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

4
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21

22 **Abstract**

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

30 **DESIGN** The literature search was performed using PubMed and Google Scholar databases
31 and restricted to literature for English-language articles published between 1990 and June
32 2018. Sensory related terms were combined with food behavior related terms to identify the
33 studies that examined the association between these two terms. The retrieved studies were
34 grouped based on the taste and smell assessment outcomes.

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

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

48

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

50

51

52 1. Introduction

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

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

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

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

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

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

102

103 **1.1. Chemo-sensation: definition and underlying sensory systems**

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

110

111 ***1.1.1. The gustatory system***

112 At the periphery, the gustatory system includes an array of taste buds in the oral and
113 pharyngeal cavities. Taste buds are located around small structures known as papillae, which
114 are found mainly on the upper surface of the tongue (but also on the soft palate, upper
115 esophagus, cheek and epiglottis). There are four known types of papillae: foliate,
116 circumvallate, fungiform and filiform, distributed on different zones of the surface of the
117 tongue (*Figure 1*) [46]. Taste perception is the result of an interaction between sapid
118 molecules and taste receptors in specialized epithelial gustatory cells present in taste buds
119 [47]. Taste buds are located on the tongue and have a lifespan of 5-20 days [17].

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

125 coupled receptors (GPCRs) [47]. The proteins called T1R1, T1R2 and T1R3 detect sweet and
126 umami tastants, while T2Rs is specific to bitter. The combination of these receptors with their
127 specific ligand (contained in the sapid molecule) triggers a series of intracellular reactions
128 [36,51]. The sensory information is transmitted to the primary taste cortex via three cranial
129 nerves that carry taste sensations from different areas: the facial nerve (VII) from the anterior
130 two thirds of the tongue; the glossopharyngeal nerve (IX), from the posterior one third of the
131 tongue; and the vagus nerve (X) from the back of the oral cavity. These sensations are then
132 transmitted to secondary or associative cortical areas common to olfactory and gustatory
133 sensations (*Figure 1*) [14,46].

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

144

145 ***1.1.2. The olfactory system***

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

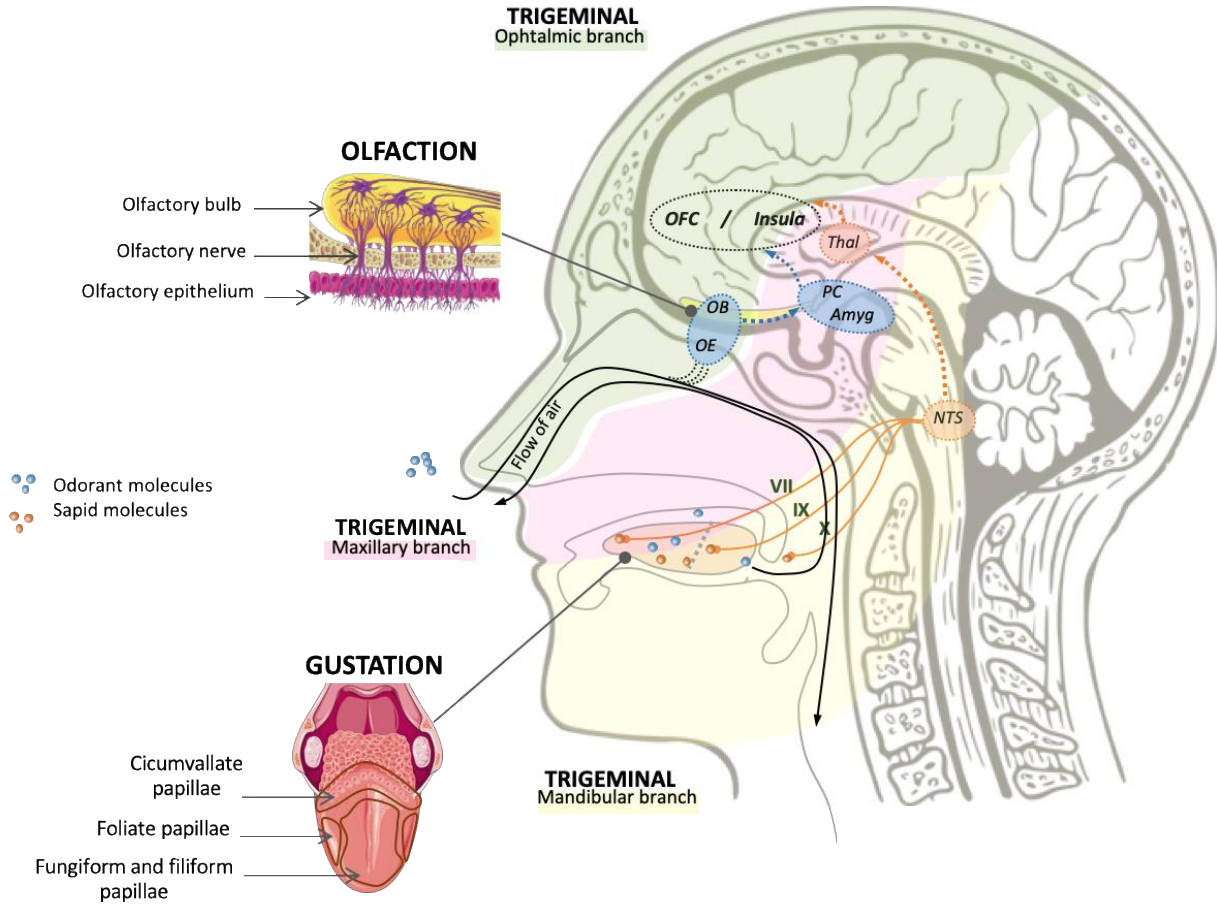
150 facilitates the detection of environmental chemical molecules [56]. These neurons are located
151 in the olfactory epithelium, a specialized tissue of about 2.5 to 10 cm² in surface area located
152 on the roof of the nasal cavity. The neurons are bipolar cells with several cilia, which contain
153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

