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Complications of Treatment

Metallic taste in cancer patients treated with chemotherapy

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ABSTRACT

Background: Metallic taste is a taste alteration frequently reported by cancer patients treated with chemotherapy. Attention to this side effect of chemotherapy is limited. This review addresses the definition, assessment methods, prevalence, duration, etiology, and management strategies of metallic taste in chemotherapy treated cancer patients.
Methods: Literature search for metallic taste and chemotherapy was performed in PubMed up to September 2014, resulting in 184 articles of which 13 articles fulfilled the inclusion criteria: English publications addressing metallic taste in cancer patients treated with FDA-approved chemotherapy. An additional search in Google Scholar, in related articles of both search engines, and subsequent in the reference lists, resulted in 13 additional articles included in this review. Cancer patient forums were visited to explore management strategies.
Findings: Prevalence of metallic taste ranged from 9.7% to 78% among patients with various cancers, chemotherapy treatments, and treatment phases. No studies have been performed to investigate the influence of metallic taste on dietary intake, body weight, and quality of life. Several management strategies can be recommended for cancer patients: using plastic utensils, eating cold or frozen foods, adding strong herbs, spices, sweetener or acid to foods, eating sweet and sour foods, using 'miracle fruit' supplements, and rinsing with chelating agents.
Interpretation: Although metallic taste is a frequent side effect of chemotherapy and a much discussed topic on cancer patient forums, literature regarding metallic taste among chemotherapy treated cancer patients is scarce. More awareness for this side effect can improve the support for these patients.

Introduction

The majority of patients with cancer will be treated with chemotherapy during the course of their disease. Remarkably, several side effects of chemotherapy seem to be accepted, whereas suitable management strategies are often not provided. Taste changes, particularly the occurrence of metallic taste, is one of these neglected side effects. Taste changes are common in 45–84% of the cancer patients treated with chemotherapy [1]. These taste changes refer to an absence of taste perception (ageusia), a decreased or increased taste sensitivity (hypogeusia or hypergeusia), a distorted taste perception (dysgeusia), or a taste perception without an external stimulus (phantogeusia) [2]. Taste alterations have been associated with a poor appetite, a decreased energy and nutrient intake, changes in food preference, and a decreased quality of life [3–9]. Cancer patients can experience taste changes during chemotherapy treatment, which can last for a few hours, weeks, or several months after chemotherapy discontinuation [3,10,11].

A metallic taste is a typical taste alteration reported by cancer patients. In a study among patients with various cancer types, 29 of 37 (78%) patients described their perceived taste change as metallic after at least two cycles of various chemotherapy treatments [12]. Another study reported physical and psychosocial complaints in 204 cancer patients [13]. The medical oncologists of these patients were also asked to specify which complaints they knew their patients encountered. A metallic taste was reported by

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approximately one-third of the patients, whereas the medical oncologists perceived this symptom only in one-tenth of these patients.

Although, a metallic taste seems to be a frequent side effect of chemotherapy, literature on this subject is scarce. For this review all available studies regarding metallic taste in cancer patients treated with Food and Drug Administration (FDA) approved chemotherapy were analyzed. This review addresses the definition of metallic taste, assessment methods, prevalence, duration, possible causes due to chemotherapy, and management strategies.

Search strategy

The electronic database PubMed was used to conduct a comprehensive search on metallic taste and chemotherapy up to September 2014. The following strategy was adapted across the database: (''Antineoplastic Agents'' [Mesh] OR ''Antineoplastic Agents'' [Pharmacological Action] OR cancer OR chemotherapy*) AND (''Olfaction Disorders/chemically induced'' [Mesh] OR ''Taste Disorders/chemically induced'' [Mesh] OR ((metal OR metals OR metallic) AND taste*)). This search resulted in 184 articles, of which 13 articles were included [2,12,14–24]. Articles not related to metallic taste in cancer patients treated with FDA-approved chemotherapy, without English translation or abstract, and animal studies were excluded. Many studies do not have metallic taste as their primary focus. As a consequence, relevant articles can be missed in a PubMed search based on titles and abstracts. Therefore, the search was expanded with a Google Scholar search on 'metallic taste AND chemotherapy' in full texts instead of titles and abstracts only. Furthermore, related articles of both search engines were examined and subsequent reference list searches were carried out. This search resulted in 13 additional articles, which addressed aspects of metallic taste in cancer patients treated with chemotherapy and articles that investigated characteristics of metal salts eliciting a metallic sensation in healthy participants [10,13,25–35]. Fig. 1 shows the flow diagram of the selection procedure of the articles. Cancer patient forums were visited to explore management strategies.

