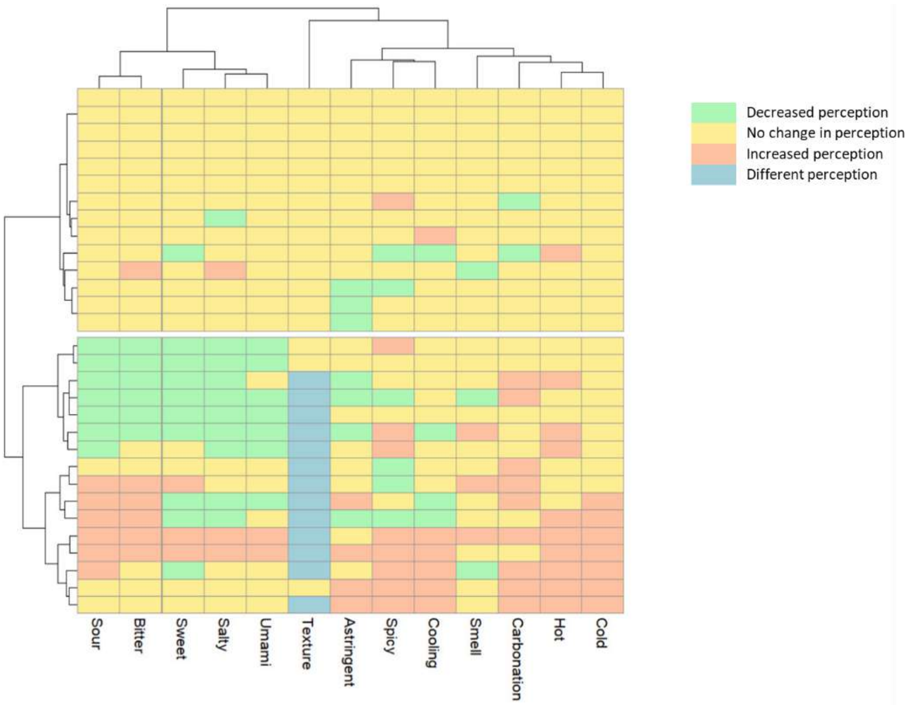

Figure 6.1. Heat-map diagram of a two-way hierarchical clustering analysis consisting of sensory perception of cancer patients.
Questions were phrased as follows "In comparison with the situation before cancer treatment, I perceive that my sensitivity towards [sensory modality] food/drink has …" with response options of "increased/ not changed/ decreased/ changed". Each row represents a patient, and each column represents their perception to each sensory modality. Top rows: no alteration group (n=14), bottom rows: alteration group (n=16).

6.3.2.2. Relationship between perceived sensory alteration and food preference.

Based on the clustering, the two groups were first compared regarding their sensory-related food preference. Patients in the alteration group demonstrated significant differences in their sensory-related food preference compared to the no-alteration group (**Table 6.2**).

Table 6.2. Distribution of responses between groups in terms of sensory-related food preference

	No alteration (n=14)	**Alteration** (n=16)	**p-value**
Salty food products			
Decreased preference	1 a	2 a	0.310
No change	10 a	7 a	
Increased preference	3 a	7 a	
Sweet food products			
Decreased preference	2a	6 a	0.152
No change	11 a	7 a	
Increased preference	1 a	3 a	
Sour food products			
Decreased preference	1 a	8 b	**0.011**
No change	13 a	8 b	
Increased preference	0 a	0 a	
Bitter food products			
Decreased preference	1 a	8 b	**0.028**
No change	12 a	8 b	
Increased preference	1 a	0 a	
Spicy food products			
Decreased preference	0 a	9 b	**<0.001**
No change	14 a	5 b	
Increased preference	0 a	2 a	
Cooling food products			
Decreased preference	0 a	7 b	**0.013**
No change	13 a	9 b	
Increased preference	1 a	0 a	
Astringent food products			
Decreased preference	3 a	12 b	**0.003**
No change	11 a	4 b	
Increased preference	0 a	0	
Carbonated beverages			
Decreased preference	1 a	6 b	**0.007**
No change	13 a	6 b	
Increased preference	0 a	4 b	
Alcohol			
Decreased preference	3 a	10 b	**0.024**
No change	11 a	6 b	
Increased preference	0 a	0	

While most of the patients in the no alteration group reported an unchanged preference compared to before their treatment, the alteration group showed a higher frequency of decreased preference towards sour (p=0.011) and bitter (p=0.028) tastes. For the alteration group, half of the patients reported decreased preference for sour and bitter food, yet only 1 patient from the no alteration group reported decreased preference. In addition, the two groups also significantly differed in their preference towards all somatosensory sub-modalities. There were more patients in the alteration group who reported decreased preference to spicy, cooling, and astringent food products as well as carbonated and alcoholic beverages.

6.3.2.3. Relationship between perceived sensory alteration and eating behaviour.

Some differences between the two groups were also observed in their responses towards eating behaviour questions (**Table 6.3**). Higher proportions of patients agreed to negatively-connotated items such as: eating smaller portion (p=0.012), eating becomes effortful (p=0.002), food aversion (p=0.006), and certain food has become unpleasant/difficult to eat (p=0.035).

Table 6.3. Distribution of responses between groups in terms of eating behaviour

	No alteration (n=14)	**Alteration** (n=16)	**p-value**
Feeling hunger when smelling/seeing food			
Disagree	0_a	5_b	**0.031**
Agree	14_a	11_b	
Eating a variety of food			
Disagree	3_a	8_a	0.107
Agree	11_a	8_a	
Trying novel food			
Disagree	2_a	6_a	0.154
Agree	12_a	10_a	
Having less appetite			
Disagree	8_a	8_a	0.491
Agree	6_a	6_a	
Feeling satiated quickly			
Disagree	7_a	9_a	0.509
Agree	7_a	7_a	
Eating smaller portion			
Disagree	11_a	5_b	**0.012**
Agree	3_a	11_b	
Eating more frequently			
Disagree	9_a	11_a	0.550
Agree	5_a	5_a	
Eating becomes demanding/effortful			
Disagree	11_a	4_b	**0.002**
Agree	3_a	12_b	
Losing eating pleasure			
Disagree	10_a	7_a	0.123
Agree	4_a	9_a	
Not feeling at ease when eating out			
Disagree	12_a	10_a	0.154

Agree	2_{a}	6_{a}	
Being the last to finish meal			
Disagree	4_{a}	5_{a}	0.596
Agree	10_{a}	11_{a}	
Disliking food before tasting			
Disagree	10_{a}	10_{a}	0.450
Agree	4_{a}	6_{a}	
Having food aversion			
Disagree	13_{a}	7_{b}	**0.006**
Agree	1_{a}	9_{b}	
Having food craving			
Disagree	6_{a}	8_{a}	0.491
Agree	8_{a}	8_{a}	
Certain food has become unpleasant			
Disagree	9_{a}	4_{b}	**0.035**
Agree	5_{a}	12_{b}	

6.3.3. Oral symptoms of head and neck cancer patients

Oral symptoms frequently experienced by more than 50% of the patients include dry mouth (80%), difficulty swallowing (67%), sticky saliva (60%), difficulty chewing (57%), food stuck in the throat (57%), and food stuck in the mouth (53%) (**Table 6.4**). Other oral symptoms that were frequently experienced were dental problem, sensitive teeth/gum, and pain in throat.

Table 6.4. Reported oral symptoms, n (%)

Oral symptoms	Never	Rarely	Sometimes	Often	Always	Subtotal [a]
Dry mouth	1 (3)	5 (17)	6 (20)	11 (37)	7 (23)	24 (80)
Difficulty swallowing	7 (23)	3 (10)	10 (33)	8 (27)	2 (7)	20 (67)
Sticky saliva	8 (27)	4 (13)	6 (20)	8 (27)	4 (13)	18 (60)
Difficulty chewing	6 (20)	7 (23)	9 (30)	6 (20)	2 (7)	17 (57)
Food stuck in the throat	11 (37)	2 (7)	10 (33)	6 (20)	1 (3)	17 (57)
Food stuck in the mouth	11 (37)	3 (10)	10 (33)	4 (7)	2 (7)	16 (53)
Avoiding certain food due to dental problem	16 (53)	1 (3)	8 (27)	1 (3)	2 (7)	13 (43)
Sensitive teeth/gum	11 (37)	6 (20)	3 (10)	7 (23)	3 (10)	13 (43)
Pain in throat	14 (47)	3 (10)	6 (20)	6 (20)	1 (3)	13 (43)
Pain/problem w teeth	17 (57)	0 (0)	5 (17)	6 (20)	2 (7)	13 (43)
Fear of eating due to pain	18 (60)	2 (7)	5 (17)	3 (10)	2 (7)	10 (33)
Painful mouth	18 (60)	3 (10)	4 (7)	3 (10)	2 (7)	9 (30)
Oral inflammation	12 (40)	9 (30)	9 (30)	0 (0)	0 (0)	9 (30)
Pain in gum	17 (57)	5 (17)	5 (17)	2 (7)	1 (3)	8 (27)
Trismus	18 (60)	5 (17)	4 (7)	1 (3)	2 (7)	7 (23)
Burning sensation in the mouth	19 (63)	4 (7)	2 (7)	2 (7)	3 (10)	7 (23)
Bleeding gum	21 (70)	4 (7)	4 (7)	1 (3)	0 (0)	5 (17)
Painful lips	22 (73)	3 (10)	3 (10)	1 (3)	1 (3)	5 (17)
Nausea	18 (60)	7 (23)	4 (7)	1 (3)	0 (0)	5 (17)

[a] Subtotal to the frequency of sometimes, often, and always for each symptom.

Correlations between oral symptom score and other variables including sensory perception, sensory-related food preference, and eating behaviour were explored (**Appendix 2.B**). Oral symptom score showed moderate positive correlations with changes in texture (r=0.49, p=0.002) and temperature (r=0.51, p=0.001 for hot and r=0.39, p=0.015 for cold) perception. In particular, oral symptoms such as difficulty in chewing and swallowing, sensitive teeth/gums, and pain surrounding the oral cavity were correlated to these changes in perception.

Oral symptom score also showed negative correlations with preference towards sour (r=-0.41,p=0.011), bitter (r=-0.31, p=0.048) spicy (r=-0.43,p=0.006), carbonated (r=-0.38, p=0.013), and astringent (r=-0.40, p=0.012) food products. In particular, oral symptoms such as difficulty swallowing, food getting stuck in the throat/mouth, dry mouth, oral inflammation, and pain surrounding the oral cavity were correlated with this decline in preference.

Regarding eating behaviour, oral symptom score was negatively correlated with consuming a variety of foods (r=-0.41, p=0.004), in particular, driven by difficulty swallowing, food stuck in the throat, and pain surrounding the oral cavity. Meanwhile, oral symptom score was positively correlated with having less appetite (r=0.38, p=0.008), eating smaller portions (r=0.41, p=0.004), effortful eating (r=0.44, p=0.002), losing pleasure in eating (r=0.38, p=0.008), feeling discomfort when eating out (r=0.43, p=0.003), not liking food before tasting (r=0.36, p=0.011), developing food aversion (r=0.60, p<0.001), and food becoming unpleasant or difficult to eat (r=0.52, p<0.001).

6.4. Discussion

More than half of the HNC patients in the study reported experiencing sensory alterations, which is in agreement with the prevalence of self-reported sensory alteration ranged between 12 and 84% seen among various cancer patients (Nolden *et al.*, 2019). Among these patients, changes in taste and somatosensory perception (texture, temperature, and chemesthesis) were reported more frequently than changes in smell perception (**Figure 6.1**), which is consistent with earlier observations (Galaniha & Nolden 2023). Previous study showed that changes in smell perception tend to be gradual and unnoticed compared to taste perception (Drareni, 2020).

The study highlights the relation between sensory alteration, sensory-related food preference, and eating behaviour. Upon categorising the patients into two distinct profiles, the alteration group demonstrated higher proportion of patients with reduced preference for all somatosensory sub-modalities as well as towards bitter and sour tastes. These findings suggest that changes in sensory perception are linked with food choice. Similar observations have been reported in previous studies, which have shown that sensory alterations can influence appetite, food appreciation, and food selection or intake (Boltong & Campbell, 2013; Dalton *et al*., 2022; Ganzer *et al*., 2015).

The presence of sensory alteration was also reflected in items concerning eating behaviour. Higher proportion of patients with sensory alteration agreed to the negatively-connotated statements compared to the no alteration group. These imply that patients with sensory alterations were more likely to experience more eating difficulties such as eating in smaller portions, having food aversion and difficulty in eating certain food. This may consequently lead to lower food intake, as it was shown that sensory alterations were correlated with a negative impact on nutritional status (Hutton *et al*., 2007; Wang *et al*., 2021).

The present study demonstrated that HNC patients experienced several oral symptoms. The oral symptoms frequently experienced by patients were dry mouth, sticky saliva, difficulty chewing, difficulty swallowing, food stuck in the mouth, and food stuck in the throat. These symptoms seem to be mediated by the lack of salivation. The perception of dry mouth and sticky saliva were experienced by 80% and 60% of patients, respectively. Xerostomia, defined as the subjective perception of dry mouth and/or sticky saliva due to reduced salivary flow, has been widely reported to be one of the most common side effects in this subpopulation of cancer (Monreal *et al*., 2022).

Difficulty in swallowing and chewing, were experienced by 67% and 57% of patients, respectively. Saliva is responsible for bolus formation during mastication, namely in "wetting and coating, hydration, and granulation" (Guo, 2021). Lack of saliva will cause the food to be more compact and cohesive, making it more difficult to chew (Bilt, 2021; Logemann *et al*., 2001). In addition to salivation, difficulty in chewing may be influenced by age, jaw muscle activity, and use of dentures (Bilt, 2021). Following mastication, the bolus needs to be optimally moistened before it can be swallowed; hence, sufficient saliva is also necessary to facilitate swallowing (Guo, 2021; Liu *et al*., 2017). Previous studies have shown that difficulty in food processing is common among head and neck cancer patients (Jin *et al*., 2021; Langius *et al*., 2010; Wang *et al*., 2021). These altogether may lead to fear of eating due to risk of choking (Pedersen *et al*., 2018).

Food sticking in the throat and mouth were experienced by 57% and 53% of patients, respectively. These, too, can be associated with salivary function. The hydrating and lubricating properties of saliva facilitate oral clearance (Pedersen *et al*., 2002), therefore the lack of it causes food to get stuck in the mouth and/or throat. The other oral symptoms that were frequently experienced by the HNC patients in this study were dental problems, sensitive teeth/gum, pain in the throat, and pain/problems with teeth. It was shown that pain surrounding the oral cavity was one of the symptoms reported by HNC patients, associated with the cancer treatments such as radiotherapy and chemotherapy (Farhangfar *et al*., 2014; Wang *et al*., 2021). Further, it was suggested that severe oral symptoms may influence physical functioning, quality of life, and nutritional status of patients (Crowder *et al*., 2018).

The correlation between oral symptoms and sensory perception was observed. Oral symptoms, such as difficulty in chewing and swallowing, food getting stuck in the mouth, and pain in the oral cavity, were correlated with texture and temperature perception. It is likely that patients affected by these oral symptoms exhibit increased awareness or caution when selecting foods, aiming to avoid food textures and temperatures that may cause pain or discomfort upon consumption. Similarly, these oral symptoms were also shown to be correlated with their preference for sour and bitter taste, spiciness, astringency, and carbonation.

In addition to the aforementioned oral symptoms, dry mouth and oral inflammation were correlated to the sensory-related food preference. Saliva serves multiple functions, including sensory perception, food oral processing, and digestion (Pedersen *et al*., 2018); hence impairment in salivary production will lead to adverse consequences to their eating experience and food intake. A previous study demonstrated that salivary quantity was related to the perception of oral comfort, depending on the food products. The food needs to have enough moisture, or compensated with some fat, in order to be easily processed and ingested (Assad-Bustillos *et al*., 2019). The amount and composition of saliva influence the perception of food texture (Engelen *et al*., 2007). Further, the interaction between salivary protein and polyphenols was shown to influence the perception of astringency (De Wijk & Prinz, 2006; Dinnella *et al*., 2009), whereas spiciness will become an irritating sensation with the presence of oral pain and inflammation.

Finally, the correlations between oral symptoms and eating behaviour also demonstrated that patients with more oral symptoms have more difficulty in eating situations. Particularly, patients with more oral symptoms were correlated with having less appetite, eating smaller portions, losing pleasure in eating, not feeling at ease when eating out, not liking food before tasting, and developing food aversion. Consequently, it was reported in previous studies that patients with more serious oral symptoms had reduced intake and higher weight loss (Farhangfar *et al*., 2014; Wang *et al*., 2021). Therefore, both sensory alterations and the presence of oral symptoms may affect the eating experience of patients, which may contribute to adverse nutritional and health outcomes.

This study has some limitations, including its small sample size and cross-sectional design. As the sensory perception was based on retrospective response, it would have higher validity if conducted in a longitudinal design comparing the perception before the cancer treatments and a few time points following the treatments. However, the study still indicates that patients' perceived somatosensory alteration together with adverse oral symptoms, are related with greater eating difficulties, that could potentially lead to deteriorated nutritional outcomes.

6.5. Conclusions

Eating is a fundamental act not only fulfilling physiological needs but also carries psychological value. The primary findings of the present study showed that more than half of the patients perceived sensory alterations, including their somatosensory perception. These alterations were associated with different aspects of eating including sensory-related food preference and eating behaviour. In addition, common oral symptoms related to salivary dysfunction were reported by patients, which also influenced their eating experience. Patients with perceived sensory alterations and oral symptoms are more likely to face challenges in eating. In order to develop holistic nutritional interventions that enhance patients' food experiences, it is necessary to consider these two aspects. Future investigations should explore whether somatosensory alterations are unique to head and neck cancer patients or extend to other cancer populations.

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Collectively, Chapters 5 and 6 indicated that sensory alteration among HNC patients extend beyond their taste and smell alterations. The objective and subjective measurements demonstrated that HNC patients experienced somatosensory alteration and oral symptoms. However, it remains to be investigated whether the phenomena occur only among HNC patients, due to the tumour site and treatments, or also prevalent in other types of cancer. The next chapter extends the investigations to explore the somatosensory perception of various cancer patients using subjective measurements.

Chapter 7

Oral Somatosensory Perception and Oral Symptoms of Cancer Patients and the Influence on Eating Behaviour

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Abstract

Purpose: Nutrition-impact symptoms such as sensory alteration and oral symptoms can influence cancer patient's eating experience. Consequently, nutrition-impact symptoms were shown to impact patients' health outcome and quality of life. To gain a comprehensive understanding of their eating difficulties, the objective of the current study was twofold: investigate the prevalence of sensory alteration and oral symptoms and explore their relationship with food preferences and eating behaviour.

Methods: An anonymous online survey was distributed among various types of cancer patients across France, Denmark, and the UK. The survey comprised questions on sensory perception, oral symptoms, sensory-related food preference, and eating behaviour.

Results: The frequently experienced oral symptoms were dry mouth, sensitive teeth, nausea, mouth soreness, and gum pain. Clustering analysis identified different groups of patients based on their sensory perception: no alteration (n=48), increased perception (n=44), and decreased perception (n=8). The three groups differed in their sensory-related food preference. Sensory perception (salty, sour, bitter, pungent, cooling, carbonation, and astringent) was significant predictor of the respective sensory-related food preference. Other predictorss include age, cancer localisation, type of treatments, duration since treatment, and oral symptoms. Sensory alteration and oral symptoms were significant predictors of eating behaviour.

Conclusion: The study highlights the importance of assessing somatosensory perception and oral symptoms in future research to understand cancer patients' eating difficulties and develop tailored management strategies.

Keywords: Oral Somatosensory Perception; Oral Symptoms; Cancer; Questionnaire; Eating Behaviour; Online Survey

7.1. Introduction

Cancer and its treatments contribute to several adverse symptoms of whichthe nutrition-impact symptoms, which compromise the ability and/or motivation to eat and drink, were the most distressing (Xiao *et al*., 2017). These include sensory alterations and several oral symptoms such as dry mouth (xerostomia), oral inflammation (mucositis), limited jaw movement (trismus), chewing difficulties, and swallowing difficulties (dysphagia) (Crowder *et al*., 2020)These symptoms negatively influence their food intake, nutritional status, and overall quality of life (Farhangfar *et al*., 2014; Hutton *et al*., 2007; Wang *et al*., 2021).

Concerning sensory alteration, sensory perception is a multimodal process involving not only the taste and smell but also the somatosensory perception. The somatosensory perception includes the perception of food texture, temperature, and chemesthesis such as the spiciness of chilling and cooling sensation of mint. Existing studies have indicated that sensory alteration is prevalent, for instance taste and smell alterations were experienced by 20-60% of various cancer patients, measured using self-reported questionnaires (Amézaga *et al*., 2018; de Haan *et al*., 2021).

A cross-sectional study showed that sensory alterations among cancer patients extend beyond their taste and smell perception but also include somatosensory perception, which was partly mediated by salivary dysfunction (Riantiningtyas *et al*., 2023). Previous studies also mentioned changed mouthfeel perception, altered perception to spices, and difficulties in eating certain food textures were experienced by these patients (Watson *et al*., 2018; Crowder *et al*., 2020; McLaughlin & Mahon, 2014). In addition, oral symptoms are also prevalent among this population. For instance, the prevalence of xerostomia, dysphagia, and mucositis among cancer patients was 92%, 79%, and 74%, respectively (Wang *et al*., 2021). However, all these studies were conducted among head and neck cancer patients, in which both the tumour site and the side effects of treatments aggressively impair the oral cavity. It remains to be investigated whether sensory alterations in other types of cancer are also comprised of somatosensory alterations. Therefore, the present study aimed to explore the somatosensory perception of various cancer patients. Secondly, to evaluate the association ofsensory alterations and oral symptoms with, food preference and eating behaviour.

