

**Individual differences in chemosensory perception amongst
cancer patients undergoing chemotherapy: A narrative review**

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Abstract

Chemotherapy is an aggressive form of treatment for cancer and its toxicity directly affects the eating behavior of many patients, usually by adversely affecting their sense of smell and/or taste. These sensory alterations often lead to serious nutritional deficiencies that can jeopardize the patient's recovery, and even continue to affect their lives once treatment has terminated.

Importantly, however, not all patients suffer from such alterations to their chemical senses; and those who do, do not necessarily describe the side effects in quite the same way, nor suffer from them with equal intensity. The origin of these individual differences between cancer patients undergoing chemotherapy treatment has not, as yet, been studied in detail. This review is therefore designed to encourage future research that can help to address the perceptual/sensory problems (and the consequent malnutrition) identified amongst this group of patients in a more customized/personalized manner. In particular, by providing an overview of the possible causes of these large individual differences that have been reported in the literature. For this reason, in addition to the narrative bibliographic review, several possible strategies that could help to improve the chemosensory perception of food are proposed.

Keywords: dysgeusia, xerestomy, food-behaviour, cancer, chemotherapy, metallic taste

1. Introduction

Malnutrition is observed in a majority of cancer patients (Van Cutsem and Arends, 2005) with an estimated 80% suffering from weight loss, even prior to their diagnosis (Walsh et al., 2019). Likewise, depending on the type of cancer, somewhere between 20-89% suffer from cachexia (Rosa-Caldwell et al., 2019), a disorder characterized by a marked weight loss, loss of muscle mass, fatigue, weakness, and a loss of appetite. Importantly, though perhaps unsurprisingly, malnutrition and weight loss predict a poorer response to chemotherapy treatment (DeWys et al., 1980), an increased frequency and severity of chemotherapy-related toxicity episodes (Andreyev et al., 1998; but see Ross et al., 2004), an increased risk of post-operative complications (Jagoe et al., 2001), and a consequent deterioration in the patient's overall self-reported quality of life (Wheelwright et al., 2013; Wickham et al., 1999). Over the last decade or so, the relationship between cachexia and mortality has been clearly evidenced (Rosa-Caldwell et al., 2019), with the former being established as the cause of death in 10% of all cancer patients (Von Haeling and Anker, 2010). Malnutrition in cancer patients is normally caused by the tumor itself, the host's response to the tumor, and the cancer treatment (see Van Cutsem and Arends, 2005).

Many of those patients undergoing chemotherapy and/or radiotherapy suffer from xerostomia (dry mouth) (Hong et al., 2009), mucositis (inflammation of the mucous membranes of the gastrointestinal tract that may cause painful sores) (Van Seville et al., 2015), nausea, vomiting (Molassiotis et al., 2008), constipation (Larkin et al., 2008), and other disorders that may affect their sense of smell and taste and thus, ultimately, their multisensory flavour perception.

In fact, it has been estimated that 45-84% of these patients suffer from alterations to their sense of taste and somewhere between 5-60% from alterations to their sense of smell

(Gamper et al., 2012). Somewhat surprisingly, however, not all of those patients who suffer from alterations to their chemical senses necessarily describe them in quite the same way, nor suffer them with quite the same intensity (Drareni et al., 2020). Taste alterations may, for example, include the absence of taste (ageusia), a decrease of taste sensitivity (hypogeusia), or the appearance of strange taste sensations in the absence of any flavourful inputs (phantogeusia). Other patients report an increase in the intensity of certain tastes (hypergeusia) and taste distortions when the taste receptors are activated by an external agent (dysgeusia; see Hong et al., 2009).

The relationship between alterations in taste and smell and the loss of appetite, and changes in patterns of consumption has now been documented in a number of studies (Sánchez-Lara et al., 2010; Zabernigg et al., 2010; Drareni et al., 2019). Sensory alterations may lead to a decreased intake of food (Sánchez-Lara et al., 2010; Brisbois, 2011; McGreevy et al., 2014; Turcott et al., 2016), weight loss (Sánchez-Lara et al., 2010; Brisbois, 2011), and hence to a consequent lowering of the patients' self-reported quality of life (Sánchez-Lara et al., 2010; Zabernigg et al., 2010).

2. Chemotherapy's primary impact on taste, smell, and flavour

Smell can be experienced in one of two importantly different ways: orthonasal and retronasal (Rozin, 1982; Wilson, 2021). Orthonasal olfaction occurs when we smell external aromas from the environment, while retronasal olfaction occurs when volatile aromatic odor molecules are pulsed out of from the back of the nose, especially when we swallow (e.g., when we eat or drink; see Ni et al., 2015; Spence, 2017a). In the latter case, one may note that smell and taste are activated at more or less the same time, thus hindering people's ability to distinguish between the respective inputs that are attributable

to each of the senses. On the other hand, taste (gustation) refers exclusively to what can be distinguished from the stimulation of sensory receptors in the oral cavity that code for basic tastes including bitter, sour, sweet, salt, and umami. These sensations appear when a substance activates certain receptors located in the mouth (though see also Trivedi, 2012). Finally, flavour refers to a multisensory perception of food or drink involving not only taste, but also retronasal smell (see Spence, 2015) and, on occasion, the trigeminal nerve (the nerve responsible for the face and motor functions that provides sensations such as temperature, astringency, or pungency; Viana, 2011) as well.