Definition of metallic taste

Cancer patients treated with chemotherapy report sensations, such as a 'metallic taste', 'chemical taste', 'drug taste', 'blood taste' and 'bitter taste' [14,15]. Of these sensations, a metallic taste is most commonly reported by patients treated with chemotherapy [10,12,16,17]. It is unclear whether all these tastes refer to the same sensation. Probably, these sensations are hard to explain for patients, since it is often the first experience with this kind of taste. Therefore, a metallic taste is difficult to recognize as compared to the primary tastes sweet, sour, salty, and bitter. Metallic taste has been described as a phantogeusia [2,18]. However, it is unclear whether this metallic taste is a true taste phantom or whether external cues are involved. In food science, metallic taste has been characterized as 'a peculiar mouthfeel, which is similar to that observed when an iron nail or metal foil is placed in the mouth' [36]. Metallic sensations are also reported as a side effect of drugs [37], specific foods [38], artificial sweeteners [39], electrical stimulation of the tongue or chorda tympani nerve [40,41], burning mouth syndrome [42], during pregnancy [43], and as a result of damage by stapedectomy or anesthesia of the chorda tympani nerve [44,45]. Furthermore, the evoked sensations of metal salts, such as iron, copper and zinc, have been described as metallic [25,26]. Especially ferrous sulfate ($FeSO_4$) has been proposed as a distinctive metallic compound and is used as a reference standard in food sensory evaluation [46].

Assessment of metallic taste

Questionnaires, interviews, and stimulation with metal salts eliciting a metallic sensation have been used to assess metallic taste. These methods will be described hereafter.

Questionnaires

Several questionnaires regarding taste changes have been used to assess metallic taste in cancer patients. A study used a self-developed 33-item questionnaire, which included an alternative 'other' response option next to the options of change in sweet, salty, sour, and bitter taste, where patients could report metallic taste [32]. Another study used a questionnaire on 12 physical symptoms associated with chemotherapy [13]. Patients had to report if and on how many days they experienced the symptoms during the preceding week. One item in this questionnaire was 'metallic taste in mouth'. No other questions regarding taste changes were included. The questionnaires used in two studies could not be retrieved [12,16]. To our knowledge, no questionnaire has been developed specifically focusing on metallic taste.

Interviews

In three studies, metallic taste in chemotherapy treated cancer patients was studied by an interview [10,15,27]. Two of these studies performed a 30-min telephone interview using a self-developed Sensory Information Questionnaire (SIQ) [10,27]. The SIQ contains open-ended as well as focused questions related to taste, smell, touch, hearing, and vision. In a third study, interviews on general health, medication use, oral symptoms, taste changes, smoking, and oral hygiene habits were held [15]. Taste changes were determined by asking the patients whether they experienced taste changes (yes/no). Next, patients with taste changes were asked regarding the type of taste change (hypogeusia, hypergeusia, dysgeusia or ageusia) and to give a specific subjective description of the experienced taste changes.

Stimulation with metal salts eliciting a metallic taste

No studies have compared the metallic taste reported by cancer patients treated with chemotherapy with the metallic sensation evoked by metal salts. The following studies give insight into the characteristics of metal salts and factors associated with the reported metallic taste evoked by these metal salts in healthy participants.