7.2. Materials and methods

7.2.1. Study design

This cross-sectional study was conducted between July 2022 and July 2023 using an online survey across France, Denmark, and the United Kingdom. Data were collected anonymously and in accordance with the General Data Protection Regulation via an online platform, Qualtrics (Provo, US). The survey includes several questionnaires which assessed sensory perception and eating behaviour. The survey was available in French, English, and Danish. The survey took 20-30 minutes to be completed. The study design was approved by the University Research Ethics Committee of the respective countries (University of Lyon France, ref : 2022-04-19-002; University of Reading, SREC 68/2022; University of Copenhagen Denmark, CASE: 504-0326/22-5000). Participants were presented with the study information sheet, and informed consent was obtained before initiating the survey.

7. 2.2. Participants

Cancer patients and cancer survivors were eligible to participate. In this survey, we conceptualised cancer patients as cancer patients who are still on active treatments, meanwhile cancer survivors as "any individual who has been cured, is in remission, or has active cancer" (Martina *et al*., 2023). The following inclusion criteria were used: 1) individuals aged 18 or over, 2) had been diagnosed with cancer, 3) had received cancer treatment between 3 months and 5 years ago. The number of participants calculated according to Yamane's (1973) formula indicates that a sample size of 200 participants is sufficient. The research partners announced the study using various methods to reach their national audiences, including online newsletters, mailing lists, social networks of cancer organisations, cancer support groups, Facebook protected pages.

7.2.3. Measures

The variables included in the present study were part of a more extensive questionnaire. The questionnaire included questions on sociodemographics (sex, age, country of residence) and self-reported clinical information (cancer localisation, types of treatment received, and duration since treatment). Furthermore, questions on sensory perception and preference adapted from (Amézaga *et al*., 2018; de Haan *et al*., 2021; Drareni *et al*., 2021; Hutton *et al*., 2007), oral symptoms adapted from (Singer *et al*., 2019), and eating behaviour adapted from (Hunot *et al*., 2016) were included. The detail of the questionnaire, including the questionnaire development process was described elsewhere (Chapter 6). Briefly, the variables relevant to the present paper are as follows:

5) *Sensory perception*: 13 questions covering different sensory modalities. Questions were phrased as follows "Compared to the situation before cancer treatment, I perceive that my *sensitivity* towards [salty/ sweet/ sour/ bitter/ smell of/ texture of/ cold/ hot/ pungent/ cooling/ astringent/ carbonated drinks/ alcoholic] product has…" with response options: "has decreased/ remains unchanged/ has increased", except for texture in which the response options were "changed/ remains unchanged". In addition, they were asked to indicate the intensity of their change with response options: "0= no change, 1= insignificant, 2= mild, 3= moderate, 4= severe"
6) *Sensory-related food preference*: 9 questions on preference were phrased "In comparison with the situation before cancer treatment, my *preference* towards [salty/ sweet/ sour/ bitter/ pungent/ cooling/ astringent/ carbonated drinks/ alcoholic] product has..". The response options were the same as the questions in sensory perception.
7) *Oral symptoms*: 19 oral symptoms (**Table 7.2**) with anchor points ranging from "1= Never" to "5=Always".
8) *Eating behaviour*: 14 different statements related to eating behaviour with response options of "1= disagree completely" to "6= agree completely". Higher scores indicate more eating difficulties; therefore, the scoring was reversed for positively connotated items (When I see or smell food that I like, it makes me want to eat; I like to eat a variety of food; I like to discover new food; I eat more frequently).

7.2.4. Statistical analyses

Descriptive statistics were used to describe the sociodemographic and clinical information. Clustering analysis was performed on patients' responses to their sensory perception to explore the different sensory profiles of patients. Two-way hierarchical clustering analysis, using Ward's method, and the heatmap was illustrated using R studio with pheatmap package. Subgroup analysis to compare the groups were performed using one-way ANOVA, for continuous data, or chi-square test, for nominal or ordinal data. A p-value of ≤ 0.05 was considered significant.

To examine the relationship between oral symptoms and sensory perception with sensory-related food preference and eating behaviour, average scores for the different variables were calculated. An oral symptom score was calculated by averaging the scores of the 19 individual oral symptoms. Likewise, the sensory alteration score was determined by averaging the intensity of changes across individual sensory modalities. Additionally, an eating behaviour score was obtained by averaging the scores of 14 individual items from the eating behaviour questionnaire. Sensory-related food preference was treated as categorical variables with 3 different levels: decreased preference, no change, and increased preference.

Multinomial logistic regression analysis was used to model the relationship between the predictor variables (sex, treatment type, duration since treatment, age, oral symptom, and sensory perception) and membership in the three sensory-related food preference categories (decreased preference, no change, and increased preference)(Farhangfar *et al.*, 2014). Individual models were calculated for each modality of the sensory-related food preference. The reference category was no change in preference.

To model the relationship between eating behaviour and independent predictors: sensory alteration and oral symptoms, multiple linear regression was performed. The model also included sex, treatment type, duration since treatment, age, but these were not significant predictors and therefore removed from the model. Furthermore, Spearman coefficients were used to evaluate the correlations between the scores of oral symptoms, sensory alteration, and eating behaviour. SPSS Statistics 23 (IBM Corporation) was used to perform descriptive and regression analyses.

7.3. Results

7.3.1. Characteristics of the study population

In total, 117 patients completed the first part of the questionnaire (sensory perception and preference). After checking for missing or invalid data, the final sample size resulted in 100 responses. Sociodemographic and clinical characteristics of patients are presented in **Table 7.1**.

The majority of the respondents were female (81%) and had been diagnosed with breast cancer (49%). The respondents were mainly from France (60%), followed by the UK (28%), and Denmark (12%). The majority (87%) of the patients received a combination of different treatments, with 90% receiving systemic treatment, 81% receiving surgery, and 64% receiving radiotherapy. Fifty-three percent of the participants responded to the survey less than one year after their treatment, including 11 participants who were still receiving the treatments.

Table 7.1. Demographic and clinical characteristics of all patients, and patients classified based on their sensory perception.

Variable	All patients (n=100)	Increased perception group (n=44)	No alteration group (n=48)	Decreased perception group (n=8)	p-value
Age	55.9 ± 11.1	58.1 ± 11.5 $_a$	53.6 ± 9.8 $_a$	58.3 ± 14.8 $_a$	0.125
Sex					0.374
Female	81	36_a	40_a	5_a	
Male	19	8_a	8_a	3_a	
Country					0.006
France	60	$24_{a,b}$	34_b	2_a	
UK	28	11_a	11_a	6_b	
Denmark	12	9_a	3_b	$0_{a,b}$	
Cancer localisation					0.004
Breast	49	$19_{a, b}$	30_b	0_a	
Bladder	3	2_a	1_a	0_a	
Colon	6	2_a	4_a	0_a	
Oesophagus	3	0_a	2_a	1_a	
Ovary	4	3_a	1_a	0_a	
Prostate	6	2_a	4_a	0_a	
Head and neck	12	$7_{a, b}$	1_b	4_a	
Other	17	9_a	5_a	3_a	
Types of treatment					
Surgery	81	36_a	42_a	3_b	0.004
Radiotherapy	64	28_a	32_a	4_a	0.660
Chemotherapy	82	35_a	41_a	6_a	0.662
Other treatments	46	19_a	24_a	3_a	0.711
Duration since treatment					0.657
< 1 year ago	53	24_a	26_a	3_a	
> 1 year ago	47	20_a	22_a	5_a	

Each subscript letter denotes a subset of sensory perception group categories whose column proportions do not differ significantly from each other at the 0.05 level on chi-square test.

7.3.2. Descriptive result on sensory perception and oral symptoms

7.3.2.1. Prevalence of altered sensory perception.

Figure 7.1 illustrates the sensory perception of cancer patients. Changes in smell perception were perceived by 29% of the respondents, with a balanced proportion of those reporting increased and decreased perception. Changes in taste perception were experienced by approximately 30% of the participants, across the 4 basic tastes. Among them, 20% reported increased perception towards sour and bitter taste while the remaining 10% reported decreased perception, meanwhile for salty and sweet there were a rather balanced proportion of participants reporting increased and decreased perception.

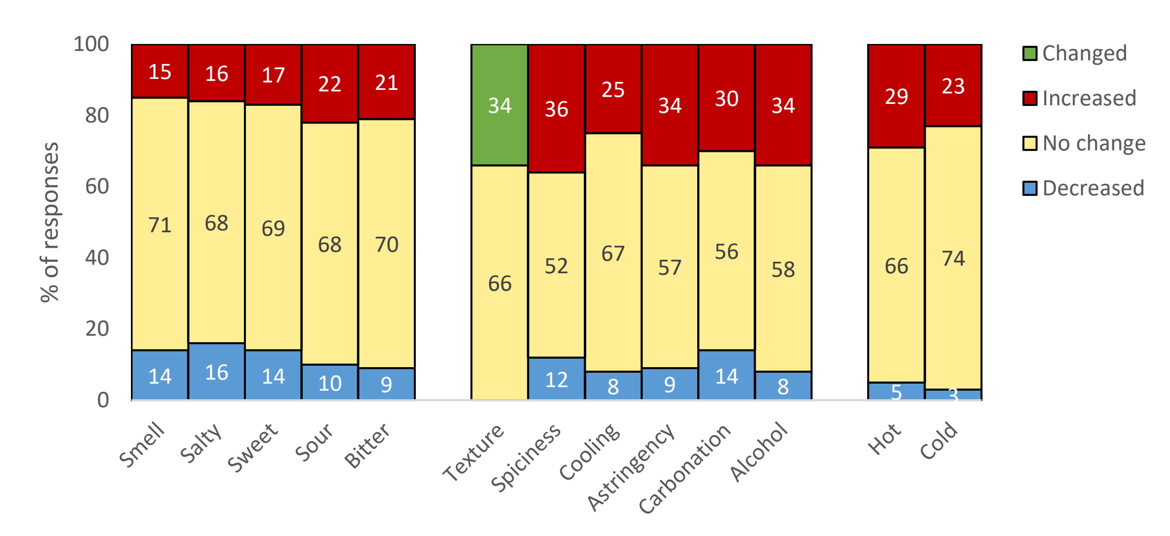

Figure 7.1. Change in sensory perception of patients
Questions were phrased as follows "In comparison with the situation before cancer treatment, I perceive that my sensitivity towards [sensory modality] food/drink has …" with response options of "increased/ not changed/ decreased", except for texture in which the response options were "changed/ remains unchanged".

For texture, the direction of change (increased or decreased) was not assessed. However, 34% of the participants reported experiencing changes in their perception towards food texture. Regarding chemesthetic sensations, between 33-48% of participants perceived altered perception, with 25-34% reporting increased sensitivity as opposed to the smaller proportion of patients (8-14%) reporting decreased sensitivity. Meanwhile, 26% and 34% of participants experienced altered perceptions towards cold and hot food, respectively, with the majority of them reporting increased sensitivity (23-29%) and only 3-5% reported decreased sensitivity.

7.3.2.2. Frequency of oral symptoms

Table 7.2 presents the frequency of oral symptoms. The most frequently experienced oral symptoms were dry mouth, sensitive teeth, nausea, mouth soreness, and gum pain. Moreover, dry mouth and sensitive teeth were experienced by more than half of the respondents.

Table 7.2. Frequency of oral symptoms experienced by patients.

	Never	Rarely	Sometimes	Often	Always	Subtotal [a]
Dry mouth	16	16	35	22	11	68
Sensitive teeth	20	14	28	22	16	66
Nausea	30	25	30	12	3	45
Mouth sore	27	31	28	12	2	42
Gum pain	30	29	31	8	2	41
Dental pain	34	28	26	10	2	38
Difficulty chewing	42	22	15	6	15	36
Food stuck in the mouth	43	22	18	13	4	35

Bleeding gum	36	30	24	7	3	34
Sticky saliva	46	21	20	7	6	33
Sore mouth	47	23	18	8	4	30
Avoid certain foods due to dental problems	50	21	15	5	9	29
Difficulty swallowing	48	23	15	10	4	29
Burning sensation in the mouth	61	13	20	5	1	26
Food stuck in the throat	56	19	14	9	2	25
Pain in throat	51	24	17	6	2	25
Fear of eating due to pain	64	16	13	5	2	20
Sore lips	54	26	13	7	0	20
Limited jaw opening	73	13	7	3	4	14

[a] Subtotal of sometimes, often, and never

7.3.4. Relationship between sensory perception and food preference.

7.3.3.1 Patient clustering based on sensory perception.

Following their responses on their sensory perception, clustering analysis resulted in three distinct sensory profiles of patients (**Figure 7.2**): 1) patients with generally increased perception (n=44), hereafter referred to as *increased perception* group; 2) patients with generally decreased sensitivity (n=8), hereafter referred to as *decreased perception* group; and 3) patients with little to no perceived alteration (n=48), hereafter referred to as *no alteration* group. The groups differed in cancer localisation (p=0.004) and surgery (p=0.004). Most of the breast cancer patients were categorised in the no alteration group, whereas most of the head and neck cancer patients were categorised in the increased and decreased perception group. Moreover, patients who received surgery were primarily classified in the increased perception and no alteration group. Age (p=0.125), sex (p=0.374), radiotherapy (p=0.660), chemotherapy (p=0.662), other treatment (p=0.771), and duration since treatment (p=0.657) did not significantly differ between groups. The information about the patient characteristics of each group is presented in **Table 7.1**.

Regarding the sensory modalities, the clustering showed the distinction between somatosensory modalities (hot, texture, cold, cooling, carbonation, pungency, and astringency) and smell/ taste modalities. Following this distinction, the sensory perception score (**Section 7.2.4**) was calculated separately for somatosensory perception and smell/taste perception.

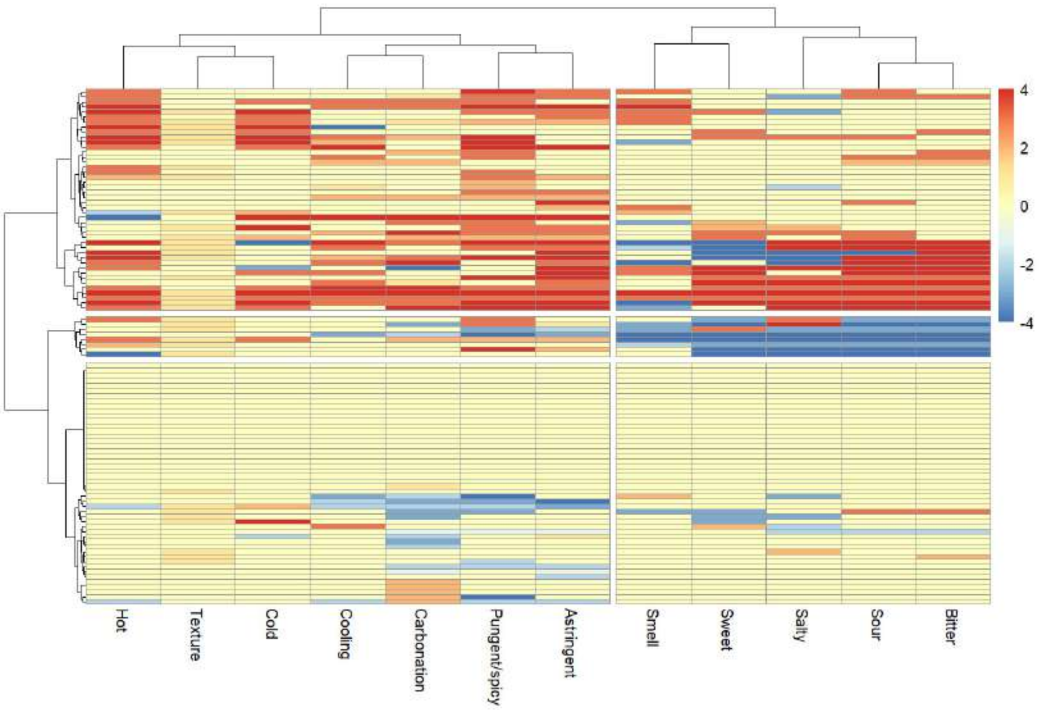

Figure 7.2. Heat-map diagram of a two-way hierarchical clustering analysis consisting of sensory perception of cancer patients.

Each row represents a patient, and each column represents their perception of each sensory modality. Red colour represents increased perception, yellow colour represents unchanged perception, and blue colour represents decreased perception. The colour saturation represents the intensity of change in perception. Top rows: increased perception group (n=44), middle rows: decreased perception group (n=8), bottom rows: no alteration group (n=48).

7.3.3.2. Change in sensory-related food preference.

Figure 7.3a illustrates the changes in sensory-related food preference for all cancer patients. In terms of basic taste, the highest percentage of patients reporting changed preference was observed for sweet food (63%), with a relatively equal proportion of participants showing increased (29%) and decreased (34%) preference. Forty-nine percent of the participants reported a changed preference towards salty food, predominantly leaning towards increased preference (34%). Conversely, most of the participants who reported a changed preference for sour and bitter food showed a decreased preference (33 and 36%, respectively). Changes in preference towards food texture were reported by 27% of participants. Regarding chemesthetic sensations, 42-55% of the patients reported changes in their preference towards spicy, astringent, and carbonated products. Among them, approximately 40% reported decreased preference towards these products. None reported increased preference towards alcoholic drinks, while 55% reported decreased preference.

7.3.3.3. Changes in sensory-related food preference in patients classified by their perception.

Subgroup analysis on the sensory-related food preference of the three groups showed that they differed in their sensory-related food preference towards: salty (p=0.024), sour (p=0.010), bitter (p=0.005), pungent (p<0.001), cooling (p=0.035), carbonation (p=0.013), and astringent (p=0.014) products. The preference towards food textures (p=0.053), sweet products (p=0.435), and alcohol (p=0.392) did not significantly differ between the groups. **Figure 7.3b** shows that in the increased perception group, there was a higher percentage of patients (> 50%) reporting decreased preference towards multiple sensory modalities, except for salty, sweet, and cooling. The pattern of preference for the decreased perception group was rather spurious, but it is important to note that this group consisted of a small percentage of the patients.

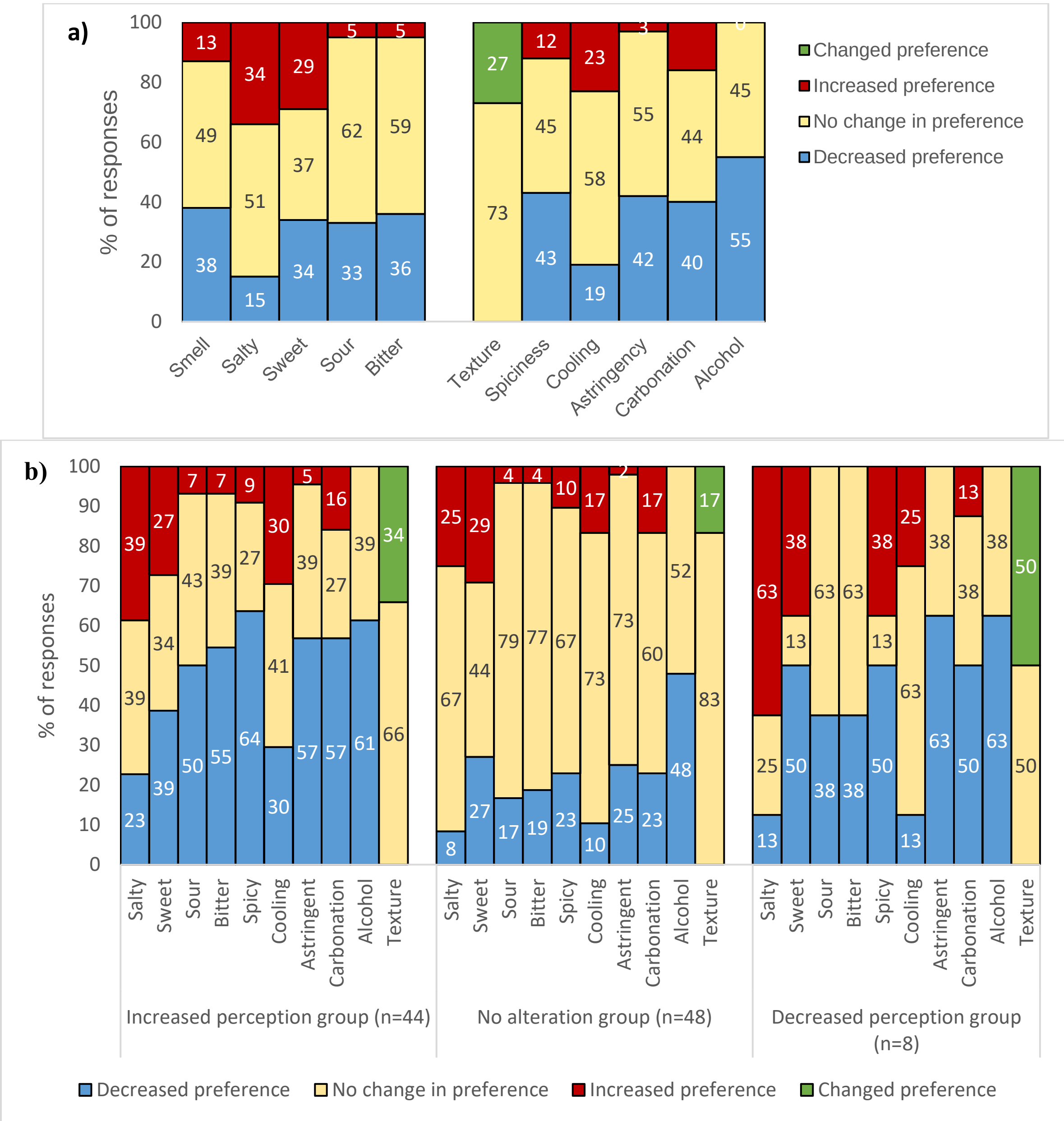

Figure 7.3. Change in sensory-related food preference of **a)** all patients and **b)** patients classified based on their sensory perception.