In the majority of cases where alterations of taste and smell have been reported, patients suffer from a decreased sensitivity to taste and smell stimuli during their chemotherapy treatment (Berteretche et al., 2004; Hong et al., 2008; Steinbach et al., 2009, Sánchez-Lara et al., 2010; Gamper et al., 2012; Boltong et al., 2014; Amézaga et al., 2018). Interestingly, a decrease in the threshold to detect bitter tastes is also commonly reported; that is, patients may exhibit a greater sensitivity to this particular basic taste (Carson and Gormican, 1977; Hutton et al., 2007; Rehwaldt et al., 2009; Turcott et al., 2016; Epstein et al., 2019). At the same time, however, the appearance of so-called ‘metallic’ taste is also a common consequence of chemotherapy (Carson and Gormican, 1977; Jensen et al., 2008; Rehwaldt et al., 2009; Turcott et al., 2016; IJpma, Timmermans et al., 2017).

Patients undergoing chemotherapy often perceive olfactory stimuli differently. According to the latest data, these sensory changes are, however, less frequent overall than alterations to their taste perception. As in this latter case, alterations in olfactory perception are also subject to large individual differences. While, in some cases, a decrease in the olfactory detection threshold is normally reported (Epstein et al., 2002; IJpma et al., 2017), an increased threshold (i.e., lower sensitivity) has been observed in (a few) other cases (Vries et al., 2018) especially in older individuals (Steinbach et al.,

2009). Meanwhile, other patients do not seem to show any alteration at all (IJpma et al., 2016; Vries et al., 2019).

Unfortunately, as yet, there is still no consensus concerning the causes that lead to some patients suffering from taste and smell alterations, nor why some patients suffer it in a different manner and/or with a different intensity than others. One may also wonder if flavour perception, more than smell or taste thresholds, may not play a key role in the abovementioned differences amongst patients.

3. Possible causes of individual differences in taste and smell alterations

3.1. Chemotherapy effects on taste and olfactory receptor cells

Among the different hypotheses that have been put forward to date regarding the aforementioned decrease in sensitivity to gustatory and olfactory stimuli, the one that proposes that some (if not all) of these alterations to taste and smell are not consequences of the disease itself, but rather of its treatment, are of particular interest (Boltong and Keast, 2015). For instance, it has been suggested that the alterations to taste and smell associated with chemotherapy treatment may be attributable to the fact that the drugs that are used attack rapidly dividing cells, such as cancerous cells, unfortunately, also affect mucosal, gustatory and olfactory receptor cells as well (Mukherjee, 2011; Mukherjee et al., 2017) thereby affecting taste and smell. Despite the fact that this occurs from the start of treatment (Comeau et al., 2001), the longer treatment lasts, the greater and more serious the side effects (Zabernigg et al., 2010; Gamper et al., 2012). Therefore, depending on the treatment cycle in which the patients happen to find themselves, the alteration in taste,

smell, and multisensory flavour perception that have just been described may be more or less severe.

This detrimental effect on taste and smell receptor cells may help to explain why it is that one of the most common alterations reported in cancer patients undergoing chemotherapy is either a decrease in gustatory sensitivity or else its complete loss (hypogeusia or ageusia, respectively). However, it is curious to note that in various studies, a decrease in the sensitivity to certain basic tastes is detected, while at the same time, an increase in the sensitivity for bitter or some bitter tastants (i.e, bitterants) is often reported.

3.2. Preservation of bitter receptors

The explanation for this apparent contradiction may perhaps lie in the fact that, despite it appearing that all taste sensations are experienced all over the tongue, physiological research suggests that different parts of the tongue display different sensitivities to gustatory stimuli (see Hoon et al., 1999) and, more importantly, are differently damaged by cytotoxic drugs (Mukherjee, 2011). Mounting evidence shows that the front of the tongue is particularly sensitive to sweet taste whereas the back of the tongue is more sensitive to bitter substances instead (Hoon et al., 1999; Feeney and Hayes, 2014). Apparently, those taste buds located on the anterior part of the tongue (fungiform papillae) are primarily damaged most by cyclophosphamine (one of the most commonly prescribed chemotherapy drugs). This may therefore ultimately result in a loss of taste in this part of the tongue (Mukherjee et al., 2013; Mukherjee et al., 2017).

In a study carried out by Mukherjee and collaborators (2011), changes in the same type of cells that are present in both fungiform and circumvallate papillae taste buds were

analyzed, after the administration of cyclophosphamine. While the number of taste cells in fungiform buds decreased within four days of the initial drug administration, the number of taste cells in circumvallate buds did not decrease until eight days after the drug's administration. As such, a possible explanation for the preponderance of the bitter taste reported by many patients would be based on the relative "preservation" of bitter taste receptors, in contrast to the much more profound damage to the other taste receptors (Reith and Spence, 2020).

