Taste and smell changes in cancer patients
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General discussion
Interpretation of the main findings and clinical implications

*Heterogeneity of taste and smell changes*

Previous studies regarding taste and smell changes in cancer patients mostly focused on heterogeneous cancer populations with various malignancies, treatments, and treatment phases. These studies have shown a highly variable pattern of taste and smell changes in cancer patients treated with chemotherapy [1]. In contrast, we focused on a homogenous population of testicular cancer patients treated in first line with cisplatin-based chemotherapy and measured taste and smell function at specific time points prior to, during, and after chemotherapy (Chapter 2). Despite the homogeneity regarding type of cancer and treatment as well as treatment phase, psychophysical taste and smell changes proved to be highly diverse in our study population. The reported palatability of oral nutritional supplements (ONS) was also notably variable among these patients (Chapter 6). For metallic taste, heterogeneity was found as well, since metallic taste was reported by cancer patients treated with chemotherapy, concomitant radiotherapy, as well as by patients treated with targeted therapy (Chapter 5). Moreover, the reported experience of metallic taste was highly variable in those patients.

The heterogeneity of taste and smell changes implicates that dietary advice should be provided on an individual base for cancer patients suffering from taste and smell changes. Offering a variety of foods with different flavours can help. Currently, the Ikazia hospital in Rotterdam is running a project using an individual approach for patients suffering from taste dysfunction [2]. First, patients perform a taste test to explore which flavours they prefer. Next, the chefs of the hospital adapt foods by means of these personal taste tests to improve food acceptance. Moreover, the hospital offers three types of bread: a fresh, a savoury, and a sweet type [3]. Patients can choose the type of bread they like the most, depending on their taste and/or smell changes. Such an individual approach can also be used for the development of ONS. A solution may be to offer ONS where patients can add sweetness, sourness, saltiness or bitterness to the product themselves depending on their taste perception to increase the pleasantness of these products.

A drawback of an individual dietary approach advice includes that patients have to try which foods they like during chemotherapy based on trial and error. In our
longitudinal study performed in testicular cancer patients undergoing cisplatin-based chemotherapy, no systematic pattern in psychophysical taste and smell changes was found (Chapter 2). Previous studies in patients with breast cancer and/or a gynaecologic malignancy showed a decrease in psychophysical taste [4,5] and smell function [5] during chemotherapy. It is currently unknown which factors are responsible for a systematic pattern of taste and smell changes. Cancer type, gender, chemotherapy regimen and/or metabolic factors may play a role. Therefore, future studies with a large cohort of cancer patients with different malignancies and treatments measuring taste and smell function at specific time points before, during, and after treatment are warranted. Data of large cohorts will allow cluster analysis to explore whether systematic patterns of taste and smell changes exist within certain groups regarding cancer type, gender and/or chemotherapy regimen. Those results can be used to give dietary advice prior to chemotherapy, based on expected taste and smell changes.

**Taste dysfunction: comparison between testicular cancer patients and survivors**

In the cross-sectional study, ten of fifty (20%) testicular cancer survivors had taste dysfunction (Chapter 3). Especially, the bitter taste threshold was higher in survivors compared to healthy controls. Based on these results, the question remains whether this taste dysfunction was due to chemotherapy or whether the survivors already had a decreased taste function prior to chemotherapy. The longitudinal study (Chapter 2) showed that the taste function of testicular cancer patients prior to chemotherapy was comparable to the taste function of healthy controls. In addition, no change in bitter threshold was found in testicular cancer patients during chemotherapy. These results suggest that the taste dysfunction in testicular cancer survivors was not an acute effect of chemotherapy.

**Weight gain in cancer survivors**

The longitudinal study showed that the percentage of fat mass in testicular cancer patients, which was comparable with healthy controls at baseline, increased during chemotherapy (Chapter 2). Results of the cross-sectional study suggest a persistent change in body composition, since testicular cancer survivors had a higher BMI, more fat mass, and more abdominal fat compared to healthy controls (Chapter 3). Given that
the body composition already changed at the start of chemotherapy and the persistent nature of this alteration, monitoring body composition should already start at the start of treatment. In addition, attention to lifestyle, dietary intake, and activity level is needed for these patients to limit the impact of cardiovascular risk factors.