A study performed in 18 healthy participants (eight men; age 19–33 years) investigated the detection thresholds of three iron salts: ferrous sulfate ($FeSO_4$), ferrous chloride ($FeCl_2$), and ferrous gluconate (FeGlu) [28]. For each stimulus, serial dilutions were made by a factor of 2.5, with 0.0125 mol/L as the highest concentration. A triangle test including the stimulus and two blanks (water) was carried out at each selected concentration, starting at the lowest concentration. The test was finished when participants made three correct discriminations in a series or when all concentrations were evaluated. The best estimated threshold for each participant was considered as the geometric mean of the concentration including the last error and the next higher concentration. Wide ranges of detection thresholds were found with median detection thresholds of 202, 81, and 13 μmol/L for $FeSO_4$, $FeCl_2$, and FeGlu respectively. Furthermore, ten of these 18 participants and three other participants (six men; age 20–42 years) were asked to describe the taste of each stimulus as sweet, sour, salty, bitter, metallic, astringent or they could describe another taste. The proportion of participants who described the iron compounds as a metallic taste decreased as the concentration increased ($F(2,24) = 8.23$, $P = 0.0019$). Higher concentrations of $FeSO_4$ and $FeCl_2$ were more frequently described as bitter and a higher concentration of FeGlu as sour. Metallic taste was more

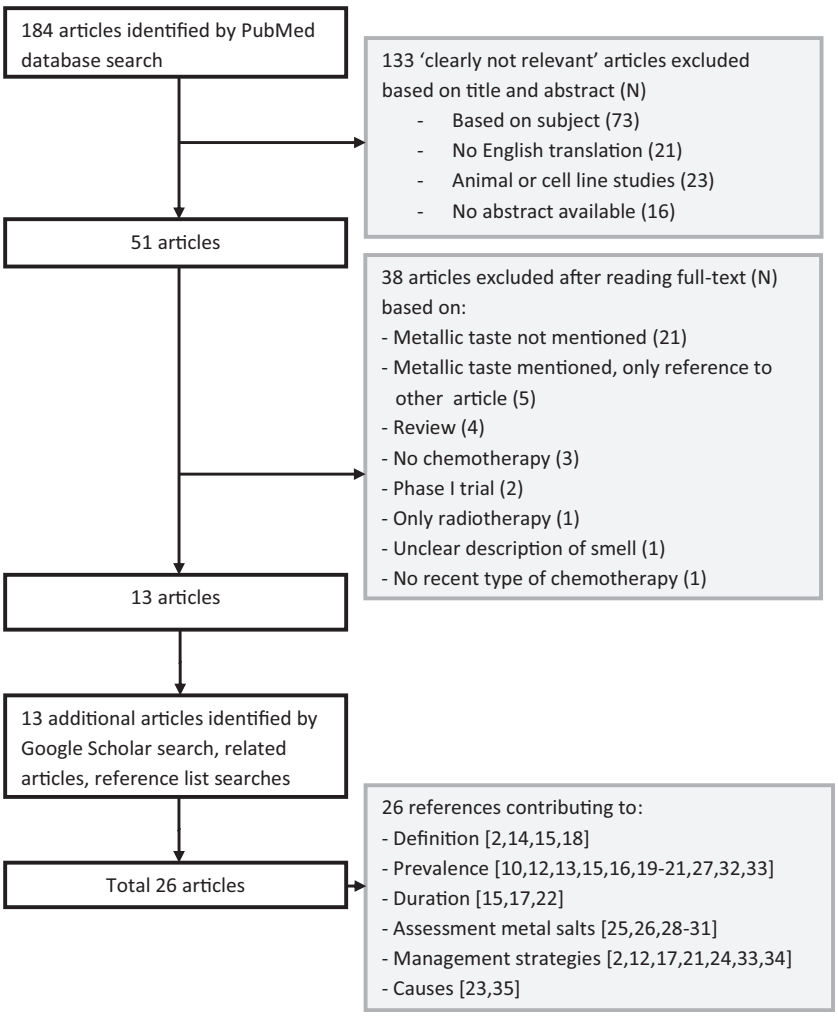

Fig. 1. Flow diagram of the selection procedure of the articles.

frequently reported for the three concentrations of $FeSO_4$ and $FeCl_2$ compared to the concentrations of FeGlu.