Questions were phrased as follows "In comparison with the situation before cancer treatment, my preference towards [sensory modality] food/drink has …" with response options of "increased/ not changed/ decreased", except for texture in which the response options were "changed/ remains unchanged".

There were 21-40% of patients in this group who reported changes in their sensory-related food preference. This implies that factors other than changes in perception may influence the change in food preference, thus multinomial logistic regression analysis was performed. The relationship between the predictor variables (intensity of change in individual sensory perception, oral symptoms, age, sex, cancer localisation, treatment, and duration since treatment) on sensory-related food preference is presented in **Table 7.3**. The models were performed on the individual sensory modality, with no change in preference as the reference category.

The intensity of change in perception of certain sensory modalities, such as sourness, bitterness, pungency, cooling, astringency, alcohol, and texture, were significant predictors of their respective sensory-related food preference. For instance, sour perception was a significant predictor for decreased preference of sour food (OR= 1.507, CI = 1.10 – 2.06, p= 0.01). The impact of each variable can be understood from the odds ratio, with odds ratio (OR) < 1 indicating reduced risk and OR > 1 indicating increased risk of belonging in the category. Therefore, when compared to patients who did not change their preference to sour food, each 1-point increase in the intensity of change in sour perception results in a 50.7% higher risk of belonging in the decreased preference to sour food. On the other hand, the perception of saltiness, sweetness, and carbonation did not show a significant relationship with their respective sensory-related food preference. For these modalities, age (for salty-preference), oral symptoms (salty and carbonation), type of treatment (salty), cancer localisation (sweet), and duration since treatment (carbonation) were shown to be significant predictors.

Table 7.3. Multinomial logistic regression model describing ther relationship between the predictor variables (sensory perception, oral symptoms, age, sex, cancer localisation, treatment, and duration since treatment) on category of sensory-related food preference (increased preference, no change, or decreased preference). The reference category is no change in preference.

Outcome	**Variable**	**OR**	**S.E.**	**P-value**	**95% CI**	
Salty Preference		Cox and Snell = 37.2%, Nagelkerke = 43.1%				
Decreased (n=15)	Age	1.082	0.035	0.026	1.01	1.159
Increased (n=34)	Oral symptoms	4.581	0.399	<.001	2.097	10.006
	Radiotherapy	3.92	0.614	0.026	1.176	13.071
Sweet Preference		Cox and Snell = 21.3%, Nagelkerke = 24.0%				
Decreased (n=34)	Localisation	1.31	0.109	0.013	1.059	1.621
Increased (n=29)	Localisation	1.344	0.113	0.009	1.078	1.677
Sour Preference		Cox and Snell = 31.2%, Nagelkerke = 38.9%				
Decreased (n=33)	Oral symptoms	2.326	0.355	0.017	1.16	4.665
	Sour perception	1.507	0.159	0.010	1.102	2.059

Bitter Preference		Cox and Snell = 37.4%, Nagelkerke = 46.2%				
Decreased (n=36)	Oral symptoms	3.225	0.385	0.002	1.517	6.856
	Bitter perception	1.692	0.166	0.002	1.222	2.341
	Sex	6.845	0.961	0.045	1.04	45.052
Pungency Preference		Cox and Snell = 44.7%, Nagelkerke = 52.1%				
Decreased (n=43)	Oral symptoms	3.482	0.414	0.003	1.546	7.842
	Pungency percept.	1.588	0.155	0.003	1.173	2.15
Increased (n=12)	Age	1.184	0.072	0.019	1.029	1.362
	Localisation	1.347	0.15	0.047	1.004	1.808
	Oral symptoms	6.773	0.719	0.008	1.655	27.707
Cooling Preference		Cox and Snell = 30.3%, Nagelkerke = 35.3%				
Decreased (n=19)	Cooling perception	1.867	0.227	**0.006**	1.197	2.912
Astringency Preference		Cox and Snell = 23.1%, Nagelkerke = 28.9%				
Decreased (n=42)	Astringency	1.355	0.134	**0.024**	1.041	1.763
Carbonation Preference		Cox and Snell = 25.9%, Nagelkerke = 29.8%				
Decreased (n=40)	Oral symptoms	2.063	0.356	**0.042**	1.027	4.144
Increased (n=16)	Duration	0.195	0.784	**0.037**	0.042	0.905
Alcohol Preference		Cox and Snell = 25.6%, Nagelkerke = 34.2%				
Decreased (n=55)	Alcohol perception	1.492	0.164	**0.015**	1.082	2.057
	Radiotherapy	0.253	0.578	**0.017**	0.081	0.784
	Duration	8.078	0.564	**<.001**	2.674	24.4
Texture preference		Cox and Snell = 32.4%, Nagelkerke = 47.1%				
Changed (n=27)	Texture perception	2.554	0.228	**<.001**	1.635	3.99

7.3.4. Impact of sensory perception and oral symptoms on eating behaviour.

Multiple linear regression was performed to test the hypothesis whether oral symptom and sensory alteration (taste/smell and somatosensory) carry significant impacts on eating behaviour. The overall regression was statistically significant (R^2 = 0.35, F (3, 96 = 17.0, p < 0.001). The R^2 = 0.35 depicts that the model explains 35% of the variance in eating behaviour score. **Table 7.4** shows that somatosensory alteration (β=0.247, t= 2.782, p=0.007), taste/smell alteration (β=0.142, t= 2.030, p=0.045), and oral symptoms (β=0.216, t= 2.014, p=0.047) were significant positive predictors of eating behaviour. This implies that the higher the frequency of oral symptoms and the greater the intensity of sensory alteration, the higher the likelihood of having more eating difficulty. Moreover, the Spearman correlation test showed that eating behaviour score was significantly correlated with somatosensory alteration (r=0.54, p<0.001), taste/smell alteration (r=0.48, p<0.001), and oral symptoms score (r=0.39, p<0.001).

Table 7.4. Linear regression model describing the relationship between the independent predictors (sensory alteration and oral symptoms) and the dependent variable eating behaviour.

Variable	β	SE	t	p-value
		R^2 = 0.35, F (3, 96 = 17.0, p < 0.001)		
Oral symptoms	0.216	0.107	2.014	0.047
Taste/smell alteration	0.142	0.07	2.030	0.045
Somatosensory alteration	0.247	0.089	2.782	0.007

7.4. Discussion

The present study investigated the prevalence of sensory alterations, including somatosensory, and their relationship with food preference and eating behaviour. In addition, the links with oral symptoms were also explored. The cluster analysis effectively categorises patients based on their sensory perception profiles. Furthermore, multinomial regression models allowed to quantify the predicted variables contributing to the food preferences and eating behaviour.

Approximately 30% of patients who completed the survey reported altered sensory perception across the different sensory modalities (30-32% for basic tastes, 29% for smell, 34% for texture, 33-48% for chemesthesis, and 26-34% for temperature). The prevalence of sensory alteration varies among previous cross-sectional studies using self-reported questionnaires. For instance, among various cancer patients (N=50), 60% of the patients reported taste alterations and 26% reported smell alterations (de Haan *et al*., 2021). In a different study which assessed individual sensory modalities (basic tastes, smell, temperature) of various cancer patients (N=151), the prevalence of sensory alterations were: 25-44% for basic tastes, 20% for smell, and 20-35% for temperature, similar to the findings in this study (Amézaga *et al*., 2018). A study among patients with gastrointestinal stromal tumours (N=65) showed that 38% of patients perceived changes in their taste perception, 23% in their smell perception, and 55% in their mouthfeel perception (van Elst *et al*., 2022). Differences in the questionnaire used, clinical characteristics of the patients, treatment type, duration since treatment, and oral symptoms may influence the findings and explain any noticeable discrepancies in the results (de Vries, Boesveldt, *et al*., 2018; Ruiz-Ceamanos *et al*., 2022).

In addition to sensory alteration, several oral symptoms were considered nutrition-impact symptoms but investigations into these symptoms were primarily conducted among head and neck cancer patients (Crowder *et al*., 2018; Farhangfar *et al*., 2014; Wang *et al*., 2021). It was shown that among these patients, oral pain, dry mouth, and chewing and/or swallowing difficulty were the most prevalent oral symptoms. Further, some of these symptoms (pain, dry mouth, difficulty swallowing, mouth sore, taste change, and mucositis) had a strong impact on their health outcomes (Farhangfar *et al*., 2014; Jin *et al*., 2021; Wang *et al*., 2021). In the current study involving various types of cancer patients, the frequent oral symptoms included dry mouth, sensitive teeth, nausea, mouth soreness, and gum pain.

More than 40% of the patients reported changes in their food preference across the different sensory modalities. Previous studies have demonstrated that altered food preference was experienced by cancer patients across different phases of cancer treatments (Coa *et al*., 2015; Crowder *et al*., 2020; de Vries, Winkels, *et al*., 2018). In terms of basic tastes, a higher percentage of people have increased their preference towards salty than sweet food, a similar finding was observed in a previous study with various cancer populations (Guerdoux-Ninot *et al*., 2016). There was also a generally decreased consumption of alcohol possibly due to health recommendations (Schwedhelm *et al*., 2016).

Previous studies showed a high individual variation in sensory perception (Belqaid *et al*., 2014; Drareni *et al*., 2021; Spotten *et al*., 2017). To gain a better understanding of the associations between perception and preference, instead of considering all patients as a single group, clustering analysis was conducted to identify different sensory profiles. The clustering analysis revealed three different profiles of patients based on their sensory perception: those with little to no sensory alterations (48%) and those with increased (44%) and decreased (8%) perception. This finding is similar to a previous study in which categorised patients based on their taste/smell perception, composed of 48% of patients in the no alteration group, and the remaining patients in the moderate and severe alteration group (Drareni *et al*., 2021). Results also revealed that within the increased and decreased perception groups, some patients reported increased perception in some sensory modalities but decreased in others, with varying intensity of change in perception. This implies that sensory alteration in cancer patients is not a unidirectional phenomenon (e.g. only decreased perception) but can be heterogenous.

Consequently, the relationship between the patients' sensory perception and sensory-related food preferences was investigated. Previous studies showed inconsistent association between sensory alterations and food preference. For instance, in the group with no alterations, the different flavoured oral nutritional supplements were rated similarly in terms of preference whereas in the alteration group, there were significant differences among the product preference (de Haan *et al*., 2021). On the other hand, there was no apparent difference in preference of flavour-enhanced eggplant creams between patients with and without sensory alterations (Drareni *et al*., 2023).

In this study, the subgroup analysis showed that the three sensory profile groups significantly differed in their food preference, namely towards salty, sour, bitter, pungent, cooling, carbonation, and astringent food products but not on sweet food, alcohol, and food texture. Further, **Figure 7.3b** illustrated that patients in the increased perception group showed a tendency of decreased preference towards several sensory modalities, whereas the majority of those in the no alteration group reported no change in preference. Nevertheless, a small percentage of patients in the no alteration group reported changes in their preference, implying that other factors may contribute to modified food preference. The multinomial regression analysis revealed that for most sensory modalities, changes in their respective sensory perception (sourness, bitterness, pungency, cooling, astringency, alcohol, and texture) were significant predictors of change in the sensory-related food preference. The results also suggested that more severe changes in sensory perception resulted in an increased risk of modified the respective food preferences.

Other factors explored in this study that contributed to modified preference were age, cancer localisation, type of treatments, duration since treatment, and oral symptoms. The oral symptoms frequently experienced by patients include dry mouth, sensitive teeth, nausea, mouth soreness, and gum pain. Previous studies also showed that food preference changes over time throughout the cancer treatments (Coa *et al*., 2015; IJpma *et al*., 2016). Furthermore, other factors such as age, gender, cancer types, and type of treatments also influenced food preference (Coa *et al*., 2015; IJpma *et al*., 2016).

Finally, the multiple linear regression showed that oral symptoms, taste/smell alteration, and somatosensory alteration significantly influenced eating behaviour. Among the three variables, somatosensory alteration was the strongest predictor of eating behaviour, followed by oral symptoms and taste/smell alteration. In this study, the higher score for eating behaviour indicates greater difficulties in relation to eating. Therefore, the more frequent oral symptoms and severe sensory alterations contributed to more eating difficulties. In previous studies, nutrition impact symptoms were shown to have negative impact on nutritional intake and weight loss in head and neck cancer patients (Farhangfar *et al*., 2014; Jin *et al*., 2021; Wang *et al*., 2021).

The current study has a number of limitations. Considering the heterogeneity of clinical characteristics of patients included and the inclusion of patients across different countries, the sample size of this study is relatively small. Additionally, a cross-sectional study involving retrospective questions ("In comparison to before the cancer treatment…") may introduce response bias depending on participants' memory. A longitudinal study that tracks individuals' perception and preference at different time points would provide a more precise depiction of their experiences.

7.5. Conclusion

The present study examined sensory perception, including somatosensory, and oral symptoms in relation to food preference and eating behaviour of various cancer patients. The results shows that sensory perception plays a role in modified food preference and eating behaviour. The study also justifies the need for future research to incorporate an assessment of (somato)sensory perception and oral symptoms. This will enable a comprehensive understanding of cancer patients' eating difficulties and facilitate the development of management strategies tailored to their symptoms.

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The investigations indicate that sensory alterations, including somatosensory alterations, were experienced by various cancer patients. Furthermore, it is important to note that those with alterations showed modified eating behaviour. Therefore, further investigation into dietary adjustments for these patients is warranted. The study also justifies the need for future research to incorporate assessment of (somato)sensory perception and oral symptoms.

Chapter 8

Designing Food Adapted to Their Senses:

Conception of the study

Abstract

Introduction: Sensory alterations and oral symptoms are prevalent among cancer patients. These factors contribute to altered eating experience. This suggests that it is crucial to conduct more research on dietary modifications, specifically the design of sensory-adapted foods, for these patients. The objectives of this study are to develop sensory-adapted food concepts and to evaluate the hedonic acceptance of the developed food concepts.

Materials and methods: This study consists of three successive parts: 1) Culinary development of food concepts, 2) Focus group discussion, and 3) Consumer test on sensory-enhanced recipes. The culinary development was assisted by the culinary chefs at Institut Lyfe research center. Culinary development was aimed at developing food concepts to stimulate salivary secretion through mechanical (texture contrast) and gustatory (sour and/or umami ingredients) stimulations. The six food concepts were tasted and evaluated first in a focus group discussion with cancer patients (n=4). The hedonic acceptance of the validated food concepts will be assessed in a consumer study.

Expected results: This study aims to compare hedonic ratings between two versions of the food concepts (standard vs sensory-enhanced), with the hypothesis that the enhanced version will receive higher ratings. Additionally, the study will examine the correlation between hedonic ratings and salivary function, self-reported sensory perception, and oral symptoms. Potential variations in ratings among patients with different cancer types and treatments will also be explored. The findings will provide insights for sensory enhancement strategies based on effect sizes of flavor and texture modifications, customized to different cancer types.

8.1 Introduction

Sensory impairment is one of the factors contributing to reduced appetite and inadequate food intake in cancer patients. Cancer patients with sensory impairment have been shown to have lower energy intake and greater weight loss, suggesting a higher nutritional risk (Brisbois *et al*., 2011; Dalton *et al*., 2022; Hutton *et al*., 2007; Messing *et al*., 2021). Alterations in taste and smell are common side effects observed in all cancer treatments. It is estimated that they affect 16-70% of cancer patients undergoing chemotherapy as well as 50-90% not undergoing active treatment (Bernhardson *et al*., 2009; Brisbois *et al*., 2006; Spotten *et al*., 2017; Zabernigg *et al*., 2010). In addition to alterations in their taste and smell perceptions, studies have indicated that cancer patients also experience changes in their somatosensory perceptions (Watson *et al*., 2018; Elfring *et al*., 2012; Loewen *et al*., 2010; Riantiningtyas *et al*., 2023). Somatosensation/somesthesia provides information about texture, temperature and trigeminal sensations (burning of chilli, refreshing of mint, tingling of fizzy drinks). These sensations are detected by mechanoreceptors, thermoreceptors and nociceptors scattered throughout the oral epithelium (Simons & Carstens, 2008). It has also been reported that HNC cancer patients experience oral symptoms such as difficulty chewing/swallowing foods (dysphagia), impaired sensitivity to spices due to oral pain (mucositis), and dry mouth (xerostomia) (Crowder *et al*., 2018; Farhangfar *et al*., 2014; Wang *et al*., 2021).

The perception of food is a complex sensation involving an intermodal interaction between gustation, olfaction and somatosensation. Consequently, alteration of one of the sensory functions will modify the entire perception of food and the eating experience (Engelen, 2012; Simons & Carstens, 2008; Small, 2012; Spence, 2016). All of these factors contribute to altering patients' overall perception of food, whether in terms of the perceived sensory quality of food or the hedonic judgement of food. Sensory changes may involve changes originating in the physical structures of the mouth or neural pathways, but also hedonic changes, i.e. food may taste the same as usual, but this taste is no longer considered pleasant, leading to an aversion to food and a decrease in the pleasure of eating (Bernhardson *et al*., 2009). The previous studies (Chapters 5-7) indicated that patients with alterations showed modified eating behaviour and that further investigation into dietary adjustments, in the form of sensory-adapted food design, for these patients is necessary.

8.1.1. Designing food for patients

The knowledge gained from previous studies (Chapters 5-7) was used as the basis of the ideation of the food concepts. The key learnings from the studies, namely the presence of sensory alterations and oral symptoms, were used to guide the directions for culinary development. Given the high prevalence of dry mouth among cancer patients and the critical role of saliva for food perception, it is necessary to address this concern through innovative food designs. The developed food concepts should aim to stimulate salivation which can be obtained through two main strategies: mechanical and gustatory stimulation (Gavião *et al*., 2004; Watanabe & Dawes, 1988).

The first strategy is to develop food with a semi-solid texture, as saliva is secreted through the mechanical act of mastication (Gavião *et al*., 2004). This food matrix will encourage some degree of mastication yet does not require extensive chewing to break down the food. As some cancer patients also demonstrated difficulty in chewing and swallowing (Crowder *et al*., 2020; Farhangfar *et al*., 2014), we also included the element of texture contrast to ease the food oral processing. For instance, a dry texture should be complemented with a moist texture, and hard/crunchy texture combined with a soft texture. In addition, from the online survey, we collected data on liked and disliked food textures, which should be taken into consideration when designing the food concepts. The preferred texture attributes include tender, melt-in-mouth, crunchy, thin, smooth, and soft. Whereas texture attributes such as rubbery, sticky, dry, tough, hard, and thick were commonly categorised as disliked textures.

The second strategy is to incorporate saliva-stimulating ingredients such as sour and umami ingredients. Sour and umami taste were shown to stimulate salivary flow (Bozorgi *et al*., 2020; Sasano *et al*., 2015; Uneyama *et al*., 2009). In addition, to facilitate food acceptance, the food concepts should aim to use familiar ingredients (Torrico *et al*., 2019). To cater possible dietary restrictions, we avoided the use of meat products.

8.1.2. The present study

The objective of the present study is twofold: 1) to develop sensory-adapted food concepts that consider the alterations of cancer patients, and 2) to evaluate the hedonic acceptance of the developed food concepts. The first part of the objective has been obtained through culinary development of six different food concepts proposed by a team of culinary chefs of Institut Lyfe Research Center, France. The culinary development was followed by a focused discussion involving a small group of cancer patients to further understand their sensory perception and eating behaviour, as well as obtain preliminary evaluation on the developed food concepts. The second objective will be obtained through a consumer test involving cancer patients. The conception of the study design of the consumer test is presented in this chapter.

8.2. Materials and Methods

This study consists of three successive processes: 1) Culinary development of food concepts, 2) Focus group discussion, and 3) Consumer test on sensory-enhanced recipe. All of the process took place in Institut Lyfe Research Center, France.

8.2.1. Culinary development

Brainstorming sessions were held to discuss the direction of the food concepts (**Section 8.1.1**). A culinary chef, the PhD student, and one representative of the supervisory team participated in the brainstorming sessions. The culinary chefs proposed six different food concepts (**Table 8.1**).

8.2.2. Focus group discussion

Following the culinary development, a focus group discussion with cancer patients (n=4) was held to understand the impact of cancer treatment on food perception, oral problems, and consumption habits. The participants were also asked to taste and evaluate the 6 food concepts that were prepared by the culinary team of Institut Lyfe Research Center.