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

174

175

176 PLEASE BE SURE TO PROVIDE US THE MOST ORIGINAL VERSION OF THIS
177 FIGURE THAT YOU HAVE AND IF THIS IS FROM ANOTHER SOURCE PLEASE
178 CITE THAT SOURCE AND IMMEDIATELY OBTAIN PERMISSION FOR ITS USE
179



180

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

191

192 **1.1.3. The trigeminal system**

193 With gustation and olfaction, the trigeminal system is the third chemosensory system
194 that contributes to flavor perception. Trigeminal sensitivity (both proprioceptive and
195 kinesthetic) of the face and associated cavities (i.e. oral and nasal) is transmitted via the three
196 branches – the ophthalmic, maxillary and mandibular - of the fifth cranial nerve also called
197 the trigeminal nerve [21] (*Figure 1*). The trigeminal nerve endings in the nasal and oral
198 cavities are sensitive to tactile and thermic information and to several molecules known to be
199 pungent, tingling, irritating or astringent [62]. Thus, the spiciness of pepper, the burning of
200 ginger, the sparkling of carbonated drinks, and the astringency of red wines, are potential
201 stimulants of the trigeminal system. Psychophysical and neurobiological investigations have
202 revealed that interactions between the trigeminal and the olfactory system may occur at both
203 peripheral (trigeminal fibers were identified in the nasal epithelium [63]) and central levels
204 [64], although compared to pure olfactory stimuli, intranasal trigeminal stimuli show specific
205 neural activations [65].

206

207 **1.2. Food behavior: definition and determinants**

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

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

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

244

245 **2. Research methodology**

246 **2.1. Data search and selection criteria strategy**

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

267 2.2. *Data extraction and processing*

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

282

283 3. **Results**

284 3.1. **Modification in cancer patients’ taste and smell in during chemotherapy**

285 Eleven of the 13 studies listed in **Table 1** showed an effect of chemotherapy treatment
286 on perceptions (including taste and smell). In studies that used subjective methods of
287 chemosensory assessment, there was high heterogeneity in chemosensory outcomes for
288 patients not only between the studies but also within the same study (**Table 1, Section A**). For
289 example, Marinho et al. [87] showed that 64% of the patients reported taste changes during
290 the chemotherapy treatment with no sensory modifications in 36%. Hutton et al. showed that
291 86% of the patients reported sensory abnormalities, of which 30% described only taste

292 abnormalities, and 5% only smell. The prevalence of olfactory and gustatory changes in
293 patients was 60% in Brisbois et al. [9] but the sensory phenotype varied according to the
294 participants: 42% declared a stronger sensation, 18% a weaker sensation, 14% a mixed
295 sensation, and 26% no change in sensation. In accordance, Mc Greevy et al. [88] showed a
296 large variability across patients, with a prominent effect of gender - for example, whereas
297 10% of the men vs. 37% of the women declared stronger sensation, 20% of the men vs. 6% of
298 the women declared sensation was weaker. Finally, 73% of patients in the study by Belqaid et
299 al. [89] declared sensory alterations with a variation in sensory phenotypes throughout the
300 treatment - from weaker sensation to stronger sensation or no effect. Such heterogeneity in
301 self-reported taste and smell modifications is confirmed by psychophysical studies based on
302 objective methods of sensory assessment. Following patients' sensory capacities, three types
303 of profiles were extracted from the papers listed in **Table 1**: (1) patients exhibiting unaltered
304 taste and smell (section B); (2) patients exhibiting reduced sensitivity or hyposensitivity to
305 taste and smell (section C); (3) patients exhibiting a increased sensitivity or hypersensitivity
306 to taste and smell (section D); These 3 types of profiles are described below.