The contribution of retronasal smell to the evoked metallic sensation of metal salts has been investigated by stimulation of metal salts with and without nasal occlusion in healthy participants. A reduction of perceived intensity to baseline was found for $FeSO_4$, whereas no reduction was seen for copper sulfate ($CuSO_4$), zinc sulfate ($ZnSO_4$), solid metals, and electric stimuli [25,29,30]. These results suggest that the metallic sensation evoked by $FeSO_4$ is likely in part due to retronasal smell.

Qualitative differences have been found between metal salts. In a study, 19 healthy participants (five men; age 20–34 years) had to sort iron ($FeSO_4$, $FeCl_2$, and FeGlu), calcium (calcium chloride; $CaCl_2$ and calcium lactate), magnesium (magnesium sulfate; $MgSO_4$ and magnesium chloride; $MgCl_2$), and zinc ($ZnSO_4$ and zinc chloride; $ZnCl_2$) on the basis of the similarity of the evoked sensation [31]. The concentrations of the divalent salts were adjusted to equalize intensity ratings. Compounds representing sweet (sucrose), sour (citric acid), salty (sodium chloride), bitter (quinine hydrochloride), and astringency (aluminum ammonium sulfate; $(NH_4)Al(SO_4)$) were also sorted. The sorting task was performed with and without nasal occlusion to eliminate retronasal cues. Next, multidimensional scaling and cluster analysis of the sorting data were performed to provide a visual representation of the pattern of similarities among the stimuli. Without nasal occlusion, four clusters among the divalent salts were found: a metallic group ($FeSO_4$ and FeGlu), a bitter group (quinine, $CaCl_2$, $MgSO_4$, and $FeCl_2$), an astringent group ($(NH_4)Al(SO_4)$, $ZnCl_2$, and $ZnSO_4$), and calcium lactate. With nasal occlusion, three clusters were found: the metallic group merged with the astringent group, whereas the bitter group and calcium lactate remained the same [31]. Another study used a trained descriptive panel (two men, five women; age 21–58 years) to determine the sensory characteristics of ten divalent salts and showed comparable results [26]. The trained panelists examined a variety of reference standards including both commercial food products and chemical references to obtain consensus for the concept of metallic sensations. At the end of training, the experience with the entire reference was set as a definition of metallic taste. Metallic taste and metallic aftertaste were most pronounced for the iron compounds ($FeSO_4$, $FeCl_2$, and FeGlu). The zinc compounds ($ZnSO_4$ and $ZnCl_2$) were most pronounced in astringency and a glutamate-like sensation. With magnesium ($MgSO_4$ and $MgCl_2$) and calcium ($CaCl_2$, calcium lactate, and glycerophosphate) the highest sensation of bitterness was reported [26]. Another study performed in healthy participants showed also that $FeSO_4$ was described as metallic and $ZnSO_4$ as astringent, whereas $CuSO_4$ was more described as bitter [25].

Solid metals and electric stimuli have also been used to investigate the metallic sensation in healthy participants [29]. Stimulation with solid stimuli (2 cm copper disk, 2 cm half zinc half copper, copper foil, and zinc foil) and electrical stimuli (1.5 and 3.0 V battery) were performed using a self-fabricated device

consisting of a plastic handle attached to the stimuli for placement on the tongue or oral tissues. Stimulation of the anterior tongue evoked the highest rated intensity, followed by the medial tongue, whereas responses to stimulation of the inside upper lip were very low. Furthermore, reports concerning metallic taste following electrical and chemical stimulation were more frequent when the word 'metallic' was predetermined on a list compared to a free-choice option.

In summary, metallic taste was most reported after stimulation with iron compounds. The type and concentration of metal salt, the presence of retronasal cues, the stimulated area of the tongue, and the way of questioning the evoked sensation influenced reporting metallic taste. No studies have been performed to investigate detection and recognition thresholds of metal salts in cancer patients.