However, potentially confusing matters somewhat here, it should be kept in mind that people often tend to confuse bitter and sour (Robinson, 1970; Wayne et al., 1974; O'Mahony et al., 1979). For example, in a study by O'Mahony and his collaborators (1979), 25% of participants stated that citric acid tasted bitter rather than sour. Given that this particular taste confusion can be corrected by defining taste adjectives properly before asking the participants about specific tastes (O'Mahony et al., 1979), one might question whether the patients in certain of the aforementioned studies received such clarificatory information prior to completing the self-reported taste and smell alteration questionnaires. Further research is therefore needed in order to fully elucidate whether the self-reported alteration in bitter taste perception always leads to an apparent higher preservation to bitter receptors.

3.3. Individual differences related to bitter taste sensitivity

It is perhaps surprising that sensitivity to bitter taste, among other possible side effects of chemotherapy, is not a consistent feature for all patients (Nolden et al., 2019). Individual (e.g., physiological) differences in terms of taste capacities may help to explain the higher incidence of this disorder amongst certain patients (see Comeau et al., 2001; Reith and

Spence, 2020). Thus, with regard to the sense of taste (gustation), three different genetically-determined taster profiles have been identified: 'super-tasters', 'medium tasters', and 'nontasters' (see Blakeslee and Fox. 1932; Bartoshuk, 1991; Burkhardt, 2014; Garnau et al., 2014). 'Supertasters' show enhanced response to all tastes (gustatory stimuli), textures (Eldeghaidy et al., 2011), and even to olfactory stimuli (see Hayes and Keast, 2011) but they are especially recognized by perceiving some bitter compounds as tasting particularly intense (Burkhardt, 2014) . If the perception of bitter taste between these three profiles is different under normal tasting conditions (Kim, et a., 2003), it should perhaps not come as any surprise to find that they also differences, in terms of taste perception, while receiving chemotherapy. Future studies addressing how individual differences in flavour perception link to these taster profiles as a function of chemotherapy treatment would therefore likely be worthwhile.

3.4. Methodolgies used in studies of taste and smell alterations in cancer patients undergoing chemotherapy

3.4.1. Different measures, different results

The majority of studies on alterations in taste, smell and flavour perception have evaluated these variations through self-reported changes (Sarhill et al., 2003; Rehwaldt et al., 2009; Zabernigg et al., 2010; Sánchez and Rihuete, 2016; IJpma, Timmermans et al, 2017; Amézaga et al., 2018; Aysegul et al., 2019), or by combining these subjective measures with more objective measures of taste and smell thresholds, either by means of the use of electrogustometry (measurement of taste threshold by application of controlled electrical current to the tongue), taste solutions, taste strips, or the use of smelling sticks (see Sánchez-Lara et al., 2010; Boltong et al., 2014; Turcott et al., 2016; IJpma et al.,

2016; Ijpma et al., 2017; Vries et al., 2018, 2019). Far from obtaining similar results, several studies that have combined both subjective and “objective” methods have highlighted some degree of inconsistency between the various measures (Soter et al., 2008; Landis et al., 2009, Ijpma et al. 2017; Vries et al., 2018, 2019, Postma et al., 2020). A possible explanation for the apparent conflict between the outcomes from different types of measure could perhaps be related to the fact that people often do not distinguish between taste and flavor (Spence, Smith, & Auvray, 2015; Spence, 2017; Nolden et al., 2019). It has been widely reported that the sense of smell contributes somewhere between 80 and 90% to the perception of flavour (though see Spence, 2015, for a critical review of the history of this statistic). However, most people are unaware of this fact and often talk about ‘taste’ (e.g., ‘I like the taste of blue cheese’) when what they really mean is flavour, due to the ubiquitous phenomenon of oral referral (see Spence, 2016, for a review). There could, therefore, be a case in which a patient reports a taste disturbance that actually comes from smell. Thus, the smell threshold would be altered but not necessarily the self-reported sense of smell.

Another relevant methodological aspect to consider in the study of the chemosensory alterations in cancer patients is its exclusive focus on orthonasal smell, to the detriment of retronasal smell (see Rozin, 1982; Wilson, 2021). Importantly, research on smell detection thresholds in cancer patients has typically focused solely on assessing orthonasal smell (Nolden et al., 2019). Taking into account the clear segregation between the two types of smell, even at the level of neural processing (see Bojanowski and Hummel, 2012), it would be interesting to determine whether the detection thresholds are also altered in the retronasal smell or not. Landis et al. (2005) carried out a study of orthonasal and retronasal olfactory differences in those suffering from olfactory loss. While test results showed a high loss of orthonasal smell, retronasal smell remained

normal or slightly altered. Thus, orthonasal detection threshold test is a useful tool to detect changes in smell function but it might not in flavour. In this sense, those questionnaires that tap self-reported sensory changes do not necessarily allow one to identify changes in taste, smell, and flavor: if people typically fail to distinguish between taste and flavour, how can we be sure that cancer patients will not do the same when addressing the changes identified in self-report questionnaires?