8.2.2.1. Participants

Cancer patients or cancer survivors aged between 18-75 years old, who had been diagnosed with cancer less than 2 years ago were recruited for the focus group discussion. The exclusion criteria were: being pregnant or currently breastfeeding, having known food allergies or intolerances, having difficulty in swallowing, having diagnosed with taste or smell alterations prior to cancer diagnosis, having oral inflammation, and having nausea in the last 24 hours.

8.2.2.2. Procedure

A semi-structured focus group was conducted at Institut Lyfe Research Center, France. The discussion was carried out in French and lead by a moderator. The discussion was audio recorded and divided into 2 parts: 1) impact of cancer and its treatments on sensory perception, food liking, and eating behaviour, 2) tasting and evaluation of the food concepts. Before presenting the food to participants, the culinary chefs briefly described the food concepts. In addition to the moderator, there were 2 members from the Innovation Team of Institut Lyfe Research Center, a representative of the supervisory team, and the PhD student who were present to observe the discussions.

8.2.3. Consumer test

8.2.3.1. Food samples

Following the focus group discussion, two validated food concepts (cromesquis and pannacotta) were developed further into two versions (standard vs. sensory-enhanced) upon discussion with the supervisory team. The two versions of cromesquis differed in terms of flavour (addition of chilli for the enhanced version) whereas the two versions of pannacotta differed in terms of texture (larger crumble size for the enhanced version). The two versions of the food samples are evaluated in terms of hedonic acceptance.

8.2.3.2. Participants

Various types of cancer patients who are still undergoing treatment are eligible for the study. The primary endpoint is the comparison in hedonic rating between the enhanced version and the standard version. Power analysis was performed using the pwr package of R (Stephane Champely, 2020). Delta was set at 0.8 and sigma was set at 2.5, obtained from a previous study and (Rahemtulla *et al.*, 2005). With an alpha risk of 5% and a power of 80%, the calculation resulted in 79 participants.

The inclusion criteria are individuals aged between 30-70 years old who are diagnosed with cancer, and have been receiving systemic oncological treatment for at least one month. The exclusion criteria include: 1) Patient undergoing radiotherapy on the head and neck region, 2) known food allergy/intolerance to food samples, 3) inability to swallow soft foods, 4) nausea or vomiting in the last 24 hours, 5) severe inflammation of the mouth or throat (ulcers, mucositis), 6) memory loss or cognitive problems, and 7) currently pregnant or breast-feeding.

Recruitment method

Patients will be recruited from the following hospitals: Hôpital de la Croix Rousse and Centre Léon Bérard. Cancer patients who are visiting the hospital for treatments will be invited to take part in the study. The study will take place during the patient's routine care, but is not part of their medical care. Patients will be interviewed on the clinical ward where they receive their treatment. The nurses/doctors will introduce the patients to the researcher, who will inform them of the study and check their eligibility. If the patient agrees to take part, the researcher then proceeds with the test.

8.2.3.3. Primary and secondary endpoints

As the main objective is to assess the impact of sensory enhancement of foods on hedonic acceptance, the main evaluation criterion is the comparison of the hedonic rating between the enhanced version and the standard version. The secondary endpoints include: 1) Salivary function, 2) Self-reported sensory perception and oral symptoms, and 3) The correlation between food appreciation, salivary function and self-reported data (sensory perception and oral symptoms).

8.2.3.4. General organization of the study

Time and location

The study will be conducted in between mealtimes, in the morning at 10.00-11.00 or in the afternoon at 15.00-16.00. The study will be conducted in two sites: Hôpital Croix-Rousse (103 Gd Rue de la Croix-Rousse 69004 Lyon) and Centre Léon Bérard (28 Prom. Léa et Napoléon Bullukian, 69008 Lyon).

Procedure

First, eligible participants will perform a saliva function test using the Saliva-BUFFER kit. It is a rapid diagnostic tool to assess salivary function which includes measurement on saliva consistency, pH, saliva volume, buffering capacity. The saliva samples collected will be discarded immediately after the aliva function test.

Afterwards, four different food samples: 2 versions of cromesquis and 2 versions of panna cotta will be presented, and participants will be invited to taste and rate their hedonic acceptance (overall acceptance, flavour intensity, texture, and ease of swallowing) of the food samples on a visual analogue scale. Finally, participants complete a self-reported questionnaire on sociodemographic information, clinical information, sensory perception, and oral symptoms (**Appendix 3**). The total duration of the study will be 20 to 30 minutes for each participant.

Type of data collected

- Demographics **:**
  - Age
  - Gender
  - Family situation
  - Level of education
  - Occupation or last occupation
- Health data
  - Height, weight
  - Smoking status
  - Cancer location

    - Treatment type and duration
- Food evaluation and self-reported questionnaires
    - Salivary function
    - Level of satiety
    - Hedonic rating of food samples
    - Sensory perception (self-reported)
    - Oral symptoms (self-reported)

8.2.3.5. Data analysis

A descriptive analysis of the populations studied will first be carried out: distributions, means and standard deviations of age, height and weight. Clinical characteristics of patients in relation (type of cancer, type of treatment, time from start of treatment to inclusion, and treatment history) will be reported as a percentage. Statistical analyses will be performed using SPSS 23, with a p-value of ≤ 0.05 considered significant. Data relating to the assessment of food samples are expressed as mean ± SD. To compare the differences between the two samples (enhanced vs. standard), a paired-t-test will be used. For self-reported sensory perception and oral symptoms, scores from 1 to 5 will be assigned for each item. A total score will be calculated for each participant.

Spearman coefficient will be calculated for assessing correlations between hedonic rating, clinical characteristics, salivary function, self-reported sensory perception, and oral symptoms. Multidimensional analysis techniques (principal component analysis or discriminant analysis) will be used for their value in exploratory research into links between different factors. These descriptive techniques enable all the results to be displayed in a reduced-dimensional set that retains most of the information. They will initially be carried out using self-reported sensory perception, in order to highlight the parameters that contribute the most to the appreciation of food samples. Secondly, all the parameters most subject to variation will be taken into account simultaneously in order to establish relationships between the different data collected.

8.3. Results

8.3.1. Description of food concepts

The six food concepts were developed based on the criteria described in **section 8.1.1**, namely: semi-solid with texture contrast, incorporation of ingredients that stimulate saliva, use of familiar ingredients, and avoid meat products. The description of each food concept including the main ingredients is presented in **Table 8.1**.

Table 8.1. Description of food concepts

Food concepts	Description	Main ingredients
Spinach pancake and tzatziki 	Pancake made with spinach to bring the slight astringency, complemented with tzatziki sauce to moisten the pancake and adds the element of sourness and freshness	Chickpea flour, spinach, milk, eggs, Greek yogurt, cucumber, mint, lemon, lime
Mushroom cromesquis 	A deep-fried croquette with crispy breading. The filling is soft and moist, made of mushroom as the umami element	Mushroom, pine nuts, soy sauce, panko, flour, eggs
Pita and green pea hummus 	Pita bread complemented with hummus incorporating green pea and lemon juice to introduce a slight sour element	Chickpea, tahini, lemon, green pea, flour, milk
Savoury muffin + whipped cream 	Mini muffin incorporating sundried tomatoes, feta cheese, and olives. A combination of umami and astringency/sourness to stimulate saliva. Topped with whipped cream to add moist to the combination	Flour, sundried tomatoes, olive, feta, egg, milk, cream
Pannacotta mango coulis + almond crumble 	Pannacotta layer added with a mango coulis layer to balance the sweetness with sourness. Almond crumble to add the texture contrast which encourage chewing	Milk, cream, gelatin, sugar, almond, mango coulis
Energy ball with dates 	Energy balls made of almond powder, crushed almond, dates, chia seed and covered with cocoa and coconut flakes	Almond, dates, almon powder, coconut flakes, cocoa powder, chia seed

8.2.4. Focus group discussion

Four cancer patients (mean age 61 years old) participated in the focus group discussion which lasted approximately 90 minutes, including the tasting and evaluation. Two of the patients were still undergoing treatments whereas the other 2 patients had completed their treatments.

Table 8.2. Characteristics of study participants.

	Sex	Age	Type of cancer	Duration since treatment
1	Female	48	Breast cancer	Under treatment
2	Female	65	Laryngeal carcinoma cancer	Completed treatment 7 mo ago
3	Male	62	Prostate cancer	Under treatment
4	Male	69	Follicular lymphoma	Completed treatment < 2 y ago

None of the participants perceived that cancer treatment impacted their food perception (taste, smell, and texture). Two of the patients reported dry mouth during their treatments, one of which has completed the treatments and thus the issue was resolved. In addition, patients also reported that their preference to food were not affected by their cancer treatments. However, the patient with laryngeal carcinoma received medical advice on reducing consumption of spicy food, sparkling water, alcohol, and hot food. Despite not perceiving changes in their perception, patients reported losing appetite during their treatments and reported that visually appealing food with familiar ingredients helped to facilitate eating.

During this session, an informal observation has led to a potential assumption that patients may have encountered alterations in their food perception without being fully aware of it. During the tasting, patients reported that some of the products were bland, but the healthy individuals who observed the discussion (**Section 8.2.2.2**) perceived the food to be flavourful. It is possible that the change has been incremental over a long period of time.

In the second part of the discussion, patients tasted and evaluated the food concepts. The summary of the evaluation is presented in **Table 8.3**. Overall, the two food concepts that were accepted were the cromesquis and the pannacota. The two concepts were perceived to be salivating. They were visually appealing, well-balanced in terms of flavour, and demonstrated texture contrast (cromesquis: crispy shell combined with the moist fillings; pannacota: crunchy crumbles combined with the soft and smooth base). In addition, the two concepts were ideally served warm and cold, respectively for cromesquis and panna cotta. Meanwhile the rejected food concepts were either too bland or too intense in flavour and had decent texture.

Table 8.3. Summary evaluation of the food concepts

Food concepts	Feedback	Conclusion
Spinach pancake and tzatziki	(+) Appealing visual appearance (+) The tzatziki has good texture and flavour (-) The flavour and texture of pancake were not well-accepted	Need to intensify the flavour of the pancake and the texture should be softer and moister
Mushroom cromesquis	(+) Apealing visual appearance (+) Flavour and texture were well-balanced (+) The products helps in salivating (-) The cromesqui was quite crumbly, thus difficult to handle	Accepted proposition
Pita bread and green pea hummus	(+) Flavour and texture of the hummus were decent (+) The product combination helps in salivating (-) The pita bread was not accepted (flavour and texture)	Rejected proposition
Mini savoury muffin with whipped cream	(+) Appealing visual appearance (+) Product helps in salivating (-) Texture of the muffin was a little dry (-) The whipped cream was bland	Addition of feta and improvement to the muffin texture (to be more moist) is needed
Pannacotta with mango coulis and almond crumble	(+) Appealing visual aspect (+) Flavour and texture were well-accepted (+) Product helps in salivating	Accepted proposition
Energy ball with dates	(+) Convenient format (+) Texture was decent (-) The flavour was too intense/ sickly	Rejected proposition

Following the focus group discussion, the accepted concepts were validated by the supervisory team. Two versions of each food concepts were developed (standard vs. sensory-enhanced). Two different sensory enhancements strategies were adapted: 1) flavour modification and 2) texture modification. For the cromesqui, flavour intensity was increased for the enhanced version (flavour-enhanced), whereas for the pannacotta, texture of the almond crumble was increased for the enhanced version (texture-enhancced). These two versions will be evaluated in the following consumer test.

8.3.3. Expected results from the consumer test

A significant difference in the hedonic rating of the two versions is expected. It is expected that the sensory-enhanced version will receive a higher hedonic rating, In addition, it is also expected that the hedonic rating is correlated with the salivary function and the self-reported sensory perception and oral symptoms. Further, we may observe differences between patients with different types of cancer and treatments. The findings from this study could provide the direction for sensory enhancement. From the effect size of the two food samples, it is possible to determine whether the flavour or texture modification will result to a greater increase in hedonic acceptance. Moreover, it is possible to adapt different strategies to adapt to the different types of cancer.

8.4. Conclusion

Food concepts were designed to adapt to the sensory alterations and oral symptoms of cancer patients. Culinary development was aimed at developing food concepts to stimulate salivary secretion through mechanical and gustatory stimulations. Six food concepts were developed following the criteria, which were then tasted and evaluated in a focus group discussion with cancer patients. The two validated food concepts were further adjusted into two different versions: standard and sensory enhanced version (texture-enhanced or flavour-enhanced). The hedonic acceptance of the food concepts with sensory enhancement will be evaluated in a consumer study with cancer patients. The study will provide direction for sensory enhancement and allow explorations on the subjective sensory perception of different types of cancer patients under treatment.

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Chapter 9

General Discussion and Conclusion

9.1. Main Findings

Numerous studies have highlighted the importance of adequate nutrition for maintaining overall health and quality of life. However, cancer patients often struggle with appetite loss and a diminished enjoyment of eating, primarily due to altered food perception (Dalton *et al*., 2022; Hutton *et al*., 2007; Messing *et al*., 2021). Changes in taste and smell perception have been observed and measured objectively and subjectively (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021; Messing *et al*., 2021). However, food perception involves a complex interplay of various sensory inputs. This includes not only taste and smell but also somatosensensation (Small, 2012; Spence, 2017). Nevertheless, investigations on cancer patients' somatosensory perception remain relatively sparse. Therefore, the overarching aim of the project is to investigate somatosensory perception of cancer patients in order to design food adapted to their senses. Based on this aim, a series of research questions were explored and presented in Chapters 3 to 8.

9.1.1 Oral Somatosensory Alterations in Head and Neck Cancer Patients: An Overview of the Evidence and Causes (Chapter 3)

Research question 1: *Are there indications of oral somatosensory alterations among head and neck cancer patients, and what are the possible causes?*

The sense of taste and smell are commonly affected in cancer patients, influencing their food perception and consequently impacting their eating behaviour, overall well-being, and health. However, food perception is also influenced by oral somatosensation (perception of texture, temperature, and chemesthesis) yet there is limited research on this area. Exploration on this topic lead to existing studies which primarily concern HNC patients. Existing qualitative and quantitative studies showed indications of somatosensory alterations among HNC patients. This sub-population of cancer patients is more vulnerable to alterations in the food-related sensory perception due to the tumour location and the treatments impacting the site of ingestion.

Through subjective measurements of their food perception, HNC patients reported that they experienced differences in their perception of textures, spices, and temperatures; although this experience differs among individuals. Objective tests confirmed that there were changes in their ability to detect tactile stimulation and temperature in specific areas of the mouth. These alterations occurred as side effects of the different cancer treatments, surgery, radiotherapy, and chemotherapy through different mechanisms. In addition, due to the cancer site, it is equally likely that the tumour in itself may interfere with the sensory processing of these patients.

Findings on texture sensitivity are less conclusive and investigations on chemesthetic sensitivity of HNC patients have not been reported. The available evidence suggests that HNC patients experience alterations in their oral somatosensory perception, which can affect their eating behaviour. Common oral complications, such as dry mouth, difficulty swallowing, oral inflammation, further impact their eating experience.

9.1.2. A Review of Assessment Methods for Measuring Individual Differences in Oral Somatosensory Perception (Chapter 4).

Research question 2: *How is oral somatosensory perception assessed?*

As the understanding of oral somatosensory perception of HNC patient is limited, the first step towards investigating it is to select the most appropriate assessment method. This proves to be challenging as there are no standardised or established methods unlike for smell and taste. This review demonstrates the variations within the existing assessment methods.

Different methods can be used to assess tactile sensitivity: point-pressure test, spatial acuity test, and stereognosis test; but each measures different aspects of tactile dimension, and more research is needed to establish their correlation with texture sensitivity. Measuring only one textural attribute may not provide a complete picture of texture sensitivity. Thermal sensitivity can be evaluated using thermal-change detection or temperature discrimination tests, whereas chemesthetic sensitivity tests involve stimulating specific areas or the entire mouth.

The choice of an appropriate method for assessing oral somatosensory sensitivity depends on factors such as research objectives and the study population. Since each method has its own strengths and limitations, there is no universally superior approach. To address some of the limitations, alternative or complementary approaches are suggested in the review. By carefully selecting and potentially combining different methods, researchers can improve the comprehensive assessment of oral somatosensory sensitivity. In addition to these objective measurement methods, subjective measurements will be equally useful for a comprehensive depiction of their food perception.

9.1.3. Oral Somatosensory Alterations and Salivary Dysfunction in Head and Neck Cancer Patients (Chapter 5) + Influence of Oral Somatosensory Perception and Oral Symptoms on Eating Behaviour of Head and Neck Cancer Patients (Chapter 6)

Research question 3: *How does the somatosensory perception of head and neck cancer patients differ from the general population? and how does it influence their eating behaviour?*

Somatosensory responses and salivary function of head and neck cancer patients (n=30) were investigated in comparison to sex- and age-matched controls (n=30). The objective measurements included tactile sensitivity, texture sensitivity, chemesthetic sensitivity, thermal sensitivity, and salivary function.

The somatosensory perception of HNC patients differed from control in several aspects. First, HNC patients showed lower textural sensitivity compared to control in terms of roughness (p = 0.003) and firmness (p = 0.003) but not on thickness (p=0.587) perception. Chemesthetic sensitivity was also lower in HNC patients compared to control for both menthol and capsaicin solutions, for the medium and high concentrations. Patients were less sensitive in terms of thermal sensitivity (p = 0.038). For tactile sensitivity, no significant differences were observed between the two groups although there was a tendency of lower sensitivity in the HNC group. The salivary function of HNC patients was significantly lower compared to the control (p=0.001), namely for the quantitative parameters of salivary functions including visual hydration level, saliva consistency and stimulated salivary flow.

For the subjective measurements, hierarchical clustering analysis was performed to categorise patients based on their sensory profile which resulted in two distinct profiles of patients: no alteration (n=14) vs alteration (n=16) group. The alteration group displayed a reduced preference for various sensory modalities, particularly in the somatosensory domain. More patients in the alteration group agreed to negatively connotated eating behaviour statements (e.g. having food aversion, eating smaller portions). Furthermore, a majority of patients reported experiencing several oral symptoms related to salivary dysfunction, such as dry mouth, sticky saliva, difficulty chewing and swallowing, and food stuck in the mouth and throat. These symptoms were found to be negatively correlated with their sensory preferences: sour taste (r=-0.41), spiciness (r=-0.43), astringency (r=-0.4), bitter taste (r=-0.31) and carbonation (r=-0.38). The correlations between oral symptoms and eating behaviour also revealed that patients with more oral symptoms encounter more difficulty in eating situations.

Altogether, the objective and subjective measurements demonstrated alterations in their somatosensory perception, partly mediated by their salivary function. Frequently experienced oral symptoms were also aligned with their lower salivary function compared to the matched controls. Patients who experience sensory alterations and oral symptoms are also more likely to experience greater difficulties in eating.

9.1.4. Oral Somatosensory Perception and Oral Symptoms of Cancer Patients and the Influence on Eating Behaviour

Research question 4: *How is the somatosensory perception of various cancer populations?*

To extend the investigations beyond HNC patients, an online survey for various cancer patients was distributed across France, Denmark and the UK. More than 30% of cancer patients experienced changes in their somatosensory perception. This was also linked to changes in their food preferences. Hierarchical clustering identified three different clusters of patients based on their sensory perception, the no alteration group (n=48) and the alteration group, with subclusters of generally increased sensitivity (n=44) and generally decreased sensitivity (n=8).

It was demonstrated that sensory alterations contributed to changes in sensory-related food preferences. Other factors that predict changes in preference include oral symptoms, age, cancer localisation, type of treatments, duration since treatment. Moreover, sensory alteration and oral symptoms were significant predictors of eating behaviour. Both sensory alterations and oral symptoms can negatively influence eating behaviour. These findings indicated that these phenomena are not exclusive to HNC patients but were also experienced by patients across various cancer types. The survey provided some guidelines on food adjustments that are needed to adapt to the needs of cancer patients.

9.1.5. Designing Food Adapted to Their Senses: Conception of the study

Research question 5: *How to design food adapted to the somatosensory perception of cancer patients?*

Designing food for cancer patients was done through three successive processes, namely culinary development, focus group discussion, and consumer tests. Findings from Studies 1 and 2 were used to guide the direction for developing food concepts tailored to the sensory perception and preference of cancer patients. The food concepts were developed during culinary development sessions, integrating the findings of the study as well as the creative input and ideas of the culinary chefs involved. The main directions for the ideation of the food concepts, is to address dry mouth due to its prevalence among cancer patients and its important role in food perception. To stimulate salivary production, two different strategies were used: 1) mechanical stimulation using semi-solid food with texture contrast 2) gustatory stimulation through incorporation of sour and/or umami ingredients.

Six different food concepts were developed. Following this session, the focus group discussion with cancer patients (n=4) was conducted to further understand their food perception and eating behaviour. The 6 food concepts were also tasted and evaluated; two concepts were validated by patients concepts (cromequis and pannacotta), two were accepted with recommendations to improve (pancake and mini muffin), and the two other were rejected (pita tzatziki and energy ball). The two validated food concepts were visually appealing, well-balanced in terms of flavour, demonstrated texture contrast, and were perceived to be salivating. The hedonic acceptance of the validated food concepts will be tested in a consumer test with cancer patients and the conception of the study design is described.