Prevalence of metallic taste caused by chemotherapy

Most studies regarding taste changes in patients treated with chemotherapy do not take metallic taste as a specific taste alteration into account. The prevalence of metallic taste in patients treated with chemotherapy has been reported in seven studies (Table 1). The prevalence ranges from 9.7% to 78% in those studies. Four studies used a questionnaire [12,13,16,32] and in the other studies an interview was carried out [10,15,27].

Two studies specifically focused on breast cancer patients, whereas the other studies investigated heterogeneous cancer populations. All studies investigated taste changes during chemotherapy in various treatment phases. One study reported taste changes in a heterogeneous cancer population consisting of patients during treatment as well as patients during follow-up [13]. Different chemotherapeutic agents evoked different sensations in patients. One study investigated sensory changes in 40 breast cancer patients receiving one to six cycles of either cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF, $N = 25$) or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF, $N = 15$) [27]. Ten of the 25 (40%) patients receiving CAF reported a metallic taste, which occurred during and after chemotherapy administration (time points not specified). In contrast, four of the 15 (27%) breast cancer patients receiving CMF reported a bitter taste, whereas the frequency of metallic taste in these patients was not mentioned. Another study found that 34 of 44 (77%) cancer patients reported taste changes directly after one to six cycles of CAF or cisplatin, of which metallic, bitter, distorted, and sweet taste were mentioned the most (prevalence per descriptor not specified) [10]. The patients treated with CAF were more likely to describe the taste change as metallic, whereas the patients treated with cisplatin described the taste change more frequently as bitter (frequencies not specified). The remaining studies did not report metallic taste for chemotherapeutic agents specifically [12,13,15,16,32]. Nevertheless, the American Cancer Society reports in a 'guide to cancer drugs' that cisplatin can cause a metallic taste [47].

A study in 248 patients with various cancer types who received at least two cycles of chemotherapy found that patients who reported metallic taste tended to be younger than patients without a metallic taste (age 54 ± 14 years versus 60 ± 15 years; $P = 0.001$) [16]. Furthermore, patients who reported nausea, reported more frequently metallic taste compared to patients without nausea (frequencies not specified).

In a study regarding food avoidance in a heterogeneous cancer population, at least 26 of 72 (36%) of the patients reported metallic taste [33]. These 26 patients received cyclophosphamide as part of their treatment and reported a slight, but lingering, metallic taste. All patients reported that this metallic taste did not affect their food intake.

Furthermore, metallic taste has been described in a case report of a 64-year old woman with a squamous cell carcinoma on the right external naris treated with 5% topical fluorouracil [19]. The patient reported a constantly present metallic taste after three days of treatment. The metallic taste did not interfere with the ability to consume food. The metallic taste lasted for four days and disappeared by itself without further sequelae. The patient continued the treatment as initially directed.

Another case report describes a 67-year old man with a 12-year history of cutaneous T-cell lymphoma treated with romidepsin and metallic taste [20]. The treatment consisted of 14 mg/m^2 romidepsin given as a 4-h infusion on day 1, 8, and 15 of each 28-day cycle. The patient reported a metallic taste during the first treatment cycle. Furthermore, ageusia was reported during the last infusion of the third treatment cycle. After a revised treatment schedule (romidepsin infusions only on day 1 and 9 of each cycle), the taste recovered gradually and returned to normal within two to three months after discontinuation of treatment.

Finally, metallic taste has been described in a case-report of a 90-year old women treated with gemcitabine for pancreatic cancer [21]. The patient reported a metallic taste starting approximately 1 h after treatment from the first to the fifth day of each chemotherapy cycle.