3.4.2. *Eating habits*

Another methodological issue to bear in mind here is that many studies did not take into account the eating habits of patients prior to, and after, the start of their chemotherapy treatment (see Nolden et al., 2019). Or, if they did, they typically did not necessarily correlate the data from any variable referring to the participant's diet with any measure of taste or smell perception. Kano and Kanda (2013) developed and validated a 'Chemotherapy-induced Taste Alteration Scale' (CiTAS) that has often been used, as a reference in subsequent research on taste alterations in those patients undergoing chemotherapy treatment (e.g., IJpma, Timmermans et al., 2017; Aysegul et al., 2019; Drareni et al., 2020). CiTAS includes questions such as: *Do you have difficulty tasting bitterness? Do you have difficulty eating meat? Have you experienced a change in taste since your diagnosis? And Do certain foods appear to taste differently than before your diagnosis?* But can we properly interpret the possible answers to these questions without knowing anything about the eating habits and food preferences of the patients concerned? It could be the case that a patient who does not consume bitter-tasting foods very often, and who continues without doing so once their treatment has started, is perhaps not going

to report a change in the sensitivity to that basic taste. However, does this necessarily mean that their bitter receptors have not been altered?

3.4.3. Different cultures, different flavour perception?

Other underrated variables that may be able to explain some of the discrepancies found between studies are more psychological, or cultural, in origin. For example, diets differ greatly around the world (see Rozin, 1983; Blank and Mattes, 1990; Anon, 2011); it is logical therefore to consider whether alterations in the perception of taste and smell may differ depending on where the study was carried out, or, more specifically, where the participants grew up.

3.5. Metallic sensations experienced by cancer patients

Many patients undergoing chemotherapy report experiencing sensations such as 'metallic taste', 'bad taste', or the 'taste of blood', among others. As these are typically not tastes/flavors with which we are necessarily familiar, it has been suggested that they may all refer to the same sensation: Namely, the so-called “metallic taste” (Ijpma et al., 2015). Importantly, however, it is worth noting that the choice of one term over another may also be conditioned by the design of the questionnaire that patients happen to be given (see Reith and Spence, 2020, on this point). For example, while some of the questionnaires only include items about the occurrence of metallic taste, others include other options such as a bad taste in the mouth or the presence of strange flavors (see Amézaga et al., 2018).

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261 3.5.1. *Is metallic a basic taste?*

262 Researchers have questioned whether metallic is, in all cases, a basic taste or not.
263 Although there is no known gustatory receptor coding specifically for metallic taste,
264 patients nevertheless do describe certain chemosensory sensations as 'metallic' (Reith and
265 Spence, 2020) and, more often than not, these sensations are referred to as tastes. In fact,
266 and perhaps because the patients who experience metallic sensations refer them to a taste,
267 the appearance of metallic sensations in patients undergoing chemotherapy is often
268 described as a taste (gustatory) alteration. Sometimes it has been treated as a phantogeusia
269 (Logan et al, 2008); That is, a particular taste that does not have its origin in an external
270 stimulus but instead in some neural dysfunction (Yanagisawa et al., 1998). However, on
271 other occasions, the appearance of these sensations has been related to external agents
272 instead (Ijpma et al., 2015, Reith and Spence, 2020). For example, metallic taste or similar
273 sensations, have sometimes been linked to the use of certain artificial sweeteners
274 (Schiffman et al., 1985), to certain drugs (e.g., some antidepressants; Doty and Bromley,
275 2008) as well as to the activation of T2R7 bitter taste receptors by certain metals (Wang
276 et al., 2019). One may therefore wonder whether the latter physiological phenomenon
277 indirectly implies that metallic taste could indeed be related to the activation of bitter
278 receptors (Reith and Spence, 2020). If so, a higher sensitivity to bitterness in general
279 would presumably increase the probability of the appearance of metallic taste. Along just
280 these lines, a study by Ijpma, Timmermans et al. (2017) confirmed the relationship
281 between bitter and metallic tastes, concluding that those patients who experienced
282 metallic taste also exhibit a greater sensitivity to bitter taste as well.

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3.5.2. Relationship between metallic sensations and smell sense and the trigeminal nerve

Lawless et al. (2004) investigated the taste and smell of various different metals in a sample of healthy participants. In this study, participants tasted FeSO₄, CuSO₄, and ZnSO₄ solutions with their external nares occluded (this being the method that is generally taken to eliminate stimulation from both retronasal and orthonasal smell; see Murphy & Cain, 1980). Metallic sensations were reduced with solutions of FeSO₄ but not with solutions of CuSO₄ or ZnSO₄. These results therefore demonstrate the retronasal smell nature of metallic sensations evoked by ferrous sulphate (see also Tamura et al., 2009). However, this study was unable to clarify the nature of the metallic sensations elicited by either copper or zinc sulphate. Similar results were obtained in a subsequent study by Skinner and collaborators (2017), who not only demonstrated the origin of ferrous metallic sensation as retronasal smell but also the orthonasal capacity to detect ferrous salts. Metallic sensations evoked by copper could not be linked to either orthonasal or retronasal smell. Taste may thus perhaps be implicated in this case but some researchers have also assessed the involvement of trigeminal mechanisms (Skinner et al., 2017). For example, Riera et al. (2007) reported that some metallic sensations activate TRPV1 receptors. In the oral mucosa, these receptors are expressed by trigeminal nerve endings and respond to painful stimulation, temperature, acid, and a wide range of molecules such as alcohol and vallinoids (e.g., capsaicin from chili pepper) (see Riera et al, 2007; Reith and Spence, 2020).