9.2. Interpretation and integration of the findings

Our findings provide evidence that sensory alterations among cancer patients extend beyond taste and smell alterations, but also oral somatosensory experiences. In addition to the sensory alterations, our results underscore the significance of oral symptoms, specifically salivary dysfunction, in influencing their food-related behaviors. Hence, strategies to enhance their eating enjoyment should include these two underlying aspects.

9.2.1. Investigating the (known and the) unknown

When starting the investigation into understanding the somatosensory perception of cancer patients, it became apparent that there were no existing reviews available on this specific topic. Therefore, the initial focus of the PhD thesis was to conduct a literature review to address this gap. Notably, the majority of studies on somatosensory perception in cancer patients had been conducted specifically on HNC patients. As a result, the initial explorations in the thesis were primarily centered around this particular sub-population of cancer patients. Given that the topic is still relatively new, conducting a systematic review or a meta-analysis was not feasible at this stage. Instead, Chapter 3 of the thesis presents a narrative review aimed at providing a broad perspective on the findings related to somatosensory perception in HNC patients. The review incorporates both qualitative and quantitative studies, while also exploring potential causes or factors contributing to the observed somatosensory changes.

The existing qualitative studies and subjective measurements revealed that sensory alterations in HNC patients extend beyond taste and smell alterations but also include changes in their perception of food texture, mouthfeel, and chemesthetic sensations (Small, 2012; Spence, 2017). In addition, oral symptoms such as dry mouth and difficulty chewing/swallowing also further impact their eating experience (Watson *et al.*, 2018; Crowder *et al*., 2020). The existing objective measurements involving psychophysical tests were conducted in the field of oral rehabilitation and have focused less on the relevance of these changes to the overall eating experience. These objective measurements were limited thermal sensitivity and tactile sensitivity, and using non-edible tools to examine texture sensitivity. These studies indicated reduced tactile and thermal sensitivity among HNC patients (Aviv *et al*., 1992; Bearelly *et al*., 2017; Bodin *et al*., 2004; Elfring *et al*., 2012; Kimata *et al*., 1999; Loewen *et al*., 2010), supporting the findings from the qualitative studies of altered perception.

Overall, there is some evidence to suggest that HNC patients experience changes in somatosensory perception, which justifies further investigations. This review identified two perspectives on the topic. First, studies examining oral somatosensory perception, specifically in relation to food perception and eating experience, primarily relied on subjective measures and lacked objective measurements (Watson *et al*., 2018; Crowder *et al*., 2020; McLaughlin & Mahon, 2014). Meanwhile, studies that employed objective measurements of somatosensory sensitivity did not explore its relationship with eating behavior. These too were limited to measurements of their tactile and thermal sensitivity, and some extent, texture sensitivity using non-edible tools (Aviv *et al*., 1992; Bearelly *et al*., 2017; Bodin *et al*., 2004; Elfring *et al*., 2012; Kimata *et al*., 1999; Loewen *et al*., 2010). Thus, it is important to combine both objective and subjective measures to gain a comprehensive and accurate understanding of the eating experience in HNC patients. Second, upon considering the potential aetiologies of somatosensory alteration, it becomes evident that exploring oral symptoms will be essential for comprehending their food perception and overall eating experience (Engelen & de Wijk, 2012; García-Peris *et al*., 2007; Logemann *et al*., 2003).

In order to investigate somatosensory perception, the initial challenge is selecting appropriate tools and methodologies. This task proves to be rather demanding due to the nature of somatosensory perception which encompasses various sub-modalities such as texture, temperature, and chemesthesis. Each of these sub-modalities needs to be studied individually, which adds to the complexity. Unlike taste and smell, there is a lack of standardised assessment methods for each of these sub-modalities. As a result, Chapter 4 aims to provide a review of existing assessment methods.

Evaluation of the different methods identified the variation in the procedure of the existing methods. The specific purpose, strengths, and limitations of each method were also reviewed. Particularly, due to the multifaceted nature of texture perception, a combination of methods or measurements of different textural attributes may be necessary to understand texture perception. The review also suggests that there isn't a one-size-fits-all approach, but each individual method has its own intended purpose that needs to be adapted depending on the study objective and target population. In addition, it was found that there were no existing questionnaires specifically designed to measure somatosensory perception.

Overall, the two reviews played a significant role in identifying the existing knowledge in the field, as well as revealing areas where further research is needed. Chapter 3 of the project guided the subsequent study by highlighting the importance of incorporating both objective and subjective measurements, as well as documenting oral symptoms. Chapter 4 proved helpful in the decision-making process for selecting the most appropriate methods for the clinical study with HNC patients (Study 1).

9.2.2. Investigating oral somatosensory perception of head and neck cancer patients

Due to the extensive variability in the cancer population (e.g. different cancer types, tumor localisations, and treatments), conducting investigations on various cancer patients would lead to significant heterogeneity. Therefore, in the first investigation, it is necessary to focus on one sub-population of cancer. Since previous studies had suggested that patients with HNC may be particularly susceptible to changes in food perception due to factors such as the tumour site and treatments (Cancer Council Australia, 2015), and to help build upon existing literature on this specific subgroup (Aviv *et al*., 1992; Bearelly *et al*., 2017; Bodin *et al*., 2004; Elfring *et al*., 2012; Kimata *et al*., 1999; Loewen *et al*., 2010), the initial investigation was conducted specifically on HNC patients. The study involved comparing HNC patients with controls (matched in age and sex) in terms of objective somatosensory responses, as well as exploring the subjective somatosensory perception of cancer patients and its relationship with eating behaviour.

Study 1 confirmed previous findings on tactile and thermal sensitivity compared to healthy controls (Elfring *et al*., 2012; Loewen *et al*., 2010). When evaluating texture sensitivity, a previous study using non-edible tool failed to detect differences in roughness detection between HNC patients and controls (Loewen *et al*., 2010). However, using our food model approach that closely resembles actual eating, significant differences were detected for roughness. Interestingly, patients who failed to accurately rank the roughness set do not always perform as poorly on ranking the firmness set, and vice versa. This justifies the reasoning to include multiple textural attributes covering the geometrical (roughness) and mechanical (firmness and thickness) texture attributes. Also, in line with the findings of a review (Liu *et* *al*., 2022), our study observed no correlation between tactile sensitivity and food texture sensitivity.

There have been no previous studies exploring chemesthetic sensitivity in cancer patients. Our findings demonstrated that the HNC patients perceived medium and high concentrations of menthol and capsaicin solutions to be less intense than control. Therefore, the present study fills this research gap by investigating chemesthetic perceptions in this population. In addition, objective measurement of their salivary function was also collected, which appears to partly mediate their perception (e.g. roughness sensitivity).

Regarding the subjective measurement, the hierarchical clustering of patients allowed the identification of two different groups of patients based on their sensory alteration profile. The first group reported perceiving little to no sensory alterations whereas the second group reported perceiving alterations in several sensory modalities including somatosensory. In this study, 1 in 2 patients reported perceiving sensory alterations, including somatosensory. Upon this classification, it was also observed that the group with perceived alterations were more inclined to have decreased food preference. This is consistent with previous studies demonstrating the influence of sensory alterations on appetite, food appreciation, and food selection or intake (Boltong & Campbell, 2013; Dalton *et al*., 2022; Ganzer *et al*., 2015). Further, in congruent with previous studies, HNC patients reported several oral symptoms: dry mouth, sticky saliva, chewing/swallowing difficulty, food stuck in the mouth or throat (Jin *et al*., 2021; Langius *et al*., 2010; Wang *et al*., 2021). These symptoms are related to insufficient saliva (Bilt, 2021; Guo, 2021; Logemann *et al*., 2001; Pedersen *et al*., 2002), which aligns with the observed lower salivary function.

Prior research has identified discrepancies between objective and subjective measurements of sensory alterations. In particular, subjective taste alterations tend to be overestimated, whereas subjective smell alterations tend to be underestimated (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021). This discrepancy may be attributed, in part, to the broad interpretation of the term "taste" which is often used to represent the overall food experience rather than just the basic taste sensations (Boltong *et al*., 2012). Perception is a complex phenomenon involving not only physiological factors but also central processing, which includes the integration of all senses, psychological aspects, and hedonic influences (Boltong *et al*., 2012; J. Chen, 2014; Small, 2012). Relying solely on objective measurements may underestimate the complex and subjective nature of the eating experience. The two measurements may indeed measure different aspects and hence a key strength of Study 1 lies in the combination of both approaches. It is important to note that, however, the results obtained from these two measurements cannot be directly compared. The objective measurements captured the current situation, while the subjective measurements of sensory perception were framed retrospectively (i.e. "in comparison to before the cancer treatment, my sensitivity has") in an attempt to compare their perception before-after the cancer treatment within the cross-sectional design.

Overall, Study 1 demonstrates somatosensory alterations in HNC patients, measured using objective and subjective measurements. Moreover, several oral symptoms linked to insufficient saliva were reported, in congruent with their reduced salivary function. Yet, it is crucial to acknowledge that HNC patients represent a rather unique sub-population of cancer, due to its site and treatments involving the oral cavity.

9.2.3. Investigating oral somatosensory perception beyond head and neck cancer patients

When conducting research, one of the primary concerns is the generalisability of findings to a larger population. In this case, it raises the question of whether the findings can be applied to other types of cancer. Therefore, the subsequent investigation was aimed at understanding somatosensory perception of various cancer patients, expanding beyond HNC. This was also needed to achieve the overarching goal to design food solutions adapted to their senses.

While the significance of incorporating both objective and subjective measurements was repeatedly emphasised, it was not practical to implement this approach for the broader investigation. Consequently, Study 2 solely relied on subjective measurements. However, the questionnaire used in this study underwent testing among HNC patients in Study 1. Therefore, the same set of questionnaires was distributed as an anonymous online survey in various cancer population to investigate their perception, oral symptoms, food preference, and eating behaviour.

It was revealed that the prevalence of somatosensory alterations is lower in various cancer populations compared to HNC patients. This confirms that HNC patients are more vulnerable to sensory alterations, potentially due to the location of the cancer affecting food perception and ingestion, as well as the aggressive treatments focused on the site of ingestion (Cancer Council Australia, 2015; Chen *et al.*, 2022). Sensory alterations in various cancer populations typically change gradually over time (Belqaid *et al.*, 2016; Zabernigg *et al.*, 2010).

Consequently, cancer patients may not always be aware of these gradual changes and it is likely that the perceptual changes may need to be severe enough for patients to perceive them. On the contrary, these changes can occur immediately following radiotherapy or surgery for HNC patients (Bodin *et al*., 1999; Chen *et al*., 2022).

It is important to note that sensory alterations can vary heterogeneously even within the same cancer type. In this study, some patients reported experiencing increased perception, while other patients with the same cancer type experienced decreased perception. Furthermore, the same patient may perceive to be more sensitive to certain sensory modalities while being less sensitive to others, consistent with previous findings (Belqaid *et al*., 2016; Spotten *et al*., 2017). Through the online survey, it remains uncertain whether patients objectively did not perceive any changes in their sensory perception or if they experienced gradual yet subtle changes that they simply adapted over time. For instance, an informal observation during the FGD (Chapter 8) hinted at this assumption. However, as the sample size was small and no objective measurements were conducted, the assumption cannot be tested during the study but was observed in previous studies (Álvarez-Camacho *et al*., 2017; Gunn *et al*., 2021).

Nonetheless, it is crucial to acknowledge that patients who did perceive changes in their sensory perception were more inclined to experience changes in their food preferences, which was supported in a previous finding of a review (Drareni *et al*., 2019). Additionally, somatosensory alteration, taste/smell alteration, and oral symptoms were significant predictors of eating behaviour. Among the three variables, somatosensory alteration was the strongest predictor, followed by oral symptoms and taste/smell alteration. Previous studies have also shown that patients who reported subjective sensory alterations had lower quality of life and nutritional status (Boltong & Keast, 2012; Hutton *et al*., 2007; van Elst *et al*., 2022). The perception of oral comfort for certain foods was previously found to be linked to salivary function (Assad-Bustillos *et al*., 2019). Previous studies have also shown the impact of oral symptoms on nutritional outcomes (Farhangfar *et al*., 2014; Wang *et al*., 2021).

Collectively, the findings suggest that sensory alterations can vary within and across different cancer types, but HNC patients may be particularly susceptible to sensory alterations due to the cancer location and treatments. Somatosensory perception and oral symptoms should be included when investigating the eating experience of cancer patients. Recognising and addressing these alterations is important, as they can have profound effects on individuals' liking, food-related behaviour, and potentially nutritional intake. A study classified healthy individuals (n=2205) based on their oral responsiveness and suggested that greater modifications in product formulation is necessary to modify the liking of the less responsive subjects (Piochi *et al*., 2021).

9.3. Methodological Considerations

***Clinical study on HNC patients (Study 1)*: **The possible limitation of the study was the cross-sectional design that does not permit an inference of causality; thus it remains to be investigated whether the alterations existed prior to the cancer treatments or were attributed to the treatments. However, existing longitudinal studies indicated the greater impairment is attributed to the cancer treatments rather than the disease itself (Bodin *et al*., 1999, 2000, 2004). Another limitation was that the study visit was conducted at different locations and times of the day, depending on the availability of the participants, this may have some influence on the measurements. For instance, saliva measurements can be influence by time of measurement (Flink *et al*., 2005)

As food perception is a multisensory experience, it is challenging to prevent participants to evaluate the texture solely based on the texture in the mouth and not be confounded by the visual texture aspect, therefore we could not conclude whether or not there are perceptual differences in thickness between patients and control. Improvements shall be made on the thickness set, to reduce the visual difference. Alternatively, serving the samples in an opaque, dark-coloured containers or explicitly instructing them to evaluate only the texture perception inside the mouth may have improved the evaluation. In line with the discussion on the multisensoriality of food perception, the investigation would have been more comprehensive if objective measurements of taste and smell sensitivity were also conducted. However, with the limit of time and to avoid fatigue of the patients this was not conducted.

***Online survey on various cancer patients (Study 2)* →** Due to the difficulty of recruiting patients in a single country, we conducted the survey across different European countries with an unbalanced proportion of respondents between countries. There might be some differences attributed to the cultural difference (e.g. questions related to food preference, visual questionnaires), yet due to the low sample size, the analyses were pooled together. We approached several cancer organisations and patient groups in each country to maximise the survey outreach. However, it also posed a selection bias due to the self-registration, only motivated patients who came across the study advertisement were responding to the survey.

***Culinary development and focus group discussion (Study 3)* →** We only conducted one FGD with a small number of patients. Ideally, multiple sessions of FGD with more diverse cancer population should be conducted. Nevertheless, the FGD provided a preliminary evaluation of the food concepts, which will be further tested in a consumer study involving a larger number of cancer patients.

9.4. Recommendations for Future Research, Clinical Practice, and Food Industry

Moving forward, it is crucial to continue exploring sensory alterations, including somatosensory and oral symptoms, in cancer patients and develop interventions that address their specific challenges. Rather than solely focusing on developing specific food products, attention should be given to creating a culinary guideline that can be tailored depending on their perception. The guide should be easy to use for patients or caregivers yet provides flexibility for incorporation into everyday meals. The CANUT (Cancer Nutrition, conducted by Institut Lyfe Research Center together with HCL and CLB) project has already developed such a guide, which is currently being tested by cancer patients. It is important to note that the act of eating is intricately connected to the psychological and social context. By improving cancer patients' overall eating experience, we may enhance their nutritional intake, quality of life, and overall well-being.

9.4.1. Recommendations for future research

- ***Nutritional outcome:*** The present study did not investigate the impact of sensory alterations on their nutritional outcome. Previous studies have shown indications of taste and smell alterations on nutritional outcome (Hutton *et al*., 2007), yet the impact of somatosensory alterations and oral symptoms on nutritional outcomes remains to be investigated. As well as investigate the impact of tailored sensory interventions on nutritional outcome of cancer patients.
- ***Bigger cohort***: To better understand the relationship between cancer and the adverse effects of treatment, future research should expand the cohort size to enable subgroup analysis that can identify which specific cancer populations are at higher risk.
- ***Longitudinal design***: A longitudinal study would be valuable in investigating how sensory perception evolves throughout different phases of cancer treatments, allowing for a deeper understanding of the effects over time.
- ***Mechanistic aspect:*** Further investigations should be conducted to explore the mechanism underlying the somatosensory alterations in cancer patients, shedding light on the underlying physiological processes and possible interventional strategies.

- ***Diagnostic tool:*** The development of a rapid diagnostic tool that can measure both objective and subjective sensory perception, including taste, smell, and somatosensory perception, would greatly enhance early detection and interventional strategies.

9.4.2. Recommendations for clinical practice

- ***Informing patients:*** To improve clinical practice, it is recommended to ensure that patients are aware of the potential sensory alterations as side effects of treatments. Previous studies have shown that some patients were not aware of these potential side effects or that patients underreported this symptom or were reluctant to complain about changes in their perception (Bernhardson *et al*., 2009; Crowder *et al*., 2020; Zabernigg *et al*., 2010). On one hand, knowing this potential side effect may possibly overwhelm patients and lead to pessimism or reluctance to undergo the treatments. On the other hand, it may also better prepare patients for what to expect.
- ***Awareness:*** Increasing awareness among healthcare professionals is essential, particularly involving multiple professionals such as doctors, nurses, dietitians, and food catering providers.
- ***Educational tool:*** It was reported that there was a lack of educational tool or sufficient guideline for healthcare professionals that can be used to address sensory alterations in patients (Galaniha & Nolden, 2023). The guideline should be concise and easily accessible, and include information on diagnostic tools and management strategies.
- ***Routine assessment***: Making sensory alteration assessment a routine part of the clinical assessment process can be beneficial in identifying and addressing these issues promptly and effectively. If the tools are available, patients can even independently assess their perception and adapt their meals accordingly.

9.4.3. Recommendations for the food industry

- ***Somatosensory aspect***: The somatosensory perception alteration appeared as an equally important sensory modality that has been probably underestimated the extent to which could contribute to the sensory alteration perceived by the patients. Therefore, this aspect should be considered in new product development by the industry such as in oral nutritional supplements.
- ***Oral discomfort:*** Oral symptom such as dry mouth can influence eating experience. In both studies and previous published studies, this was shown to be prevalent among cancer patient and hence can be addressed through food designs.

- ***Savoury options:*** Considering that increased in preference in salty food was observed, the development of savoury food option seems justified.

9.5. Conclusion

Adequate nutrition intake is essential for cancer patients. However, this can be challenging when patients experienced loss in appetite and diminished food enjoyment. In addition to meeting their physiological needs, food also carries psychological and social significance. Thereby, efforts should be made to improve cancer patients' eating experience and maintain eating pleasure. While previous studies have primarily focused on taste and smell, our research provided evidence that the somatosensory aspect should not be underestimated.

Certain cancer populations have been found to be more susceptible to somatosensory alterations, as evidenced by HNC patients' declined sensitivity to various somatosensory aspects. These findings were supported by their self-reported assessments of somatosensory perception. The study also suggests the important role of saliva and oral symptoms on food perception. The investigations conducted on diverse groups of cancer patients further emphasised the importance of somatosensory perception and oral symptoms. These studies collectively demonstrated the relationship between perception, preference, and eating behavior. Based on these findings, some food concepts were developed taking into consideration not only taste and smell, but also the somatosensory aspect.

Given the potential influence of sensory alteration on food intake, nutritional status, and quality of life, it is important to assess the sensory perception of cancer patients during different phases of their treatments. However, this can be challenging due to the absence of a comprehensive diagnostic tool that encompasses all sensory modalities, highlighting the necessity for its development. The present work addressed some knowledge gaps in this area, although it may only cover a portion of the numerous research questions that may continue to emerge in the future following this work.

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List of Papers

Paper I

Riantiningtyas RR, Carrouel F, Bruyas A, Bredie WLP, Kwiecien C, Giboreau A, Dougkas A. Oral Somatosensory Alterations in Head and Neck Cancer Patients-An Overview of the Evidence and Causes. Cancers (Basel). 2023 Jan 24;15(3):718. doi: 10.3390/cancers15030718. PMID: 36765675; PMCID: PMC9913236.

Paper II

Riantiningtyas RR, Dougkas A, Kwiecien C, Carrouel F, Giboreau A, Bredie WLP. A review of assessment methods for measuring individual differences in oral somatosensory perception. *Submitted October 2023.*

Paper III

Riantiningtyas RR, Valenti A, Dougkas A, Bredie WLP, Kwiecien C, Bruyas A, Giboreau A, Carrouel F. Oral somatosensory alterations and salivary dysfunction in head and neck cancer patients. Support Care Cancer. 2023 Oct 13;31(12):627. doi: 10.1007/s00520-023-08086-7. PMID: 37828382; PMCID: PMC10570204.