Duration of metallic taste alteration

Studies investigating the duration of the metallic taste in this population are scarce. Both onset and duration of the metallic taste are unclear. Besides, it is unclear whether the metallic taste is a continuous sensation or an evoked sensation by food products. One longitudinal study found that 15 of 45 (33%) breast cancer patients reported a metallic or drug taste in the second or third week after the sixth cycle of adjuvant chemotherapy with cyclophosphamide, epirubicin or methotrexate, and 5-fluorouracil (CEF or CMF) [15]. Six months after chemotherapy no patients reported a metallic or drug taste anymore. No other studies have investigated the prevalence longitudinally. In a study regarding the experience and coping strategies of taste changes in breast cancer patients receiving docetaxel or paclitaxel, one patient receiving docetaxel described a metallic taste approximately four or five days after the treatment during a semi-structured interview [22]. Semi-structured interviews in ten colorectal cancer patients treated with oxaliplatin-containing chemotherapy reported a metallic taste that was constantly present in the mouth (number of patients not specified) [17].

Possible causes of metallic taste due to chemotherapy

Several mechanisms may be involved in causing a metallic taste. Metallic taste has been described as a phantogeusia [2,18]. It has been hypothesized that localized taste damage can result in taste phantoms as a result of inhibitory interactions among areas of the central nervous system which receive input from the cranial nerves mediating taste [45]. Taste phantoms can be produced when the input of one taste nerve is interrupted and releases its inhibition and, as a consequence, neural signals from other taste nerves are intensified. Nevertheless, it is unclear whether metallic taste is a true taste phantom or whether external cues are involved. Reported external cues are described hereafter.

The metallic taste may originate from the taste of chemotherapeutic agents, implying a direct influence on taste in the mouth. Many drugs are secreted in saliva and gain direct contact with taste-receptors [48]. Several chemotherapeutic agents, such as cisplatin and carboplatin, contain the metal compound platinum. Patients may taste this platinum compound during chemotherapy treatment. It is unclear whether the quantity of chemotherapeutic

Table 1
Characteristics of studies which addressed metallic taste prevalence in cancer patients treated with chemotherapy.

Author, year	*N*	Cancer population	Treatment (*N*)	Treatment phase	Assessment method	Prevalence taste changes, *N* (%)	Prevalence metallic taste, *N* (%)
Bernhardson et al. [32] 2008	518	Breast, gastrointestinal, gynecological, other	Cyclophosphamide, fluorouracil, epirubicin 73 Paclitaxel/docetaxel: 73 Fluoruoracil, calcium folinate, oxaliplatin: 65 Paclitaxal/docetaxel, carboplatin: 58 Fluorouracil, calcium folinate, irinotecan: 38 Fluorouracil, calcium folinate: 34 Vinorelbine 27 Gemcitabin: 22 Cisplatin/carboplatin: 15 Other: 133	After CT for ⩾6 weeks (=after 2–100 CT cycles, of which 50% of the patients received 4–8 cycles)	Self-developed 33-item questionnaire (Swedish) Metallic taste as alternative 'other' taste change	347 (67)	50 (10)
Jensen et al. [15] 2008	76	Breast *N* = 45 CT *N* = 31 no CT	CT group: CEF: 43 CMF: 2 Radiotherapy: 39 Hormonal therapy: 37 No CT group: Radiotherapy: 16 Hormonal therapy: 1	– Longitudinal: – Before CT/baseline – During CT: in the 2nd or 3rd week after the 6th CT cycle – 6 months after CT – 1 year after CT	Personal interview	CT: Before: 0 During: 38 (84) 6 months after:10 (22) 1 year after: 9 (20) No CT: Baseline: 3 (10) 1 year after: 5 (16)	CT: Before: 0 During: 15 (33) After CT: 0 ('metallic or drug taste') No CT: Baseline: 0 1 year after: 2 (6)
McDaniel et al. [27] 1998	40	Breast	CAF: 25 CMF: 15	After 1–6 CT cycles Interview about sensations before, during, and after CT	Telephone interviews using Sensory Information Questionnaire (SIQ)	CAF: 20 (80) CMF: 12 (80)	CAF: 10 (40) CMF bitter: 4 (27)
Newell et al. [13] 1998	204	Colorectal, breast, head/neck, stomach, lung, other	Most prescribed: Fluorouracil, cyclophosphamide, methotrexate, leucovorin	During treatment: 122 (60), last treatment: 1–7 days ago: 47 (23) 1–2 weeks ago: 37 (18) 2–3 weeks ago: 90 (44) >3 months ago: 33 (16)	12-item questionnaire 'Metallic taste in mouth' yes/no, how many days during preceding week	Not asked	121 (32)
Rehwaldt et al. [12] 2009	37	Breast, lung, ovarian, other (with taste changes)	Cyclophosphamide: 14 Carboplatin: 7 Cisplatin: 3 Doxorubicin: 1 Other: 3	Follow-up: 82 (40) After at least two CT cycles or after at least 3 weeks of weekly CT	Questionnaire (unknown)	37 (100)	29 (78)
Rhodes et al. [10] 1994	44	Most frequent: Breast, lung	Cisplatin: 29 CAF: 15	After 1–6 CT cycles (majority of patients during 2nd, 4th, and 6th cycle)	Telephone interview using Sensory Information Questionnaire (SIQ)	34 (77) Cisplatin: 20 (69) CAF: 14 (93)	Most common: metallic, bitter, decreased, distorted, and sweet
Wickham et al. [16] 1999	284	Colorectal, breast, lung, lymphoma, ovarian, other	5-FU, cyclophosphamide, doxorubicin, leucovorin, carboplatin, cisplatin, paclitaxel, etoposide, methotrexate	After at least two CT cycles	Self-developed 41-item questionnaire (unknown)	193 (68)	89 (31)