It can be questioned whether cancer survivors need the same strategy to lose weight as overweight or obese people without a history of cancer. Results of the cross-sectional study showed that a lower testosterone level was associated with the higher BMI, fat mass, and abdominal fat distribution in testicular cancer survivors (Chapter 3). Nutritional support in hospitals is mainly focused on the management of malnutrition and weight loss. Patients experiencing weight gain are often referred to dieticians in primary care. Since other mechanisms probably underlie the weight gain in cancer survivors, treatment should not be focused on reducing energy intake only. Other factors, like testosterone level, may need to be monitored as well. Since activity level affects body composition, changes in activity level may be involved in the change of body composition after chemotherapy as well. We assessed the sports level among testicular cancer patients only at baseline using a crude measure (reported sport frequency per week). Future studies regarding body composition in cancer patients have to take detailed information regarding possible changes in sports- and/or activity level into account.

**Metallic taste**

Metallic taste is a taste alteration frequently reported by cancer patients treated with chemotherapy, with a prevalence ranging from 10% to 78% (Chapter 4). Despite the high prevalence, the cause of metallic taste in cancer patients is still unknown. Data regarding the mechanism of metallic taste will help to decrease or even prevent the occurrence of metallic taste in cancer patients. Besides, a better understanding of this sensation will help to find suitable management strategies to support cancer patients experiencing a metallic taste.

So far, metallic taste in cancer patients has been assessed using questionnaires and interviews. Nevertheless, other methods are needed to explore the mechanism of this sensation. A stimulus that reflects the metallic taste experienced by cancer patients can be of help. Ferrous sulfate (FeSO₄) is a good candidate, since the evoked sensation of this compound has been described as metallic by healthy participants (Chapter 4).
Besides, such a stimulus can be used to imitate metallic taste in healthy participants to explore suitable strategies to mitigate effects of metallic taste. The metallic sensation of FeSO$_4$ is likely in part due to retronasal smell, since the perceived intensity of the perceived sensation decreases with nasal occlusion in healthy participants. The role of retronasal smell in the metallic taste sensation can be investigated by examining the perceived sensation in cancer patients experiencing metallic taste with and without a nose clip. Moreover, saliva measurements can be performed to detect chemotherapeutic agents in cancer patients with and without the experience of metallic taste to investigate a possible direct influence on taste in the mouth. These measures will add information to the possible mechanism of a metallic sensation as experienced by cancer patients. First, metallic taste may be a specific taste alteration like a change in threshold for sweet, sour, salty or bitter taste. Exploring a detection threshold for metallic taste in cancer patients can test the hypothesis whether cancer patients have a decreased threshold for metallic. Second, metallic taste may be a combination of a gustatory and olfactory sensation. When both taste and smell are involved, ‘metallic flavour’ would be a better term for the experienced sensation than a ‘metallic taste’. Third, metallic taste may be a particular bad taste in the mouth due to the taste of chemotherapeutic agents.

For cancer patients experiencing a metallic taste, specific types of ONS can be developed, taking into account management strategies to cope with metallic taste. Specific types of ONS for patients bothered by a metallic taste could be effective to improve their nutritional status. Several management strategies for cancer patients experiencing metallic taste can be recommended, including the use of plastic utensils, eating cold or frozen foods, adding strong herbs, spices, sweetener or acid to foods, and eating sweet and sour foods (Chapter 4). Sweet and sour flavoured ONS may be preferred by patients experiencing metallic taste. Moreover, frozen ONS can be helpful. Possibly, these ice-cream style ONS evoke more positive emotions and associations compared to the available clinical drinks, resulting in increased food enjoyment. Furthermore, ONS with added spices or herbs to overpower the metallic taste can be useful to develop. Adding spices or herbs are better options than adding salt to products, given the adverse effects of salt on blood pressure and cardiovascular health [6]. Finally, juice-based ONS seem to be the least suitable ONS for cancer patients experiencing a metallic taste, since the metallic taste of this ONS type increased during chemotherapy (Chapter 6).
**Methodological considerations for future research**