3.5.3. Metallic sensations associated with blood

It may also be the case that this metallic taste (or flavour, perhaps) sometimes appears as a consequence of other side effects of chemotherapy, such as, for example, mucositis or

oral candidiasis (which usually appears when a patient's immune system is weakened). In these cases, sores (or wounds, in the case of oral candidiasis) usually appear in the oral cavity and, in many cases, these bleed. The iron contained in hemoglobin can thus give rise to a metallic odour on the oral mucosa or in the blood itself (Glindemann et al., 2006) and, therefore, perhaps also explain (partially, at least) the appearance of 'metallic taste'.

In summary, the appearance of metallic taste seems to have multiple origins. Perhaps, therefore, this mysterious sensation may be nothing more than a phantogeusia and also appear as a consequence of external agents such as the intake of some drugs as seen earlier. It may be that metallic sensations are just a bin/label that is given to all strange chemosensory sensations perhaps primed by the wording that is used in so many questionnaires (see Reith and Spence, 2020). This variety of possible causes of metallic sensations would also help to explain the differences between the patients' percepts and, thus, the lack of consensus regarding the description of the term.

3.6. Different alterations in smell amongst cancer patients

3.6.1. Genetic individual differences

As seen earlier when talking about supertasters, there are also genetic individual differences in odour receptors that can lead to significant differences in olfactory perception (e.g., Keller et al., 2007; Reed and Knaapila, 2010) and thus, presumably, to differences in self-reported changes in olfaction. For instance, the pleasantness of cinnamon seems to be highly heritable (Reed and Knaapila, 2010) and that could therefore also lead to different ways to describe smell perception of cinnamon and, if it is the case, to describe alterations in this odour. Apparently, there is still much to learn about heritable

response to odours (Reed and Knaapila, 2010). Thus, one can imagine that there are still undetected individual genetic differences in odor receptors that could perhaps explain some of the individual differences in smell function. Here, one might wonder whether it could even explain why some patients experience a metallic sensation and others do not.

3.6.2. Phantosmia

The fact that some patients suffer from phantosmia also deserves special consideration. This alteration has often been described as a hallucination that can appear in those who have undergone an intense emotional experience (Comeau, et al., 2001, Hong et al., 2008). In this sense, and by way of example, patients sometimes claim to perceive the smell of the hospital when they think about their chemotherapy treatment (Bartoshuk, 1990). Taking into account the circumstances in which the patients find themselves, it is perhaps not surprising that phantosmia may be experienced by a large number of patients. Phantosmia has been linked to alterations in flavour perception and food-behaviour. One recent example is found in a number of those COVID-19 patients who suffered from anosmia. Once the disease has retreated, some patients started experiencing strange flavours and tastes when eating/drinking (e.g., coffee smelling ‘like car fumes’; Webber, 2020), potentially resulting in a decrease of nutrient intake. It would not be surprising, therefore, that the appearance of phantom smells experienced by cancer patients (e.g., hospital smell) was also capable of modulating flavour perception and eating-behaviour.

3.7. Xerestomy and saliva

Saliva is especially important when it comes to helping us to chew food, to form and swallow the food bolus, and to digest starch (Mandel, 1987). Saliva, likewise, is the medium through which taste receptors receive the gustatory and aromatic components of food (Neyraud et al., 2012; Spence, 2011). According to recent studies, saliva may also play a key role in capturing the aromas of food which may affect their subsequent release (see Canon et al., 2018; Running, 2018). When referring to smell, most studies refer to volatiles released from food into the air phase but few concentrate on the volatiles that may be captured by the saliva. Note, however, that saliva might have an impact on the aroma release in the mouth (Taylor, 1996). H  lary et al. (2014) have also demonstrated the ability of α -amilasa (one of the compounds in saliva) to retain aroma molecules and so to decrease the release of certain aroma compounds from saliva (thus meaning they may not be available retronasally). Given that recent research has also highlighted large individual differences in saliva composition (Neyraud et al., 2012; Canon et al., 2018; Mu  noz-Gonz  lez et al., 2018), it is plausible that the differences in the composition of saliva may lead to inter-individual differences in multisensory flavor perception too.

Furthermore, some studies have demonstrated that other characteristics of saliva such as salivary proteins, buffer capacity (i.e., the capacity of the saliva to resist changes in pH), and the ionic composition of saliva are also capable of modulating taste sensations (Mu  noz-Gonz  lez et al., 2018). However, the specific way in which saliva influences taste and flavour perception has not, as yet, been yet fully worked out, so we do not know how the alterations in saliva suffered by many cancer patients may finally affect their perception of food.

Another common side effect of chemotherapy that is related to the lower sensitivity to taste, and the appearance of bad tastes is dry mouth or xerestomia (Am  ezaga, 2018).