307

308 *The “Unaltered taste and smell” profile*

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

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

323

324 *The “Hyposensitivity to tastes and/or smells” profile*

325 This profile identifies patients who experience decreased gustatory and/or olfactory
326 function (**Table 1, Section C**). Three studies showed a decrease in both olfactory and
327 gustatory perceptions [85,91,92], and two reported a reduced ability to identify gustatory
328 stimuli [20,93]. In a longitudinal study, IJpma et al. [85] assessed the olfactory and gustatory
329 capabilities in 21 patients with a diagnosis of testicular cancer undergoing cisplatin
330 chemotherapy. The results showed a transient decrease of subjective taste and smell
331 perception, associated with a decrease in sensitivity for salty taste. This effect was prominent
332 during the first week of each chemotherapy cycle. Similarly, De Vries et al. [94] assessed the
333 olfactory and gustatory functions in 28 women with a diagnosis of breast cancer, during, and
334 6 months after the completion of chemotherapy. Patients reported their taste and smell
335 functions as lower during chemotherapy and shortly after chemotherapy, yet improved 6
336 months after the completion of chemotherapy. In the same study, objective psychophysical
337 tests showed a lower olfactory and gustatory sensitivity during chemotherapy, especially for
338 salty taste. The decrease of subjective taste and/or smell perception was also found in a larger
339 group including 117 women with breast cancer [92].

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

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

347

348 *The “Hyper- sensitivity to tastes and smells” profile*

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

355 In sum, there is a high incidence of alterations in chemosensation while cancer
356 chemotherapy is administered, as well as at times high inter-individual variability between
357 patients and likely across treatments and cancer types. The observed heterogeneity is
358 supported by the findings of several studies, which reported unaltered [19], decreased [18,95–
359 99], or intensified gustatory and/or olfactory capabilities in patients who were treated with
360 chemotherapy [15,100,101]. This inter-individual variability with regards to the effect of
361 chemotherapy on the taste and smell perception of cancer patients could be attributable to a
362 number of putative factors as discussed in the section below.

363

364 **3.2. Putative factors modulating taste and smell profiles**

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

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

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

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

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

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

411 Olfactory function also exhibits inter-individual variation in a non-pathologic state,
412 and this may explain the different olfactory phenotypes during cancer and chemotherapy.
413 Prevalent genetic variations in olfactory receptors leads to differences in odor perception
414 [112]. Moreover, human oral physiology and food oral processing, which determine the
415 amount of released aroma in the nasal cavity are not similar across people [113,114].

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

421

422 **3.3. Food behavior as a function of taste and smell profiles**

423 Of the 13 studies listed in **Table 1**, nine studies examined patients' food intake
424 (energy or macronutrients intake), and three studies assessed food or macronutrients
425 preferences. Surprisingly, most of these studies did not report difference in patients' energy
426 and macronutrients intake: three studies showed no effect of chemotherapy on food intake
427 [85,90,93], and four studies did not mention the results related to food intake at the group
428 level [8,9,31,88]. Four studies reported a decrease in food intake but only when the group was
429 stratified following the severity of chemosensory complaints [9,20,31,88]. The more severe
430 were the sensory complaints (hypo or hyper sensitivity), the lower was the energy intake of
431 patients. The 3 sub-sections that follow summarize the effects of chemotherapy on food
432 behavior as a function of sensory profiles (unaltered, hypo, hyper) in patients with a diagnosis
433 of cancer.

434

435 *The "unaltered taste and smell" profile*

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

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

448

449 *The “hyposensitivity to tastes and/or smells” profile*

450 Studies showing a decrease in patients’ taste and/or smell function reported either an
451 unchanged [10,85] or a decreased energy intake [92] throughout the treatment. IJpma et al.
452 [85] showed that food intake assessed by the Food Frequency Questionnaire in 21 men with a
453 diagnosis of testicular cancer remained stable over time. Lara-Sanchez et al. [10] showed that
454 nutrient intake assessed with the SNUT program [118] of patients after 2 cycles of
455 chemotherapy and controls were similar. However, a positive correlation between
456 modification in sweet threshold/bitter recognition score and food intake was highlighted in
457 some patient groups. While De Vries et al. [119] using a 24-h dietary recall reported a
458 significantly lower energy, protein, and fat intake in 117 women with a diagnosis of breast
459 cancer compared to 88 healthy controls [119]. This decrease in food intake was significantly
460 correlated with a reduced self-reported taste function. Similarly, Boltong et al. [20] reported
461 reduced energy intake in accordance with a reduced ability to identify tastes.