Paper IV

Riantiningtyas RR, Valenti A, Dougkas A, Bredie WLP, Kwiecien C, Bruyas A, Giboreau A, Carrouel F. Influence of oral somatosensory perception and oral symptoms on eating behaviour of head and neck cancer patients. *In preparation.*

Paper V

Riantiningtyas RR, Dougkas A, Bredie WLP, Kwiecien C, Giboreau A, Carrouel F. Oral somatosensory perception and oral symptoms of cancer patients and the influence on eating behaviour. *In preparation.*

Dissemination activities

International conferences

- Reisya R. Riantiningtyas, Anestis Dougkas, Camille Kwiecien, Wender L.P. Bredie, Amandine Bruyas, Agnès Giboreau, Florence Carrouel*Oral somatosensory alterations in head & neck cancer patients and food intake*. Nutrition Live ASN, Online (Poster). June 2022.
- Reisya R. Riantiningtyas, Anestis Dougkas, Camille Kwiecien, Wender L.P. Bredie, Amandine Bruyas, Agnès Giboreau, Florence Carrouel. *Oral somatosensory perception in head and neck cancer patients – a review.* Altered taste symposium, Lyon FR (Oral). June 2022
- R.R. Riantiningtyas, A. Giboreau, A. Bruyas, A. Dougkas, C. Kwiecien, F. Carrouel, W. L.P. Bredie. *Mouthfeel perception and oral somatosensations- A review of assessment methods in consumer and cancer patients.* Eurosense 2022, Turku FI (Flash poster). September 2022.
- Reisya R. Riantiningtyas, Anestis Dougkas, Camille Kwiecien, Wender L.P. Bredie, Amandine Bruyas, Agnès Giboreau, Nathalie Boireau, Florence Carrouel. *Somatosensation and oral comfort in cancer patients: Neglected aspects of tailored-food solutions?* Pangborn Symposium 2023, Nantes FR (Oral). August 2023.
- Reisya R. Riantiningtyas, Anestis Dougkas, Camille Kwiecien, Wender L.P. Bredie, Amandine Bruyas, Agnès Giboreau, Nathalie Boireau, Florence Carrouel. *Somatosensation and oral comfort in cancer patients.* FENS 2023, Belgrade RS (Poster). November 2023.

Dissemination to industry, institutional, and general public

- Oral-somatosensory perception in cancer patients: Variability and influence on eating experience. Research & Innovation Committee, Lyon FR. October 2021
- Oral-somatosensory perception in cancer patients: Variability and influence on eating experience. VetAgroSup, Lyon FR. December 2021.
- Oral-somatosensory perception in cancer patients: Variability and influence on eating experience. ISARA, Lyon FR. March 2022.
- Altérations somatosensorielles orales chez les patients atteints de cancer de la tête et du cou et prise alimentaire. CLARA Grand Publique, Lyon FR. May 2022
- *Mouthfeel perception and oral somatosensations- A review of assessment methods in consumer and cancer patients.* SFAS General Assembly, Online. March 2023.
- Somesthésie chez les patients atteints de cancer - Variabilité et influence sur l'expérience alimentaire. Assemblée générale Nutrition Méditerranéen Santé, Massingy FR April 2023.
- Somatosensation and oral comfort in cancer patients. Institut Paul Bocuse Research Center Seminar, Lyon FR. April 2023.

Words of Gratitude

All praise to God, The Most Gracious, The Most Merciful, who has bestowed countless blessings, including the opportunity to embark on this PhD project and all the support needed for me to complete it.

Completing this PhD marathon is my biggest accomplishment thus far. One that allowed me to grow not only professionally but, without doubt, personally. Therefore, it is with utmost gratitude and joy that I look back to everyone who has supported me over the years, without whom this thesis would not have been possible.

I would like to thank ***Association Nationale Recherche Technologie*** (ANRT), ***La Ligue contre le cancer***, and ***Danone Nutricia Research*** for financing this PhD project.

Words cannot express how thankful I am to my supervisors, for trusting me and guiding me through the project. ***Anestis Dougkas,*** I knew we would work along well since the first interview. Thank you for being such an empathetic mentor, you have always been so supportive and understanding, especially during the toughest times. Thank you for the evening talks when we were the last to leave the office and for always reminding me to take breaks. ***Florence Carrouel***, who is always super responsive whenever I need any help or someone to discuss with, you always reassure me with full confidence that I will make it and always remind me that I can contact you whenever I need. Thank you for the tremendous help in figuring out all the administrative procedures which often get me frustrated. Someone who gently checks up on me when things are not going well. ***Wender L.P. Bredie***, an inspiring mentor without whom I would not have embarked on this project. I have always enjoyed our talks where you would share your wisdom about research or life in general. You always tried your best to figure out ways to help me. ***Agnes Giboreau***, for putting your faith in me, you have always helped in bridging the different partners and always come up with different solutions when things get complicated. Thank you for stepping in to review my thesis. ***Camille Kwiecien***, for the weekly catch-up meeting. For giving snippets of life in the industry, and for helping me to be more organised. You are always at the forefront to help me prepare the posters and presentations. ***Amandine Bruyas***, for referring the patients, and for providing invaluable help and feedback on the clinical aspects.

It has been a great honour to learn from these great minds. Not only their expertise, but I also admire their humility.

I am very thankful to the reviewers ***Dr. Carole Tournier,*** and ***Prof. Erminio Monteleone,*** and the jury members ***Prof. Claire Falandry, Dr. Dominique Dardevet***, ***Dr. Helene C. Reinbach,*** and ***Prof. Wim Tissing,*** for your time and invaluable feedback on the thesis.

I would also like to sincerely thank ***Stella Lignou*** and ***Garmt Djiksterhuis*** for kindly agreeing to be part of my thesis assessment committee. Thank you for giving an external outlook on the project and giving constructive feedback. For the time that you have given, insightful advice, encouragement, and help in connecting me to different people.

My sincere gratitude to those who offered me such warm friendships despite the distance. ***Dena,*** who has always been my best confidant, even in the toughest times. For being the wisest advisor, for teaching me to look at things through a different lense, for always reminding me that things will be okay in the end "*terbentur, terbentur, terbentur, terbentuk"*. ***Casia***, who gives first-hand examples of how to survive a PhD while being far from home. For being there whenever I need someone to talk to, for giving sincere advice, and for growing and navigating through PhD life with me. ***Lita***, my best friend, you radiate so much positivity which helps me get through the days. For reminding me who I truly am, whenever I get lost. ***Dominique (Ching),*** my first friend in Copenhagen who continued to be a cherished friend, research partner, colleague, and travel buddy. For giving me advice on research and in life, I may not be in this path if we did not pair up for the insect project. For reminding me that we'll eventually get through this, somehow.

Moving yet to another country was a tough feat. I underestimated the struggle by thinking that if I made it all the way from Indonesia to Denmark, moving from Denmark to France would be relatively easy. Navigating life in France without properly knowing the language was one of the biggest hurdles in my first year, but I was extremely fortunate to meet kind-hearted individuals along the way. ***Lauric,*** you made me see my life in Lyon in a new light through your light-hearted jokes and attitude. Thank you for the anime nights and the running sessions. *Merci de m'avoir appris beaucoup de français*. You taught me not to always take things too seriously but to always have a plan. ***Simon,*** who helped me find the way back to myself, your compassion helped me see myself from a different perspective, and your passion for cycling inspired me to explore different hobbies. Thank you for all your help, for the road trips, the climbing sessions, and for the shared passion for food.

I was overjoyed to discover the Indonesian students and expats, who made Lyon a little less foreign and a little more like home. ***Hari***, my first Indonesian friend in Lyon, the extrovert who adopted this introvert, someone who challenged me to be less timid. Thank you for the last-minute trip and (often spontaneous) catch-up sessions. Thank you for inspiring me to dream big, you showed me firsthand to believe in your dreams and not to let anyone bring you down. ***Kintan***, for all the help, insightful talks, and laughter shared over good food. Thank you for your encouragement in the most uncertain times. Thank you for bringing me to the *pengajian*, and taking me out of my self-imposed isolation. To ***Mba Poppy, Mba Eka, Mba Adek, Mba Diah,*** and ***Mba Tiwi*** **and their family** for all the home-cooked meals and the conviviality that reminds me of home.

I would like to express my gratitude to everyone in the Centre de Recherche, Institut Paul Bocuse who always greet me with a smile and have been so welcoming and helpful whenever I need help, for volunteering in the different studies, for the countless *goûter* sessions, for the chats during lunch and breaks. ***Raphaëlle*** and ***Julie***, for helping me with the ever-so-confusing administrative tasks. To the ***INNO team***: ***Estelle, Justine, Jeremy, and Marion B***, for always being so friendly and accommodating for my requests, your help in setting up experiments, recruiting volunteers, and the chefs ***Marie, Gautier, Marion E, Julien***. Thank you for your help in developing and preparing the recipes. ***Adri*** and ***Kenza***, for being so supportive and encouraging whenever I doubt myself. To the ***SNUT team: Audrey, Sarah, Caterina, Angelica, and Nina,*** for the continuous help, advice, and encouragement throughout the whole project. To everyone who helped in the preparation of my experiments and the data collection: ***Justine***, ***Melinda***, ***Solen***, and ***Sarah***. My special thanks to ***Alexandre,*** who has been a positive and very reliable teammate during the most crucial period. For helping me reflect and make decisions through your curious yet thought-provoking questions.

I sincerely thank my PhD comrades (***Laura, Matteo, Maxence, Arnaud, Clara, Caterina, Angelica, Sarah, Nina, Olga, Sabrina, Maeva, Dori, Fateme)*** and former PhDs (***Morgane, Fairley, Damien, Rafael, Abi, Erika, Kenza***) who made things more bearable through the monthly meetings, sharing of advice and encouragements. Thank you for making my days at work more enjoyable and fun, and also for the *soirée* outside work**.**

Laura, the lovely and cheerful movie enthusiast. Thank you for initiating a lot of activities together, to explore Lyon + the neighboring towns together. We still have a lot of things to do and places to explore on our list. Thanks to my breakfast buddies Matteo and Maxence, for the trips, board games, and supply of PhD-related memes. ***Matteo,*** the creative storyteller who always makes whatever story sounds captivating. Thank you for cheering me on during the final sprint of my thesis, and for making me laugh uncontrollably during lunch breaks or board games. You always find ways to light up the mood. ***Maxence,*** the quirky adventurer who knows all the good bakeries, café, and ice cream shops around the neighbourhood. Thank you for the playful banter during breaks. Your stories in different corners of the world never failed to amaze me. ***Arnaud***, the genius who knows everything and the chill guy who always gets everything done. Thank you for teaching me a lot of French slang and culture, and for your encouragement and advice during our end-of-day chat. ***Clara*** and ***Caterina****,* who would always check up on me when they found out that something wasn't going so well with my project, thank you for being so caring and sweet.

I would also extend my gratitude to members of the Section of Food Design and Consumer Behaviour. University of Copenhagen. Especially ***Belinda Lange*** and ***Charlotte Dandanell*** who have kindly helped me since my master's and continue to help me in this PhD. For the tips and advice on the correct way to do sensory tests, and for encouraging me to be more social as a heads-up for life in Lyon.

To friends in Copenhagen (***Nuria, Andika, Ilona, Gabriele, Reza)*** who are always so welcoming and keep me company whenever I visit. Thank you for your kind words and support. I also greatly appreciate ***Max,*** for the support and constant reminder to grow stronger and ***Ricky***, for continuously believing that I will make it. Thank you ***Mas Riva*** for designing the illustration for the cover page despite my last minute request.

I am deeply thankful to the team at HCL. Especially ***Melanie Roche, Justine Dubreuil, Eloise Aubret,*** and ***David Dayde*** for helping with the recruitment and tremendous help in setting up the experiments in the hospitals. Thank you to ***Nathalie Boireau*** and ***Irene Fernandez Gonzalez*** for providing yet another point of view for the thesis.

Of course, the thesis would not have been possible if it weren't for the incredibly kind ***patients*** and ***volunteers*** who have participated in the different studies. For their dedication and valuable time in participating in the studies. For sharing their experience and giving me new perspectives in life. Also, for being so gentle and forgiving towards my broken French.

My life journey would not have been possible if it weren't for the unwavering support, affection, encouragement, and prayers of my family. ***Mama*** and ***Papa*** for giving me the courage to always try my best – yet remind me to be humble with whatever the outcome will be. "*Sing penting wis usaha, sisane di luar kendalimu, nak*". Thank you for selflessly allowing your only daughter to be so far away from home, pursuing her dreams, even though it's also tough for you. ***Bimo,*** who gave me the strength not to give up, even when things were difficult. ***Mas Wisnu*** *and* ***Ka Tiwi,*** who inspired me to go abroad. I wouldn't even think of pursuing a master's abroad, l*et al*one a PhD, if it weren't because of you.

…

They said, "*It takes a village to raise a child*". Apparently, it also takes an entire community of supportive individuals to "raise" a PhD. It was a rewarding experience, and I am delighted to have gone through this journey with the support of each of you. May kindness return to you in abundance ♡

PS.

Inspired by a friend, I decided to name this section "Words of Gratitude" instead of "Acknowledgements". Only acknowledging their contributions to my journey wouldn't fully express how much they mean to me, I am sincerely grateful for having been surrounded by these kind-hearted souls. And the concept of gratitude has always been the driving force throughout the 3 years, it also aligns perfectly with the quote in the preface.

Appendix 1B – Participant booklet (Chapter 5)

La SOMESThésie chez des patients atteints de cancer : la variabilité et l'influence sur l'expérience ALIMentaire

SOMEST'ALIM

INVESTIGATEUR PRINCIPAL : Dr Amandine BRUYAS

CAHIER D'OBSERVATION

Numéro du centre : **|__|__|**[1]

Numéro patient : **|__|__|**[2]

Initiales patient : **|__|__|__|**[3]

1ère lettre PRENOM - (Tiret) -1ère lettre NOM[4]

Exemples : ***Jean Dupont : J-D***

Jean-Paul Dupont : JPD

Maria Da Silva : MDS

Cahier d'observation

[1] Les numéros de centre seront les suivants : 01 Hôpital de la Croix Rousse, service oncologie médicale 02 Hôpital de la Croix Rousse, service ORL 03 Hôpital Lyon sud, service radiothérapie 04 Institut Paul Bocuse

[2] Le numéro de patient est donné lors de l'inclusion par le centre

[3] Première lettre du prénom et première lettre du nom

[4] Ces informations sont à reporter en tête de chaque page

Etude SOMESTALIM-1 Population patient : |_| Numéro patient : |_|_| Initiales patient : |_|_|_|	Visite d'inclusion	Date |_|_| / |_|_| / |_|_|_|_|

Relevé du petit déjeuner et mesure de l'appétit

☐ Je n'ai pas pris de petit déjeuner

☐ Pain, biscotte, pain de mie
☐ Beurre, margarine
☐ Confiture, miel
☐ Pâtes à tartiner

☐ Céréales
☐ Viennoiseries, pâtisseries, biscuits
☐ Fruits
☐ Yaourt
☐ Fromage
☐ Jambon, charcuterie
☐ Œufs

☐ Lait
☐ Boissons végétales
☐ Café
☐ Thé
☐ Jus de fruits
☐ Autres, précisez…………..

En ce moment, à quel point avez-vous faim ? |_|_|_|
En ce moment, à quel point êtes vous rassasié ? |_|_|_|
En ce moment, à quel point avez-vous envie de manger ? |_|_|_|
En ce moment, quelle quantité pensez-vous pouvoir manger ? |_|_|_|

Evaluation de la fonction salivaire

Salive non stimulée

Évaluation visuelle du **niveau d'hydratation** > 60s ☐ (1) < 60s ☐ (3)

Évaluation visuelle de la **consistance** de la salive : collante, visqueuse ☐ (1) quelques bulles ☐ (2) claire, aqueuse ☐ (3)

pH 5,0 – 5,8 ☐ (1) 6,0 – 6,6 ☐ (2) 6,8 – 7,8 ☐ (3)

Salive stimulée

Volume de salive recueilli en 5 min < 3,5 ml ☐ (1) 3,5 – 5 ☐ (2) > 5 ml ☐ (3)

Pouvoir tampon : 0– 5 points ☐ (1) 6 – 9 points ☐ (2) 10 – 12 points ☐ (3)

Score total : ……….

Tests sensoriels

Date de la visite : |_|_| / |_|_| / |_|_|_|_|

Sensibilité tactile orale (monofilament de Von Frey)

Ordre	Taille	Stimulus	Réponse du participant	
1	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
2	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
3	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
4	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
5	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
6	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
7	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
8	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
9	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
10	**0,008/0,02/0,04**	**Présent/Absent**	**Présent/Absent**	**Certain/incertain**
1	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
2	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
3	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
4	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
5	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
6	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
7	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
8	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
9	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
10	**0,008/0,02/0,04**	**Présent/Absent**	**Présent/Absent**	**Certain/incertain**
1	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain

2	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
3	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
4	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
5	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
6	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
7	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
8	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
9	0,008/0,02/0,04	Présent/Absent	Présent/Absent	Certain/incertain
10	**0,008/0,02/0,04**	**Présent/Absent**	**Présent/Absent**	**Certain/incertain**

Sensibilité trigéminale

	Echantillon 1	Echantillon 2	Echantillon 3
Evaluation du rafraichissement	|_|_|_|	|_|_|_|	|_|_|_|
Evaluation du piquant	|_|_|_|	|_|_|_|	|_|_|_|

Sensibilité de texture

	Le plus	Intermédiaire	Le moins
Fermeté numéro échantillon	|_|_|_|	|_|_|_|	|_|_|_|
Fermeté évaluation de l'échantillon	|_|_|_|	|_|_|_|	|_|_|_|
Consistance numéro échantillon	|_|_|_|	|_|_|_|	|_|_|_|
Consistance évaluation de l'échantillon	|_|_|_|	|_|_|_|	|_|_|_|
Rugosité numéro échantillon	|_|_|_|	|_|_|_|	|_|_|_|
Rugosité évaluation de l'échantillon	|_|_|_|	|_|_|_|	|_|_|_|

Sensibilité thermique

Ordre	Température eau	Evaluation intensité 1= froid; 2= rafraîchissant ; 3 =au milieu; 4= réchauffant; 5=chaud.
1	3°C/20°C/55°C	|_|_|
2	3°C/20°C/55°C	|_|_|
3	3°C/20°C/55°C	|_|_|
4	3°C/20°C/55°C	|_|_|
5	3°C/20°C/55°C	|_|_|
6	3°C/20°C/55°C	|_|_|
7	3°C/20°C/55°C	|_|_|
8	3°C/20°C/55°C	|_|_|
9	3°C/20°C/55°C	|_|_|

FIN D’ETUDE

Date de fin d’étude : |__|__|/|__|__|/|__|__|__|__| *(JJ/MM/AAAA)*

☐Fin normale de protocole ☐Sortie prématurée

Motif de la sortie prématurée:

☐Non-respect des critères d’éligibilité
Préciser : ………………………………………………………………………………………………………

☐Patient ayant retiré son consentement
Raison : ………………………………………………………………………………………………………

☐ Arrêt du projet thérapeutique médical
Préciser :………………………………………………………………………………………………………

☐ Nécessité de mise en place d’une alimentation artificielle dans le cadre du soin du patient. Préciser : ………………………………………………………………………………………………………

☐Violation du protocole
Préciser : ………………………………………………………………………………………………………

☐Patient décédé Date : |__|__|/|__|__|/|__|__|__|__| *(JJ/MM/AAAA)*
Préciser la cause : ………………………………………………………………………………………………………

☐Evènement indésirable (autre que décès)
Préciser le n° de l’EI: |__|__|

☐Patient perdu de vue

☐Autre, détailler :
Préciser : ………………………………………………………………………………………………………

Appendix 2 – Questionnaires (Chapters 6 and 7)

SURVEY_Somest'alim

Q1.1

STUDY INFORMATION SHEET

Food perception and preference of cancer patients

Aim

The objective of this study is to investigate food perception and preferences of cancer patients.The results of this study will contribute to the knowledge of sensory impairment in cancer patients. The knowledge gained from this study will allow development of food or meals tailored to the perception and preferences of cancer patients. It will also provide practical recommendations to patients and their families to maintain the pleasure of eating, thus improving patients' nutrition and well-being.

Who would we like to participate in the study?

We are looking to recruit individuals older than 18 years old who have or had cancer and have received their cancer treatment between 3 months and 5 years ago.

What will happen if I take part?

The following survey is online only and will take between **20 and 30 minutes** to complete. The study is completely anonymous, no information allowing the direct identification of the person will be collected during the study. You will answer questions on your: sociodemographic information (gender and age) and health condition (primary site of cancer, type of treatment, duration since treatment) dietary habits and food preferences subjective sensory perception and oral condition.

Do I have to take part?

It is up to you to decide whether you wish to participate in the study. You are free to withdraw your participations, or data at any time, without giving a reason and will not receive any repercussions simply by closing the web browser.

Are there any adverse consequences to my health as a result of being a volunteer on this study?

There is no health risk associated with taking part in this study.

Data protection and confidentiality

The Research Ethics Committee of Science and Health, University of Copenhagen (Denmark) and Research Ethics Committee of the University of Lyon (France), and the School of Chemistry, Food and Pharmacy Research Ethics Committee of the University of Reading have given a favorable opinion (19/05/22, CASE: 504-0326/22-5000 Denmark; 14/06/2022, N/réf: 2022-04-19-002, France; SREC 68/2022, UK, respectively). The study is entirely anonymous, so your anonymity will be entirely preserved. Your data will be included in presentations scientific conferences and/or publication in scientific journals but the publication of the results of the study will not include any individual results. All information collected during this trial will be treated as confidential. Only those responsible for the study will have access to this data. The data may be shared with other research institutions in Denmark or another country within the EU/EEA (Institut Paul Bocuse Research Center, France/ University Lyon 1, France). The data may be used in other research projects after the end of this project. All data will be stored in secured databases for a maximum of 5 years after

publication.
If you have any questions about the research, please contact:somestalim@institutpaulbocuse.com

Q1.2 **INFORMED CONSENT**

By pressing the "→" button, you certify that you have read and understood the above information and that you give your consent to participate. You also certify that you have been informed that ou can withdraw your participation from the study at any time, simply by closing the web browser. In case you have answered some parts of the questionnaire and wish your previous answers to be removed, you may answer the question "I wish to withdraw from the study and have my data removed", which will be proposed at the end of each section.