Although xerestomia is not an alteration of taste or smell *per se*, it might be the case that insufficient salivary flow can significantly alter multisensory flavour perception (see Spence, 2011). Importantly, saliva contains proteins that protect us against pathogenic microorganisms. Some researchers suggest that an insufficient flow of saliva increases the risk of suffering from fungi or oral infections (Matsuo, 2000; Muñoz-González et al., 2018; Canon et al., 2018). Interestingly, these infections or fungi can also lead to a bad taste in the mouth and even bleeding, thus perhaps promoting the experiencing of metallic taste.

The appearance of dry mouth (xerestomia) and the individual differences in saliva, in terms of quantity and probably in terms of compounds, could therefore also help to explain some of the differences in the perception of taste, smell and flavour that have been reported by cancer patients. However, to the best of our knowledge, no study has delved into this topic as yet.

3.8. Nausea and vomiting

Nausea and vomiting are frequently experienced by those patients undergoing chemotherapy. While effective antiemetic therapies have been developed against vomiting in recent years, nausea still remains a serious problem in these patients (Glaus et al., 2004; McGrath et al., 2020). The appearance of nausea has been reported to exert a negative impact over food intake (Bergkvist and Wengstrom, 2006; Molassiotis et al., 2008; McGrath et al., 2020). Nausea has also been associated with other behavioural alterations such as fatigue, a lack of enjoyment of food, sleep disturbance, and anxiety (Bergkvist and Wengstrom, 2006). Additionally, nausea has also been related to some taste disturbances (e.g., ‘strange taste’, ‘nasty taste’, as described by two of the patients

in a study by Molassiotis et al., 2008). On the other hand, negative taste changes have not only been identified as a consequence of nausea but also as the cause (Molassiotis et al., 2008). In the latter study, the majority of participants reported the presence of food to be one of the main triggers for nausea. Even the mere thought of food seeming to induce nausea, in many cases.

Several studies looking at alterations of taste and smell as a result of chemotherapy treatment collect information concerning the occurrence of nausea and vomiting from participants. However, as far as we are aware, data from these measures (e.g., the presence/absence of vomiting and/or nausea and their severity) have never been included in any detailed analysis, together with other variables (e.g., the appearance of xerostomia, the increase/decrease of sensory thresholds).

3.9. Chemotherapy treatment

Several previous studies have pointed out that the differences between patients in terms of the chemotherapy drugs administered during their treatment could, at least in part, help to explain the marked individual differences observed in the appearance of some disorders of taste (Zabernigg et al., 2010; Gamper et al., 2012; Amézaga et al., 2018), and even the appearance of metallic taste sensations (IJpma et al., 2015). For instance, Amézaga et al. concluded that those patients who were administered anthracyclines, paclitaxel, carboplatin, and docetaxel regimes appeared to report greater alteration to their senses of taste and smell than those who were administered oxaliplatin, cisplatin, irinotecan, 5-fluorouracil, or vinorelbine regimes.

3.10. Cancer-induced inflammation

A recent pilot study suggests that cancer-induced inflammation may have an even more negative influence on taste perception than chemotherapy (Schalk et al., 2018). In fact, the relationship between inflammation and taste disorders has already been established (see Wang et al., 2009). It is only recently that researchers have proposed a hypothetical association between cancer-induced inflammation and taste alterations (Murtaza et al., 2017).

The study conducted by Schalk and collaborators (2018) tested taste sensitivity, by using taste solutions, in three different groups: cancer patients, hospitalized patients with non-malignant inflammatory diseases, and healthy control participants. The results revealed the presence of alterations in taste detection thresholds in the two groups of patients, with those in cancer patients being greater. The authors argued that the difference between the two patient groups may have been attributable to the more ‘complex inflammatory processes of cancer-induced inflammation’. Interestingly, the study also revealed that patients with acute inflammatory disease experienced an increased taste threshold for umami. That being the case, differences in inflammation severity could then also lead to differences in sensory acuity. The results of the study carried out by Schalk and collaborators may perhaps stimulate further research to establish the possible role of inflammation in taste and flavour perception.

3.11. Changes in zinc metabolism

In 1981, Shatzman and Henkin demonstrated that zinc can affect both taste and gustin. Gustin is the major zinc-containing protein in human parotid (salivary gland) saliva. It

has been associated with the growth and development of the taste buds (see Shatzman and Henkin, 1981). Zinc is found in several foods (e.g., red meat, seeds, and fortified grains). Interestingly, an often unrecognized and under-diagnosed inadequate zinc intake is estimated in a 17% of the worldwide population (Gooding et al., 2019) and hypogeusia is one of the most common symptoms reported. In fact, low levels of zinc in saliva have often been observed in those patients suffering hypogeusia (Hambidge et al, 1972; Gooding et al., 2019). Thereby, individual differences in zinc levels during the chemotherapy treatment (e.g., due to the different diets) may also aggravate or lead to differences in taste perception alterations.