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

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

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

475

476 *The “hypersensitivity to taste and smell” profile*

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

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

491

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

494

495 **4. Conclusions and perspectives**

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

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

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

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

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

540 chemosensory assessments combined with efficient measures of food behavior. Such
541 screening approaches and the resulting recommendations should be done using a patient-
542 centered intervention approach rather than a group approach in order to meet the needs of
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553

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

	Reference	Study type	• Groups (n) • Mean age • Men (n) • Women (n)	Cancer histology • Chemotherapy (CT) regimen	Chemosensory assessment and approach	Food behavior measure	Main effects of chemotherapy on gustatory and olfactory perceptions	Main effects of chemotherapy on food behavior	Chemosensory/Food interaction
Section A: Heterogeneous chemosensory outcomes	Hutton et al., 2007 [31]	Cross sectional	• Patients (66) • 65.4 years • Men (30) • Women (36)	→ All types except digestive and oro-nasal cancers • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	• Food intake: 3-day diet diary • Food attitude and changes to food: Targeted interview	<i>Gustation and Olfaction:</i> • Altered in 86% of the patients	• Not mentioned	• Chemosensory complaints score VS. Energy intake: Negative correlation • Chemosensory complaints score VS. Food enjoyment: Negative correlation
	Brisbois et al., 2011 [9]	Cross sectional	• Patients (192) • 64.3 years • Men (97) • Women (95)	→ Lung → Breast → Genitourinary → Gastrointestinal → Neuroendocrine → Skin → Hematologic → Other • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	• Food intake: 3-day diet diary	<i>Gustation and Olfaction:</i> • Altered in 60% of the patients	• Not mentioned	• Severity of chemosensory complaints VS. Energy/Protein intake: Negative correlation • Increased olfactory sensitivity VS. Energy intake: Negative correlation
	McGreevy et al., 2014 [88]	Longitudinal study T0 = baseline (before CT) T1=2 m T2=4 m T3=6 m	• Patients (89) • 67 years • Men (40) • Women (49)	→ Lung • CT not specified)	<i>Gustatory and olfactory modifications:</i> • Interviews + TSS (subjective)	• Food intake: 3-day diet diary + PGSGA	<i>Gustation and Olfaction:</i> • Altered in 68.5% of the patients (Gender differences)	• Not mentioned	• At the time point with the highest TSS score, severity of chemosensory complaints VS. Energy/Protein intake: Negative correlation
	Belqaid et al., 2016 [127]	Longitudinal T0=Baseline T1=30-99 d T2=After 100 d	• Patients (52) • 66.8 years • Men (21) • Women (31)	→ Lung • CT not specified	<i>Gustatory and olfactory modifications:</i> • TSS (subjective)	• Nutritional status: FAACT + PG-SGA	<i>Gustation and Olfaction:</i> • Altered in 73% of the patients (Individual differences: weak to strong effects depending on stimuli and individuals)	• <i>Food intake/appetite (case reports):</i> Loss of appetite and lower food intake, lower food enjoyment (T2)	• <i>From case reports:</i> Insufficient food intake due to taste changes and loss of appetite (T2)
	Marinho, 2017 [87]	Longitudinal study T0=Baseline T1=Intermediate cycle T2=Last cycle	• Patients (55) • 51.5 years • Women (55)	→ Breast • Docetaxel • Paclitaxel • FAC • CMF	<i>Gustatory modification:</i> • Qs developed for the study (subjective)	• Hunger • Food enjoyment • Appetite for food categories: Visual scale developed for the study	<i>Gustation:</i> • Changes more frequent at T1 (p = 0.044)	• <i>Food enjoyment:</i> Decrease in meal enjoyment at T1 (p= 0.021) • <i>Appetite:</i> Increased overall appetite with appetite for salty food (p = 0.0028)	• Taste and food availability are the main determinants of food choice (self-reported by 52.2% of patients at T2)
e r	Ovesen et	Longitudinal study	• Patients (52)	→ Lung	<i>Gustatory threshold:</i>	• Food intake: 3-	<i>Gustation and Olfaction:</i>	• <i>Food intake:</i> No	• Chemosensory