As a result of our research experience, several methodological considerations for future research need to be addressed. We measured taste function using taste strips (Chapter 2 and 3). This method consists of four concentrations of sweet, sour, salty, and bitter taste, resulting in a score ranging from zero (no concentrations correctly identified) to four (all concentrations correctly identified) per taste. A total taste score is derived by summing the scores of each taste. This is an appropriate method to find a rough answer to the question whether patients have a normal or impaired taste function. However, when the aim is to investigate relationships between taste thresholds of each taste quality and other factors, such as dietary intake or food preference, an ordinal variable (range 0-4) limits statistical analyses. Therefore, a ‘more continuous’ variable by using more concentration steps of each taste quality is required. This will allow researchers to investigate taste changes more specifically and to explore the specific relationship between taste thresholds and possible associations, such as dietary intake, food preference, and body composition.

We used pictures of sweet and savoury foods varying in fat and protein content to assess food preference (Chapter 2 and 3). It can be questioned whether using food pictures reflects true food preference in cancer patients. Cancer patients may rely on their memory whether they like a product or not during a test using food pictures and may therefore override their changes in taste and smell perception. This may be especially the case for foods that have not been consumed during their treatment. Using real foods instead of food pictures may better predict changes in food preference in cancer patients.

The study regarding the palatability of ONS, included questions regarding liking, wanting, and attributes of ONS using a seven-point scale (Chapter 6). To measure ONS preference, the two milk-based (vanilla and strawberry), two juice-based (apple and orange) and two yoghurt-based (vanilla-lemon and peach-orange) ONS were ranked based on their liking score. With this method the most preferred ONS or ranked preference cannot be retrieved when multiple ONS have the same liking score. Asking participants to rank the products from the most to the least liked product or using a 100-mm visual analogue scale (VAS) will add more detailed information regarding food preference. These measures may better predict food choice.
To estimate the magnitude of the change in taste and smell function in cancer patients due to chemotherapy, a baseline measurement prior to chemotherapy is crucial. Nevertheless, the recruitment of cancer patients for research before the start of their treatment is difficult. Often, the time span between diagnosis and start of treatment is short. Moreover, this is a difficult and stressful period for most patients since the diagnosis of cancer has a major impact. In addition, studies concerning taste and smell changes require significant effort and concentration of participants. This may be difficult for some patients who are about to start with treatment. Measurements during treatment are easier to realize as long as patients are not too nauseated or tired to perform the tests. These difficulties concerning recruitment are less relevant for cancer survivors, which makes recruitment of this study group easier compared to cancer patients. Future researchers should consider whether their research question regarding taste and smell changes can be answered without a measurement prior to chemotherapy or whether the study can be performed in cancer survivors instead of cancer patients undergoing treatment.

In brief, future studies regarding taste and smell changes in cancer patients have to include: 1) measurement of taste and smell function with continuous outcome variables, 2) offering a variety of foods with a diversity of flavours and flavour intensity, 3) product ranking regarding preference. The combination of these aspects will provide useful information regarding food preference and management strategies for patients with taste and/or smell changes. These data can be used as guideline by health care professionals to support patients reporting taste and smell changes.

Conclusion

Taste and smell changes appear to be heterogeneous, even when focusing on a homogeneous cancer population. This implicates that dietary advice should be given on an individual base for cancer patients suffering from taste and smell changes. This seems also to be the case for cancer patients experiencing a metallic taste. Furthermore, the body composition of testicular cancer patients changes already during chemotherapy. This implicates that intervention strategies aimed to limit the impact of cardiovascular risk factors should probably start during treatment.
References


General discussion