Besides, and perhaps more importantly, the administration of zinc seems to improve taste, smell and flavour perception in certain conditions (see Schatzman and Henkin, 1981; Gooding et al., 2019). Lycholm and collaborators (2012) carried out a study in which zinc supplements were administered to cancer patients suffering from taste and smell alterations. The authors suggested that chemotherapy treatment could be related to a metabolic deficiency of zinc that may, in turn, lead to alteration in taste and smell perception. The results of this study, however, did not show significant improvements in taste or smell perception from the administration of zinc supplements. However, as the authors suggested, there are, at the same time, so many other factors that can influence taste, smell, and flavour perception, it remains possible that the effectiveness of zinc could have been obscured by these other factors.

3.12. Flavour perception: A multisensory experience

As we have seen above, it seems obvious that we cannot understand flavour by considering only the sense of smell or just the sense of taste. Moreover, basic psychology

and cognitive neuroscience have revealed, in the last decades, how flavour perception depends on the complex interaction (and integration) between signals from all of the senses (Bult et al., 2006; Spence and Piqueras-Fiszman, 2014; Spence, 2015c). Thus, the stimulation not only of taste and smell but also of hearing, touch, or sight, are capable of modifying the perception of what we eat, often by modulating our expectations prior to tasting (see Piqueras-Fiszman and Spence, 2015, for a review). The alterations of these variables can increase or decrease two of the most relevant factors of eating disorders in patients with cancer: motivation and satisfaction.

4. Possible strategies to improve taste, smell and flavour perception

4.1. The correct choice of the ingredients

There are some studies carried on by some private institutions aimed at improving the nutrition in cancer patients undergoing chemotherapy by means of modifying the perception of what they eat. Although it would be necessary to reproduce the studies following a more rigorous methodology, apparently their conclusions are being useful for patients (Fundació Alícia, 2018).

Thus, for example, Fundació Alícia has published several culinary dietary recommendations (available in Fundació Alícia webpage) which include recommendations on the use of strategic ingredients to improve taste and smell alterations. For those patients who suffer from ageusia, Fundació Alícia recommends the consumption of flavorful seasonings, salt, citrics, flavour enhancers such as bouillon cubes or the addition of flavorful ingredients such as cured cheese or serrano ham (see also Boltong et al., 2012). Interestingly, the Foundation also recommends to choose liquid

or juicy ingredients in order to promote the dissolution of flavours and warm or hot temperatures to enhance flavors, except in case of suffering from hiperosmia (a high odour sensitivity). Being that the case, cold elaborations are recommended since less odours are given off (Fundació Alícia, 2018).

As already seen, experiencing a bad taste in the mouth or a metallic taste is commonly reported by cancer patients undergoing chemotherapy. An interesting possible course of action to reduce the presumed perception of an ‘excessively’ bitter, metallic or bad taste in food would perhaps involve distracting the patient’s attention from the bitter (and/or metallic/bad) taste with the addition of those components that draw their attention to their nose (such as, for example, happens with wasabi, horseradish, or mustard), intensify other tastes and flavors, by means of using certain seasonings (see NCI recommendations; see Rehwaldt et al., 2009; Carney et al., 2018, Fundació Alícia, 2018), or else mask the bitterness by adding sweeteners (Faisal et al., 2018) or salt (see Breslin and Beauchamp, 1997), or mask metallic taste by adding citric fruits such as lemon, orange, pineapple or kiwi or by drinking mint or lemon tea before and after the meals (Alicia Foundation, 2018). Following-up on this idea, a pilot study by Wilken and Bernadette (2012) in which dried miracle fruits were given, before food intake, to a group of patients undergoing chemotherapy treatment who were suffering from some alteration in their sense of taste is worth mentioning. The miracle fruit berry contains a protein called miraculin that binds to sweet receptors and, has the ability to temporarily modify sour taste to sweet (Brouwer et al., 1968). Apparently, sweet can suppress other basic tastes at medium or high intensities (see Capitano et al., 2011). With a sour taste in mouth, miraculin induces an intense sweet taste sensation (see Wong and Kern, 2010). This could probably explain why the berry-induced sweet taste improved, in the study by Wilken and collaborators (2012), the patients' taste perception, and reduced the excessive bitterness (and metallic

sensations) perceived, as measured in a questionnaire administered after food intake. That said, miracle fruit or any products derived from the fruit such as pills, does not seem to have caught on in quite the way that one would imagine, perhaps because of the long-lasting nature of the effects (c. 2-3 hours minutes).

4.2. Multisensory strategies

As Albert Einstein once said: “*You can’t solve a problem on the same level that it was created. You have to rise above it to the next level*”. Although some strategies aimed at overcoming/compensating for taste and smell alterations in cancer patients have been implemented, with more or less success (Ellender and Coveney, 2021), the efforts have normally been focused on preventive, therapeutic, and palliative interventions (basically, oral hygiene, saliva substitutes, or zinc supplements; Braud and Boucher, 2020), or administering the proper nutrients to the patient with oral nutritional supplements. It may perhaps be necessary to go further in trying to improve the patients’ flavor perception by designing strategies that are based on the multisensory nature of flavour perception or manipulating their expectations (regarding the taste, the smell, the texture, and even the temperature of the food) before and during food intake or even trying to evoke certain emotions aroused from the memories of eating some foods.