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

	[92]	assessment= random days during the full cycle of CT	<ul style="list-style-type: none"> • Women (117) • Controls (88) • 53.5 years 	<ul style="list-style-type: none"> • Anthracyclines • Taxanes + anthracyclines 	• AHSP (subjective)	FFQ • Food intake: 2 24h dietary recalls during the overall CT	taste, smell in comparison with the controls:	appetite and hunger in patients. • <i>Food intake:</i> Patients had a lower energy intake and lower appetite during CT (not before)	Energy intake: Positive correlation • Self-reported smell perception ability <i>VS.</i> Energy intake: No correlation
	De Vries, 2018 [91]	Longitudinal T1=Baseline T2=During CT T3=1-3 wks > CT T4=6m after the end of CT	<ul style="list-style-type: none"> • Patients (28) • 51 years • Women (28) • Controls (28) • 51.8 years 	→ Breast <ul style="list-style-type: none"> • Taxanes • Anthracyclines + taxanes • Platinum-containing 	<i>Gustatory and olfactory function:</i> <ul style="list-style-type: none"> • Qs developed for the study (subjective) • Sniffin' Sticks (objective) • Taste strips (objective) 	• Food preferences: MTPRT • Taste preference: Preference task [100,129]	<i>Gustation:</i> <ul style="list-style-type: none"> • Decreased self-reported and objective gustation <i>Olfaction:</i> <ul style="list-style-type: none"> • Decreased self-reported and objective olfaction (lower sensitivity) 	• <i>Food preferences:</i> Decreased liking for high fat and high protein products at T2. Higher liking for savory food at T0 and T3	• Self-reported taste perception ability <i>VS.</i> Preference for high-protein food, low energy food, savory food, sweet food: Positive correlation • Self-reported smell perception ability <i>VS.</i> Preference for low energy food and sweet food: Positive correlation at all time-points
Section D: Hyper-chemosensation	Turcott, 2016 [8]	Longitudinal study T0= Baseline T1= After 2 cycles	<ul style="list-style-type: none"> • Patients (40) • 55.5 years • Men (20) • Women (20) 	→ Lung <ul style="list-style-type: none"> • Paclitaxel + cisplatin 	<i>Gustatory function:</i> • RMT (objective)	<ul style="list-style-type: none"> • Body weight • Food intake: SNUT program • Nutritional impairment: PGSGA • FAACT • Body composition: Bioelectric impedance analysis 	<i>Gustation:</i> <ul style="list-style-type: none"> • Higher sensitivity to bitter and umami tastes (p=0.02). 	<ul style="list-style-type: none"> • <i>Food intake:</i> Not mentioned • <i>Body weight:</i> Loss of weight at T1 (p=0.001) • <i>Body composition:</i> No effect • <i>Nutritional impairment:</i> No effect 	<ul style="list-style-type: none"> • Increase of sweet detection threshold (T1) <i>VS.</i> Decrease of protein intake (T1): Positive correlation (p=0.01)
<p><i>AHSP: Appetite Hunger and Sensory Perception (a self-report questionnaire that measures appetite, hunger and perception including taste and smell functions, [130]); CMF, cyclophosphamide + methotrexate + 5-fluorouracil; CT: Chemotherapy, d: day(s), DEXA: Dual Energy X-ray Absorptiometry (objective measure of body composition); FAACT: Functional Assessment of Anorexia Cachexia Therapy Questionnaire (an anorexia and cachexia assessment questionnaire [131]); FAC, 5-fluorouracil + adriamycin + cyclophosphamide; FEC, 5-fluorouracil + cyclophosphamide + epirubicin; FFQ: Food Frequency Questionnaire (questionnaire for dietary intake assessment, [132–135]); ISO 3972:2011: International Standards Organization 3972:2011 (a standardized sensory analysis-methodology-method of investigating sensitivity of taste), m: month(s), MTPRT: Macronutrient and Taste Preferences Ranking Task (a computer-based preference task with food pictures[136]); NS: Not Specified; PGSGA: Patient Generated Subjective Global Assessment (questionnaire for assessing nutritional status in patients with cancer [137]); RMT: Rinsing Mouth Test (a test that measures gustatory threshold based on aqueous solutions); Sniffin' Sticks: (a pen-based test that measures olfactory function, [138]); SNUT program: Nutritional Assessment System Habits and Nutrient Intake (a software that calculates the daily intake of calories, macronutrients and micronutrients, [118]); TSS: Taste and Smell Survey (a self-report questionnaire on Taste and Smell, [120]); Taste strips: a paper-based test that measures gustatory function, [139]; wks: week(s)</i></p>									

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

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