Only adults are allowed to participate in the study, so by continuing you certify that you are 18 years of age or older. As a reminder, the target population sought for this study includes **individuals who have or had cancer and have received their treatments between 3 months and 5 years ago.** If you do not meet these criteria, the questionnaire will end and a thank you message will appear.

Q1.1 You are ?

- ○ a female (1)
- ○ a male (2)
- ○ I prefer not to answer (3)

Q1.2 How old are you ?

____

Q1.3 Where do you live?

- ○ France (1)
- ○ Denmark (2)
- ○ Netherlands (5)
- ○ UK (7)
- ○ Ireland (6)
- ○ Other (4) ____

Q1.4 Primary tumor site:
(multiple responses allowed)

- ☐ Breast (1)
- ☐ Lungs (2)
- ☐ Colorectal (3)
- ☐ Pancreas (4)
- ☐ Ovary (5)
- ☐ Prostate (6)
- ☐ Liver (7)
- ☐ head and neck (8)
- ☐ Other (please specify) (9) ________________

Q1.5 What treatments have you undergone?
(multiple responses allowed)

- ☐ Surgery (1)
- ☐ Radiotherapy (2)
- ☐ Chemotherapy (3)
- ☐ Others (please specify): (5) ________________

Q1.6 When did you receive your last treatment?

- ○ Less than 1 year ago (specify how many months) (5) ________________
- ○ More than 1 year ago (specify how many years) (7) ________________

Q2.1
Sensory sensitivity
This second part of the questionnaire will assess different aspects of your perceptions (taste, smell, texture, temperature, etc.) in relation to your food experiences.
There is no “right” or “wrong” answer. The information you provide will remain strictly confidential.
The following questions are similar for each sense studied. We ask you to answer according to your **SENSITIVITY** and not your appetite/preference.

Q2.2
Compared to the situation before the cancer treatment, I perceive that my sensitivity to:

	Decreased (1)	Unchanged (2)	Increased (3)
...salty products	○	○	○
...sweet products	○	○	○
...sour products	○	○	○
...bitter products	○	○	○
...smell of food/drinks	○	○	○

Q2.3
How would you rate changes in your sensitivity:

	No change (1)	Insignificant (2)	Mild (3)	Moderate (4)	Severe (5)
...salty products	○	○	○	○	○
...sweet products	○	○	○	○	○
...sour products	○	○	○	○	○
...bitter products	○	○	○	○	○
...smell of food/drinks	○	○	○	○	○

Q2.4
TEXTURE

Compared to the situation before cancer treatment:

	Strongly disagree (1)	Disagree (2)	Somewhat disagree (3)	Somewhat agree (4)	Agree (5)	Strongly agree (6)
I have noticed changes in my perception of textures	○	○	○	○	○	○

Q2.5
Compared to the situation before cancer treatment:

	Decreased (1)	Unchanged (2)	Increased (3)
My sensitivity to hot food/drinks has:	○	○	○
My sensitivity to cold foods/drinks has:	○	○	○

Q2.6
TEMPERATURE

	No change (1)	Insignificant (2)	Mild (3)	Moderate (4)	Severe (5)
How would you rate changes in your perception of temperature?	○	○	○	○	○

You are now going to answer questions about other types of oral sensations.

Q2.7
- ***Astringency*** refers to a sensation in the mouth most often described as "drying or rough". It is caused by a wide variety of foods and beverages, including strong teas, red wines, nuts, and various (usually unripe) fruits.
- ***Pungency*** is the condition of having a strong, irritating/pungent odor or flavor. This is the characteristic of foods commonly referred to as hot or pungent. It is found in foods such as chilli, peppers, mustard, garlic, arugula, wasabi.
- ***Carbonated drinks*** are drinks containing dissolved carbon dioxide. They include sparkling water and soft drinks (lemonade, soda, coca cola, orangina, champomy, Schweppes). They do not include alcoholic beverages (e.g. champagne, beer).
-Alcoholic **drinks** are beverages containing 3 to 50% alcohol (eg beers, wines, spirits). They do

not include fermented drinks with an alcohol content < 0.5% or non-alcoholic alternatives (e.g. kombucha, low alcohol beer 0.5%).

Compared to the situation before the cancer treatment, I perceive that my sensitivity to:

	Decreased (1)	Unchanged (2)	Increased (3)
...spicy/pungent products (e.g. chili, curry)...	○	○	○
...cooling products (e.g. mint)...	○	○	○
...astringent products (e.g. wine, green tea)...	○	○	○
...carbonated drinks...	○	○	○
...alcoholic drinks...	○	○	○

Q2.8
How would you rate changes in your sensitivity:

	No changes (1)	Insignificant (2)	Mild (3)	Moderate (4)	Severe (5)
...to spicy/pungent product...	○	○	○	○	○
...to cooling products...	○	○	○	○	○
...to astringent products...	○	○	○	○	○
...to carbonated drinks...	○	○	○	○	○
...to alcoholic drinks...	○	○	○	○	○

Q2.9
How long have you been experiencing these changes in sensitivities:

	Not applicable (6)	< 1 month (1)	1-6 months (2)	7-12 months (3)	> 1 year (4)	I do not know (5)
Taste	○	○	○	○	○	○
Smell	○	○	○	○	○	○
Texture	○	○	○	○	○	○
Temperature	○	○	○	○	○	○
Other sensation	○	○	○	○	○	○

Now you will answer questions about your food preferences

Q3.1 In comparison with the situation before cancer treatment, my preference towards

	has decreased (1)	no change (2)	has increased (3)
... salty products	○	○	○
... sweet products	○	○	○
... sour products	○	○	○
...bitter products	○	○	○

Q3.2. Please group the textures into textures you like and textures you don't like.
Drag and drop the words into one of the boxes, you need to sort them all to move on to the next question.

Food textures that I like	Neutral	Food textures that I don't like
______ thick (31)	______ thick (31)	______ thick (31)
______ thin (32)	______ thin (32)	______ thin (32)
______ rubbery (33)	______ rubbery (33)	______ rubbery (33)
______ tender (34)	______ tender (34)	______ tender (34)
______ soft (47)	______ soft (47)	______ soft (47)
______ hard (48)	______ hard (48)	______ hard (48)
______ crispy/ crunchy (49)	______ crispy/ crunchy (49)	______ crispy/ crunchy (49)
______ purees (36)	______ purees (36)	______ purees (36)
______ homogeneous (38)	______ homogeneous (38)	______ homogeneous (38)
______ rough (39)	______ rough (39)	______ rough (39)
______ smooth (50)	______ smooth (50)	______ smooth (50)
______ dry (51)	______ dry (51)	______ dry (51)
______ sticky (40)	______ sticky (40)	______ sticky (40)
______ melt in the mouth (52)	______ melt in the mouth (52)	______ melt in the mouth (52)

Q3.3 In comparison with the situation before cancer treatment, my preference towards

	has decreased (1)	no change (2)	has increased (3)
spicy/pungent products (e.g. chili, curry)	○	○	○
refreshing products (e.g. mint)	○	○	○
astringent products (e.g. wine) (6)	○	○	○
carbonated drinks (e.g. soda, sparkling water) (7)	○	○	○
Alcoholic drinks (8)	○	○	○

Q4.1
You will answer questions on your eating habits

Q4.2
How have your eating habits changed from before treatment?

	Strongly disagree (1)	Disagree (2)	Somewhat disagree (3)	Somewhat agree (4)	Agree (5)	Strongly agree (6)
When I see or smell food I like, it makes me want to eat	○	○	○	○	○	○
I like a wide variety of foods	○	○	○	○	○	○
I am interested in tasting new food I haven't tasted before	○	○	○	○	○	○
I have less appetite	○	○	○	○	○	○
I get full more quickly	○	○	○	○	○	○
I eat in smaller portions	○	○	○	○	○	○
I eat more frequently	○	○	○	○	○	○

Q4.3 **How have your eating habits changed compared to before treatment?**

	Strongly disagree (1)	Disagree (2)	Somewhat disagree (3)	Somewhat agree (4)	Agree (5)	Strongly disagree (6)
Eating takes more effort	○	○	○	○	○	○
I lost the pleasure of eating	○	○	○	○	○	○
I feel uncomfortable eating outside my home	○	○	○	○	○	○
I am often the last to finish the meal	○	○	○	○	○	○
I often decide that I don't like a food before tasting it.	○	○	○	○	○	○
I have started to strongly dislike or avoid certain foods	○	○	○	○	○	○
I have a strong desire or craving to eat certain foods	○	○	○	○	○	○

Q4.4 **How often have you consumed the following foods/drinks in the past week?**

	More than once a day (1)	Once a day (2)	4-6 times a week (3)	2-3 times a week (4)	Once a week (5)	Less than once a week (6)	Never (7)
Red meat (E.g. beef, lamb)	○	○	○	○	○	○	○
White meat (E.g. chicken, turkey)	○	○	○	○	○	○	○
Fish	○	○	○	○	○	○	○
Seafood	○	○	○	○	○	○	○
Processed meat (E.g. hamburger deli meats, sausages)	○	○	○	○	○	○	○
Vegetables	○	○	○	○	○	○	○
Fruits	○	○	○	○	○	○	○
Legumes (E.g. lentils, beans, chickpeas)	○	○	○	○	○	○	○
Starchy food (E.g. pasta, rice, potatoes)	○	○	○	○	○	○	○
Bread	○	○	○	○	○	○	○

Q4.5 **How often have you consumed the following foods/drinks in the past week?**

	More than once a day (1)	Once a day (2)	4-6 times a week (3)	2-3 times a week (4)	Once a week (5)	Less than once a week (6)	Never (7)
Milk	○	○	○	○	○	○	○
Dairy products (E.g. cheese, yogurt)	○	○	○	○	○	○	○
Chips	○	○	○	○	○	○	○
Chocolate (chocolate bar)	○	○	○	○	○	○	○
Alcohol	○	○	○	○	○	○	○
Soft drinks (E.g. soda, sparkling water)	○	○	○	○	○	○	○
Sugary drinks (E.g. juice, smoothie)	○	○	○	○	○	○	○
Hot drinks (E.g. tea, coffee)	○	○	○	○	○	○	○
Ice cream (E.g. hard ice, soft ice)/ cold drinks (Ex. iced tea and coffee)	○	○	○	○	○	○	○

Q6.1
You will now evaluate 16 pairs of food. Please use the scale below to indicate your level of liking of the food.

Q7.1
Thin yogurt

Q7.2

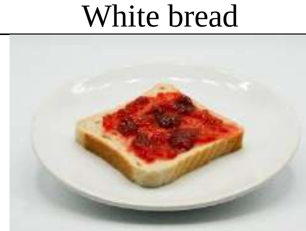
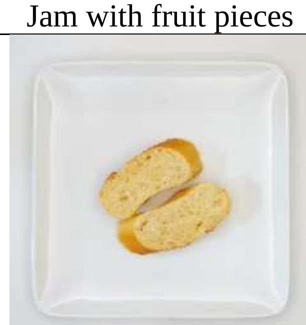
	Dislike extremely	Neutral	Like extremely

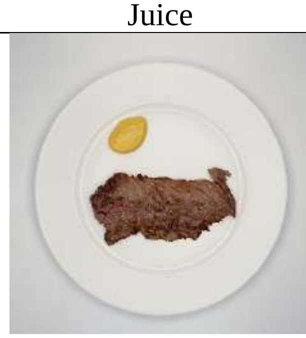
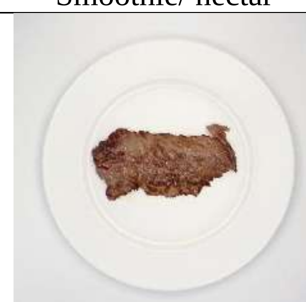
Q7.3 Thick yogurt

Q7.4

	Dislike extremely	Neutral	Like extremely

Sub modality	Pair A	Pair B
Texture	 Thin yogurt	 Thick yogurt

Texture	 Apple slices	 Apple compote
Texture	 Thick soup	 Thin soup
Texture	 White bread	 Toasted bread
Texture	 Jam with fruit pieces	 Jam without fruit pieces
Texture	 Baguette	 Biscotte

Texture	 Smooth mashed potatoes	 Mashed potatoes
Texture	 Juice	 Smoothie/ nectar
Chemesthetic	 Meat with mustard	 Meat without mustard
Chemesthetic	 Pasta without pepper	 Pasta with pepper

Chemesthetic	 Still water	 Sparkling water
Chemesthetic	 Alcoholic beer	 Non-alcoholic beer
Chemesthetic	 Tea	 Mint tea
Chemesthetic	 Chocolate	 Mint chocolate

Temperature	 Cold water	 Room-temperature water
Temperature	 Warm soup (~40°C)	 Hot soup (> 60°C)

Q30.2

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
I have mouth sores	○	○	○	○	○
I limit the amount or kind of food I eat because of dental problems	○	○	○	○	○
I have difficulty biting or chewing certain hard foods such as meat or an apple	○	○	○	○	○
I have difficulty swallowing	○	○	○	○	○
My teeth or gums are sensitive to cold, hot or sugary foods	○	○	○	○	○
Food gets stuck in my mouth	○	○	○	○	○
Food gets stuck in my throat	○	○	○	○	○
I dread the moment of eating because I have pain	○	○	○	○	○
I am limited in my ability to open or move my jaw	○	○	○	○	○

Q30.3

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
I have a dry mouth	○	○	○	○	○
I have sticky saliva	○	○	○	○	○
I feel nauseous	○	○	○	○	○
I have pain on my gums	○	○	○	○	○
I have bleeding gums	○	○	○	○	○
I have sore lips	○	○	○	○	○
I have a sore mouth	○	○	○	○	○
I have a burning sensation in my mouth	○	○	○	○	○
I have a pain in my throat	○	○	○	○	○
I have dental pain/ problems	○	○	○	○	○

Q31.1 What is your height (cm)?

____

Q31.2 What is weight (kg)?

____

Q31.4 Are you a smoker?

○ Yes, regular (1)

○ Yes, occasional (2)

○ No (3)

○ Former smoker (4)

Appendix 2.B – Correlation table (Chapter 6)

Correlations

			OralSUM	Sweet	Salty	Sour	Bitter	Umami	Smell
Spearman's rho	OralSUM	Correlation Coefficient	--						
		Sig. (2-tailed)	.						
		N	30						
	Sweet	Correlation Coefficient	-.010	--					
		Sig. (2-tailed)	.956	.					
		N	30	30					
	Salty	Correlation Coefficient	.017	.735**	--				
		Sig. (2-tailed)	.931	<.001	.				
		N	30	30	30				
	Sour	Correlation Coefficient	.189	.450*	.564**	--			
		Sig. (2-tailed)	.316	.013	.001	.			
		N	30	30	30	30			
	Bitter	Correlation Coefficient	.213	.579**	.579**	.883**	--		
		Sig. (2-tailed)	.258	<.001	<.001	<.001	.		
		N	30	30	30	30	30		
	Umami	Correlation Coefficient	.145	.691**	.809**	.666**	.599**	--	
		Sig. (2-tailed)	.443	<.001	<.001	<.001	<.001	.	
		N	30	30	30	30	30	30	
	Smell	Correlation Coefficient	.047	.326	.000	.111	.118	.123	--
		Sig. (2-tailed)	.803	.078	1.000	.560	.535	.516	.
		N	30	30	30	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

			OralSUM	Texture	Hot	Cold	Spicy	Cooling	Astringent	Carbonation	Alcohol
Spearman's rho	OralSUM	Correlation Coefficient	--								
		Sig. (2-tailed)	.								
		N	30								
	Texture	Correlation Coefficient	537**	--							
		Sig. (2-tailed)	.002	.							
		N	30	30							
	Hot	Correlation Coefficient	560**	.523**	--						
		Sig. (2-tailed)	.001	.003	.						
		N	30	30	30						
	Cold	Correlation Coefficient	419*	.472**	613**	--					
		Sig. (2-tailed)	.021	.008	<.001	.					
		N	30	30	30	30					
	Spicy	Correlation Coefficient	.159	.089	429*	387*	--				
		Sig. (2-tailed)	.402	.640	.018	.035	.				
		N	30	30	30	30	30				
	Cooling	Correlation Coefficient	.121	.028	.186	372*	.491**	--			
		Sig. (2-tailed)	.526	.883	.324	.043	.006	.			
		N	30	30	30	30	30	30			
	Astringent	Correlation Coefficient	.169	.018	100	463**	.417*	.417*	--		
		Sig. (2-tailed)	.372	.924	.598	.010	.022	.022	.		
		N	30	30	30	30	30	30	30		
	Carbonation	Correlation Coefficient	.108	.609**	.236	488**	.033	366*	.170	--	
		Sig. (2-tailed)	.568	<.001	.209	.006	.862	.047	.370	.	
		N	30	30	30	30	30	30	30	30	
	Alcohol	Correlation Coefficient	.297	.165	293	459*	.513**	443*	.683**	.269	--
		Sig. (2-tailed)	.111	.383	.117	.011	.004	.014	<.001	.150	.
		N	30	30	30	30	30	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

			OralSUM	Desire_Smell Visual	Variety	Novel	Loss_appetit e	Quick_satiati on	Smaller_port ion	Frequent_eati ng	Effortful_eatin g	Losing_pleas ure	Eating_out	Finish_last	Disliking_bef ore	Aversion	Craving	Unpleasant/di fficulty
Spearman's rho	OralSUM	Correlation Coefficient	—															
		Sig. (2-tailed)	.															
		N	30															
	Desire_SmellVisual	Correlation Coefficient	-.332**	—														
		Sig. (2-tailed)	.005	.														
		N	30	30														
	Variety	Correlation Coefficient	-.467**	.422*	—													
		Sig. (2-tailed)	.006	.020	.													
		N	30	30	30													
	Novel	Correlation Coefficient	-.174	.337	.323	—												
		Sig. (2-tailed)	.357	.069	.081	.												
		N	30	30	30	30												
	Loss_appetite	Correlation Coefficient	.240	-.299	-.259	-.191	—											
		Sig. (2-tailed)	.202	.109	.167	.311	.											
		N	30	30	30	30	30											
	Quick_satiation	Correlation Coefficient	.120	-.120	.019	-.046	.330	—										
		Sig. (2-tailed)	.528	.529	.923	.633	.075	.										
		N	30	30	30	30	30	30										
	Smaller_portion	Correlation Coefficient	.414*	-.299	-.259	-.046	.454**	.464**	—									
		Sig. (2-tailed)	.023	.109	.167	.633	.010	.010	.									
		N	30	30	30	30	30	30	30									
	Frequent_eating	Correlation Coefficient	.062	-.063	-.049	.267	-.236	-.235	-.094	—								
		Sig. (2-tailed)	.667	.740	.797	.155	.209	.209	.619	.								
		N	30	30	30	30	30	30	30	30								
	Effortful_eating	Correlation Coefficient	.513**	-.447*	-.206	-.151	.267	-.194	.267	.141	—							
		Sig. (2-tailed)	.004	.013	.271	.426	.153	.401	.153	.456	.							
		N	30	30	30	30	30	30	30	30	30							
	Losing_pleasure	Correlation Coefficient	.331	-.331	-.451*	-.233	.530**	.120	.395*	.095	.471**	—						
		Sig. (2-tailed)	.074	.074	.012	.215	.003	.528	.031	.617	.009	.						
		N	30	30	30	30	30	30	30	30	30	30						
	Eating_out	Correlation Coefficient	.484**	-.337	-.167	.023	.191	.040	.312	.373*	.603**	.395*	—					
		Sig. (2-tailed)	.007	.069	.378	.900	.311	.833	.094	.042	<.001	.035	.					
		N	30	30	30	30	30	30	30	30	30	30	30					
	Finish_last	Correlation Coefficient	-.063	.293	-.196	.263	.175	-.262	.029	.309	.073	.219	.230	—				
		Sig. (2-tailed)	.740	.116	.299	.160	.355	.161	.878	.097	.702	.136	.221	.				
		N	30	30	30	30	30	30	30	30	30	30	30	30				
	Disliking_before	Correlation Coefficient	.429*	-.443*	-.342	-.373*	.047	.189	.047	-.200	.283	.095	.053	-.154	—			
		Sig. (2-tailed)	.018	.014	.064	.042	.804	.317	.804	.289	.130	.617	.783	.405	.			
		N	30	30	30	30	30	30	30	30	30	30	30	30	30			
	Aversion	Correlation Coefficient	.573**	-.443*	-.342	-.053	.622**	-.046	.477**	-.050	.565**	.381*	.373*	.154	.138	—		
		Sig. (2-tailed)	<.001	.014	.064	.780	.000	.810	.008	.793	.001	.038	.042	.416	.386	.		
		N	30	30	30	30	30	30	30	30	30	30	30	30	30	30		
	Craving	Correlation Coefficient	.147	-.063	-.157	.191	-.062	-.330	-.330	.520**	.000	.144	-.043	.262	.094	-.047	—	
		Sig. (2-tailed)	.439	.744	.407	.311	.743	.075	.075	.003	1.000	.448	.823	.161	.619	.804	.	
		N	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	
	Unpleasant/difficulty	Correlation Coefficient	.541**	-.211	-.247	.081	.276	.003	.413*	.190	.471**	.207	.375*	.101	.048	.618**	.009	—
		Sig. (2-tailed)	.002	.264	.189	.670	.139	.982	.023	.314	.009	.273	.041	.594	.801	<.001	.962	.
		N	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