Along just such lines, a few years ago, Jordi Roca (the award-winning pastry chef from the three-star Michelin restaurant ‘El Celler de Can Roca’) and collaborators carried out an intriguing project with the main aim of bringing the flavor of chocolate back to a group of people suffering from dysgeusia. They focused their efforts in stimulating the other senses and memories associated with chocolate. Surprisingly (and quite fortunately), the majority of the participants were able to evoke chocolate flavours when eating the

chocolate dessert prepared and served by the chef Jordi Roca. As a result, participants could enjoy eating and, more importantly, exhibited an enhanced appetite. As the otolaryngologist Josep De Haro Licer suggested during the documentary concerning this project: ‘the senses work according to experiences and memories’; and, thus, experiences and memories affect the way in which people describe their experience of tasting and smelling, at least to a certain extent (see Anon., 2019; Keeley, 2019; Spence, in press). In line with this project, Casas et al., (2012) carried out a study using adapted ice creams as a supplement in cancer patients. Spence, Navarra and Youssef (2019) raised the possibility of using ice-cream as an effective mean of supplying food to the malnourished elderly (see also Spence and Youssef, 2021, on this theme). Ice cream is easy (and pleasant) to eat thanks to its melting creamy mouthfeel (see also Hyde and Witherly, 1993). But, as the authors also say, ice-cream has the ability to return us to childhood, to comfort us on an emotional level (see also Spence, 2017a).

It is intriguing to note here how early neurogastronomy conferences were attended by cancer patients, scientists and even renowned North American chefs working together to make foods more pleasant for cancer patients (Albright, 2015; Spence, 2015; Smith, 2016). However, in practice, scientific advances in several fields such as culinary science, psychology, and physiology have been used by renowned chefs to enhance the experiences of diners or, by food industry, to make their products more attractive. Sadly, only a very few of these advances have, thus far, been used to help reduce malnutrition in cancer patients over the longer-term.

4.3. Culinary medicine chef

In recent years it has been pointed out the importance of combining nutrition with the art of cooking in patient’s diet (Mauriello and Artz, 2019). The patients normally receive

567 guidelines from the dietitian to maintain a balanced diet at home. However, this often
568 involve adding ingredients that are uncommon to the patient's diet. In order to ensure a
569 good adaptation of patients to the new diets, recent studies have indicated the need to
570 offer culinary training by gastronomists under the leadership of dietitians (Mauriello and
571 Artz, 2019, Mutlu and Dogan, 2021).

572 This trend is known by the term 'culinary medicine' (Kalaichandran, 2019, Mauriello and
573 Artz, 2019, Mutlu and Dogan, 2021) and has been already put in practice in a pilot study
574 for head and neck cancer patients (Allen-Winters et al, 2020). The study piloted a month
575 cooking class which included cooking and nutrition formation. As a result, they
576 concluded patients improved their dietary choices and gained confidence cooking. Most
577 of them added more fruits, vegetables and other dairy products in their meals in a more
578 attractive way than before. Further studies are needed to demonstrate if their nutrition
579 improves in the long term.

581 5. Conclusions & future directions

582 Despite the urgent need to attend to the specific nutritional requirements of cancer
583 patients, many relevant questions concerning how chemotherapy affects the perception
584 of taste and smell still remain unanswered. It is therefore necessary to delve into the study
585 of the relationship between chemotherapy and taste and smell alterations and to design
586 strategies aimed at improving perception in these senses in those patients undergoing
587 chemotherapy with severe feeding difficulties.

588 The medication, the type of cancer treatment, the large individual differences such as the
589 number of taste buds, the occurrence of xerostomy and/or nausea, the format of the meal,

or the patient's eating habits and diet, are all variables that, to the best of our knowledge, have not been addressed thoroughly, in terms of their possible impact on patient nutrition, as yet. However, many (if not all) of them may easily help to anticipate the needs of the patients, and ultimately provide customized nutritional/gastronomic solutions to them, thus hopefully helping to reduce malnutrition, in at least some cases.

Future research on genetic individual differences related to taste and smell perception (Bartoshuk, 2000; Reed and Knaapila, 2010) would probably help in the understanding of the different alterations in cancer patients taste, smell and flavour perception. Similarly, greater recognition of the role played by the composition of saliva and its capacity to modulate flavour perception may also prove important. Besides, and perhaps more importantly, future research that focuses on naturalistic flavour perception instead of merely the evaluation taste and smell thresholds separately may be able to solve the apparent contradictions seen earlier (Liu et al., 2019). One cannot ignore the need to clarify the numerous confusions between the terms smell, flavour, and taste (and even between basis taste descriptors such as bitter or sour) either, especially to participants in taste, smell and flavour perception studies.

Finally, studies on multisensory nutritional strategies seems worth being developed as an alternative or complementary way to improve cancer patient's nutrition. Well known chefs can modulate flavour perception by appealing to comensals memories and feelings and stimulating all their senses. Jordi's Roca project demonstrated it can also work with people suffering from taste, smell or flavour distortions. Why should not we keep working on it?

6. Conflicts of interest

The authors have no conflicts of interest to declare.

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