			OralSUM	Salty preference	Sweet preference	Sour preference	Bitter preference	Spicy preference	Cooling preference	Astringent preference	Carbonation preference	Alcohol preference
Spearman's rho	OralSUM	Correlation Coefficient	—									
		Sig. (2-tailed)	.									
		N	30									
	Salty preference	Correlation Coefficient	.229	—								
		Sig. (2-tailed)	.225	.								
		N	30	30								
	Sweet preference	Correlation Coefficient	-.119	.112	—							
		Sig. (2-tailed)	.530	.554	.							
		N	30	30	30							
	Sour preference	Correlation Coefficient	-.505**	.105	.221	—						
		Sig. (2-tailed)	.004	.582	.240	.						
		N	30	30	30	30						
	Bitter preference	Correlation Coefficient	-.336	.164	.336	.710**	—					
		Sig. (2-tailed)	.069	.387	.070	<.001	.					
		N	30	30	30	30	30					
	Spicy preference	Correlation Coefficient	.524**	.011	-.318	-.655**	-.634**	—				
		Sig. (2-tailed)	.003	.953	.087	<.001	<.001	.				
		N	30	30	30	30	30	30				
	Cooling preference	Correlation Coefficient	.341	.141	-.116	-.373*	-.570**	.477**	—			
		Sig. (2-tailed)	.066	.469	.541	.042	<.001	.008	.			
		N	30	30	30	30	30	30	30			
	Astringent preference	Correlation Coefficient	.508**	.261	-.293	-.690**	-.505**	.531**	.583**	—		
		Sig. (2-tailed)	.004	.163	.117	<.001	.004	.003	<.001	.		
		N	30	30	30	30	30	30	30	30		
	Carbonation preference	Correlation Coefficient	.434*	.111	.054	-.151	.037	.163	.500**	.394*	—	
		Sig. (2-tailed)	.017	.559	.776	.424	.844	.388	.004	.031	.	
		N	30	30	30	30	30	30	30	30	30	
	Alcohol preference	Correlation Coefficient	.446*	.071	-.062	-.584**	-.321	.336	.391*	.772**	.324	—
		Sig. (2-tailed)	.014	.709	.744	<.001	.084	.070	.033	<.001	.081	.
		N	30	30	30	30	30	30	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix 3 – Questionnaire (Chapter 8)

- **Sex** : ☐ Male ☐Female
- **Age:** ....
- **Height:** .... cm **Weight:** ...... kg
- **Living situation:** ☐ living alone ☐ living with others (partner/children/etc)
- **Occupation held or last held:** ☐ Agriculteurs farmers ☐ Artisans, shopkeepers and company directors ☐ Cadres and higher intellectual occupations ☐ Professions intermediaries ☐Employés ☐ Ouvriers ☐ Student ☐ Unemployed
- **Level of education**: ☐Without diploma ☐CAP-BEP ☐Bac à Bac +2 ☐Bac +3 à Bac +4 ☐Bac +5 and more

- **Are you a smoker:** ☐ Yes ☐ former smoker ☐ No
- **Type of cancer (location)**: ....
- **Your current cancer treatment :**

  ☐ Chemotherapy ☐ Hormone therapy ☐ Immunotherapy ☐ Targeted therapies

  ☐ Other:...............................
- **How long have you been receiving the current treatment for your cancer?**

  ☐ Less than a year ago (**specify how many months**): .... months

  ☐ More than one year previously (**specify how many years**): .... years
- **Do you have any previous treatments**

  ☐ No ☐ Yes (please specify): ....

Appetite measurement

Draw a line to indicate where you are on the perception scale:

Are you hungry?

I'm not hungry at all I'm extremely hungry

Assessment of salivary function (to be completed by the researcher)

<u>Unstimulated saliva</u>

Visual assessment of **hydration level** > 60s c (1)< 60s c (3)

Visual assessment of saliva **consistency**: sticky, viscous c (1) a few bubbles c (2) clear, watery c (3)

pH 5.0 - 5.8 c (1) 6,0 - 6,6 c (2) 6,8 - 7,8 c (3)

<u>Stimulated saliva</u>

Volume of saliva collected in 5 min < 3.5 ml c (1) 3.5 - 5 c (2)> 5 ml c (3)

Buffer power: 0- 5 points c (1) 6 - 9 points c (2) 10 - 12 points c (3)

Total score: ....

Food sample tasting - cromesquis

Sample N^{o} : ____

Overall, how much do you appreciate this sample?

I don't like it at all **I like it a lot**

How much would you appreciate this sample before your cancer treatment?

I don't like it at all **I like it a lot**

Please give your opinion on the intensity of the taste of the sample.

Much too little **Just about right** **Much too intense**

In terms of texture, this sample is ... in the mouth

Very unpleasant **Very pleasant**

This sample is ... to swallow

Very difficult **Very easy**

Sample Nº : ____

Overall, how much do you appreciate this sample?

I don't like it at all **I like it a lot**

How much would you appreciate this sample before your cancer treatment?

I don't like it at all **I like it a lot**

Please give your opinion on the intensity of the taste of the sample.

Much too little **Just about right** **Much too intense**

In terms of texture, this sample is ... in the mouth

Very unpleasant **Very pleasant**

This sample is ... to swallow

Very difficult **Very easy**

Please indicate to what extent you perceive these two samples as different/similar?

Very different **Very similar**

Food sample tasting - panacotta

Sample Nº : ____

Overall, how much do you appreciate this sample?

I don't like it at all **I like it a lot**

How much would you appreciate this sample before your cancer treatment?

I don't like it at all **I like it a lot**

Please give your opinion on the intensity of the taste of the sample.

Much too little **Just about right** **Much too intense**

In terms of texture, this sample is ... in the mouth

Very unpleasant **Very pleasant**

This sample is ... to swallow

Very difficult **Very easy**

Sample N° : ____

Overall, how much do you appreciate this sample?

I don't like it at all **I like it a lot**

How much would you appreciate this sample before your cancer treatment?

I don't like it at all **I like it a lot**

Please give your opinion on the intensity of the taste of the sample.

Much too little **Just about right** **Much too intense**

In terms of texture, this sample is ... in the mouth

Very unpleasant **Very pleasant**

This sample is ... to swallow

Very difficult **Very easy**

Please indicate to what extent you perceive these two samples as different/similar?

Very different **Very similar**

Sensory perception

	Never	Rarely	Sometimes	Often	Always
I notice (unpleasant) odour(s) that were not present before my treatment.	○	○	○	○	○
I perceive odour(s) that are not perceived by others	○	○	○	○	○
All smells seem unpleasant to me	○	○	○	○	○
I have an unpleasant taste in my mouth	○	○	○	○	○
I have a metallic sensation in my mouth	○	○	○	○	○
I've got a bitter taste in my mouth	○	○	○	○	○
The food/drink tastes the same, but I don't find it as tasty as I used to.	○	○	○	○	○
I avoid certain foods because of their texture	○	○	○	○	○

Compared to the situation before the cancer treatment, my sensitivity concerning :

	has decreased significantly	Has decreased slightly	is unchanged	has increased slightly	has increased significantly
Tastes in general	○	○	○	○	○
The bitter taste	○	○	○	○	○
the acid taste	○	○	○	○	○
the salty taste	○	○	○	○	○
the sweet taste	○	○	○	○	○
Food odours in general	○	○	○	○	○
Hot food/drinks	○	○	○	○	○
Cold food/drinks	○	○	○	○	○
Spicy/harsh foods/drinks (e.g. chilli, curry)...	○	○	○	○	○
Refreshing foods/drinks (e.g. mint)...	○	○	○	○	○
Astringent foods/drinks (e.g. wine, green tea, grapes)...	○	○	○	○	○
Carbonated beverages (e.g. soft drinks, sparkling water)	○	○	○	○	○
Alcoholic beverages...	○	○	○	○	○
Food textures in general	○	○	○	○	○

Oral symptoms

	Never	Rarely	Sometimes	Often	Always
I have difficulty swallowing	○	○	○	○	○
I have trouble chewing	○	○	○	○	○
My mouth is dry	○	○	○	○	○
My saliva is sticky	○	○	○	○	○
My teeth or gums are sensitive to cold, hot or sweet foods	○	○	○	○	○
Food gets stuck in my mouth	○	○	○	○	○
Food gets stuck in my throat	○	○	○	○	○
I have a pain in my mouth	○	○	○	○	○
I have a burning sensation in my mouth	○	○	○	○	○
I've got a sore throat	○	○	○	○	○

List of Appendix

Appendix 1.A – Scales used in Study 1 (Chapter 5)

Relevé du petit déjeuner et mesure de l'appétit

Relevé du petit déjeuner avant le repas test

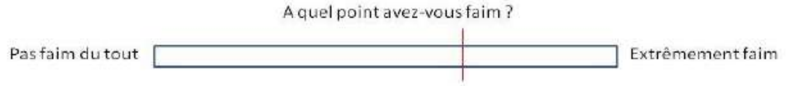
Qu'avez-vous consommé pour votre petit déjeuner ce matin ? *Cochez autant de cases que nécessaire*

☐ Pain, biscotte, pain de mie	☐ Fruits	☐ Café
☐ Beurre	☐ Yaourt	☐ Thé
☐ Confiture, miel	☐ Fromage	☐ Jus de fruits
☐ Pâtes à tartiner	☐ Jambon, charcuterie	☐ Autres, précisez……………
☐ Céréales	☐ Œufs	
☐ Viennoiseries, pâtisseries, biscuits	☐ Lait	
	☐ Boissons végétales	

☐ Je n'ai pas pris de petit déjeuner

Exemple

Nous vous proposons d'utiliser une sorte de thermomètre de la faim, qui permet de mesurer l'intensité de la faim.
L'intensité de la faim peut être définie par un trait tracé sur l'échelle comme dans l'exemple ci-dessous :



L'extrémité de droite correspond à la faim maximale imaginable.
Plus le trait est proche de cette extrémité, plus la faim est importante.
L'extrémité gauche correspond à pas de faim du tout.
Plus le trait est proche de cette extrémité, moins la faim est importante.

Merci de répondre à l'ensemble des questions posées en suivant ce même modèle.

Appétit

En ce moment, à quel point avez-vous faim ?

Pas du tout ________________________________ Extrêmement

En ce moment, à quel point êtes-vous rassasié ?

Pas du tout ________________________________ Extrêmement

En ce moment, à quel point avez-vous envie de manger ?

Pas du tout ________________________________ Extrêmement

En ce moment, quelle quantité pensez-vous pouvoir manger ?

Pas du tout ________________________________ Extrêmement

<u>Questionnaire d'évaluation de la sensibilité de texture</u>

1. Goûtez l'échantillon comme indiqué.
2. Evaluez et notez la texture en plaçant une ligne verticale sur l'échelle ci-dessous.
3. Vous pouvez avaler ou cracher les échantillons dégustés.
4. Pensez à toujours rincer votre bouche avec de l'eau avant d'évaluer un échantillon.

   Au total, 3 échantillons seront testés dans chaque catégorie

<u>EXEMPLE</u>

<u>Fermeté</u>

1. Placez l'échantillon dans votre bouche, entre la langue et le palais.
2. Comprimez l'échantillon entre votre langue et votre palais.
3. Evaluez et notez la **fermeté** de l'échantillon (la force requise pour comprimer l'échantillon entre la langue et le palais).
4. Rincez votre bouche avec de l'eau avant d'évaluer l'échantillon suivant.

	Echantillon.
Celui avec le moins de fermeté	123
Celui avec une fermeté intermédiaire	456
Celui avec le plus de fermeté	789

5. **Quelle est la fermeté de l'échantillon ?**

Fermeté

1. Placez l'échantillon dans votre bouche, entre la langue et le palais.
2. Comprimez l'échantillon entre votre langue et votre palais.
3. Evaluez et notez la **fermeté** de l'échantillon (la force requise pour comprimer l'échantillon entre la langue et le palais).
4. Rincez votre bouche avec de l'eau avant d'évaluer l'échantillon suivant.

	Echantillon.
Celui avec le moins de fermeté	
Celui avec une fermeté intermédiaire	
Celui avec le plus de fermeté	

Quelle est la fermeté de l'échantillon ?

Pas ferme **Très ferme**

Consistance

1. Placez l'échantillon dans votre bouche, entre la langue et le palais.
2. Manipulez l'échantillon avec votre langue.
3. Evaluez et notez la **consistance** de l'échantillon (le degré de résistance quand vous manipulez l'échantillon entre la langue et le palais).
4. Rincez votre bouche avec de l'eau avant d'évaluer l'échantillon suivant.

	Echantillon.
Celui avec le moins de consistance	
Celui avec une consistance intermédiaire	
Celui avec le plus de consistance	

Quelle est la consistance de l'échantillon ?

Pas consistant **Très consistant**

Rugosité

1. Placez l'échantillon dans votre bouche, entre la langue et le palais.
2. Faites glisser votre langue contre le palais.
3. Evaluez et notez la **rugosité** de l'échantillon (le degré d'abrasivité de la surface de l'échantillon perçu par la langue).
4. Rincez votre bouche avec de l'eau avant d'évaluer l'échantillon suivant.

	Echantillon.
Celui avec le moins de rugosité	
Celui avec une rugosité intermédiaire	
Celui avec le plus de rugosité	

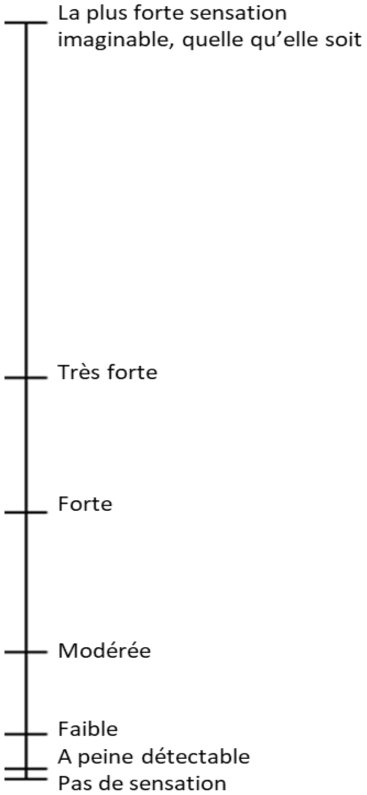
Quelle est la rugosité de l'échantillon ?

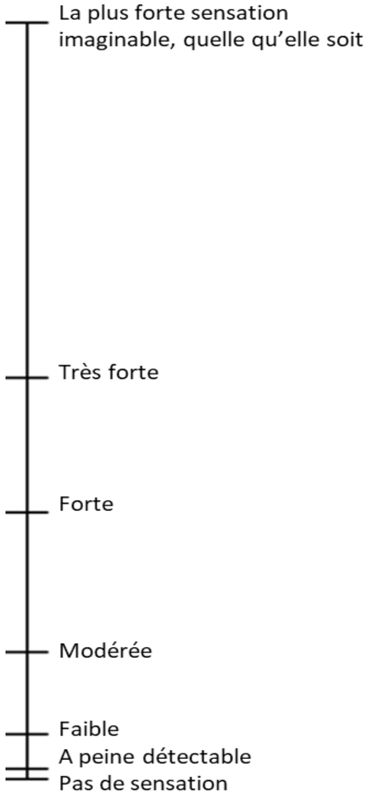
Pas rugueux **Très rugueux**

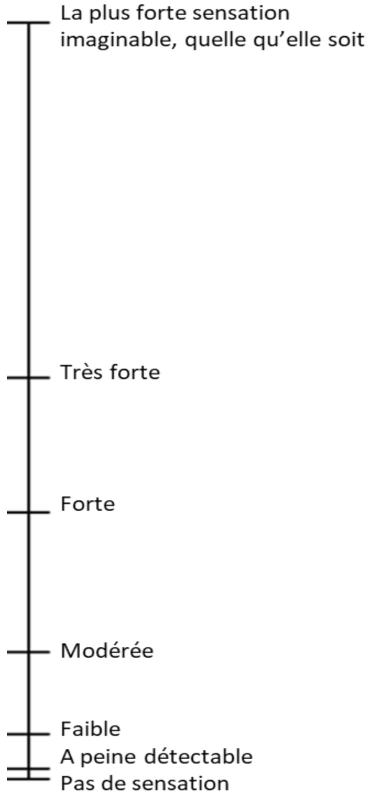
<u>Questionnaire de l'évaluation de la sensibilité trigéminale</u>

1. Prenez l'intégralité de la solution dans votre bouche et gardez la pendant 10 secondes sans avaler. Evitez au maximum les mouvements excessifs de la bouche pendant que la solution est dans la bouche.
2. Après 10 secondes, crachez la solution dans le crachoir (gobelet en papier blanc)
3. Après 10 secondes supplémentaires, jugez de l'intensité du rafraichissement de la solution en bouche.
4. Buvez de l'eau pour rincer la bouche et pour retirer toute sensation persistante.
5. Attendez 4 minutes supplémentaires avant d'évaluer l'échantillon suivant.

Evaluez la sensation de <u>rafraichissement</u> sur l'échelle suivante de l'échantillon



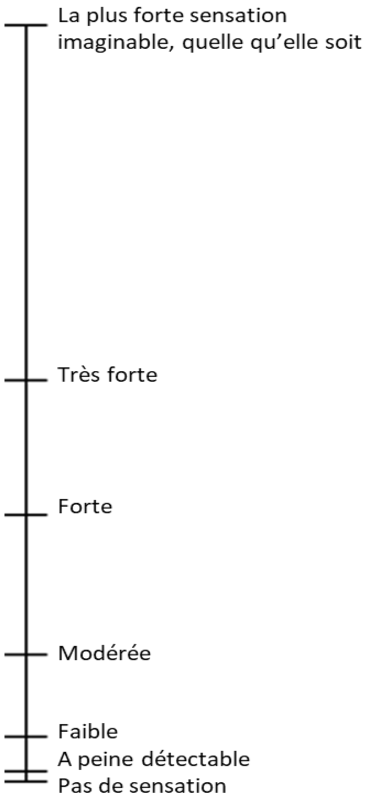


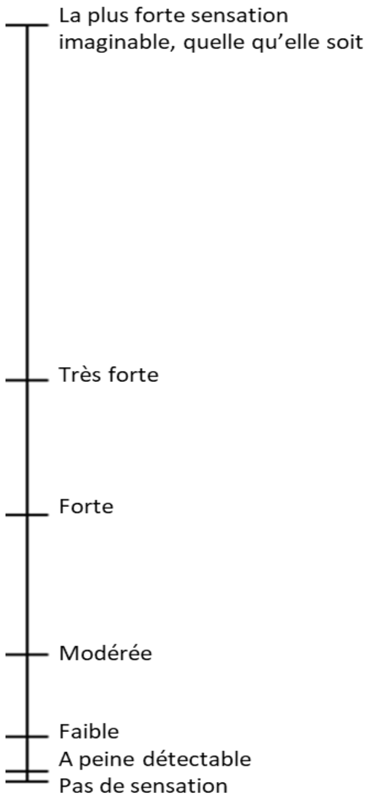


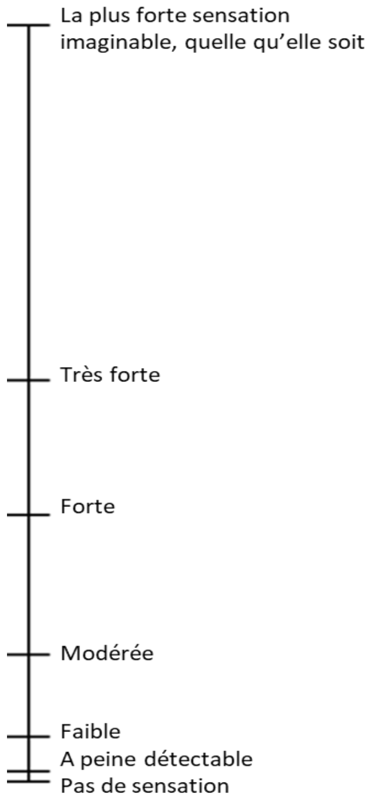
Questionnaire de l'évaluation de la sensibilité trigéminale

1. Prenez l'intégralité de la solution dans votre bouche et gardez la pendant 10 secondes sans avaler. Evitez au maximum les mouvements excessifs de la bouche pendant que la solution est dans la bouche.
2. Après 10 secondes, crachez la solution dans le crachoir (gobelet en papier blanc)
3. Après 10 secondes supplémentaires, jugez de l'intensité du piquant de la solution en bouche.
4. Buvez de l'eau pour rincer la bouche et pour retirer toute sensation persistante.
5. Attendez 4 minutes supplémentaires avant d'évaluer l'échantillon suivant.

Evaluez la sensation de piquant sur l'échelle suivante de l'échantillon


La plus forte sensation
imaginable, quelle qu’elle soit
Très forte
Forte
Modérée
Faible
A peine détectable
Pas de sensation


La plus forte sensation
imaginable, quelle qu’elle soit
Très forte
Forte
Modérée
Faible
A peine détectable
Pas de sensation


La plus forte sensation
imaginable, quelle qu’elle soit
Très forte
Forte
Modérée
Faible
A peine détectable
Pas de sensation