CT = chemotherapy, CEF = cyclophosphamide, epirubicin, and 5-fluorouracil, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, CAF = cyclophosphamide, doxorubicin, and 5-fluorouracil.

agents detected in saliva reflects the metallic taste and its intensity experienced by cancer patients.

A metallic taste could also be due to a decreased detection threshold for metals in cancer patients treated with chemotherapy. This could explain the commonly used management strategy of using plastic utensils instead of metallic silverware during eating by patients [2,34]. Patients can experience a bitter or metallic taste during the consumption of red meat [21]. This might be due to the iron containing compounds in red meat. The metallic taste may cause an aversion for red meat, which is often seen in cancer patients [49]. Based on clinical experience, some patients describe a 'blood taste' during chemotherapy. Possibly, the iron-containing compounds in blood could explain this effect. The taste of metallic silverware and iron-containing compounds may be experienced more intense by cancer patients because of a lower threshold for metals.

Possibly, retronasal smell plays a role as well. As previously mentioned, the perceived intensity of the metallic sensation following $FeSO_4$ stimulation decreased when the nose of healthy participants was occluded, implying the development of retronasal smell [25,29]. This retronasal perception in the mouth may develop due to a biochemical reaction, lipid oxidation. Lipid oxidation is catalyzed by metals and contributes to the production of odorous compounds, including carbonyls that cause a metallic taste sensation. A recent study investigated the effect of stimulation with ferrous (Fe^{2+}), cupric (Cu^{2+}), cuprous (Cu^{+}), and ferric (Fe^{3+}) ion solutions on salivary lipid oxidation in healthy participants (22 participants, age 19–53 years participated in various parts of the study) [35]. Salivary lipid oxidation (measured as malondialdehyde (MDA) concentration) was significantly higher after rinsing the mouth with the Fe^{2+} solution compared to the control solution (reagent water) (0.33 ± 0.12 μmol/L versus 0.12 ± 0.03 μmol/L ($P < 0.001$) in 19 participants (11 men, age 24–53 years). Furthermore, stimulation with Fe^{2+} resulted in the highest lipid oxidation, followed by Cu^{2+}, Cu^{+}, and Fe^{3+} in 13 participants (seven men, 24–53 years). Differences in qualitative perception between the stimuli were not reported.

A recent longitudinal study investigated the relation between taste and smell changes, salivary parameters, and salivary lipid oxidation in 22 patients with primary malignant brain tumors and 22 healthy controls [23]. Treatment consisted of six weeks radiation in combination with temozolomide followed by six monthly cycles of temozolomide. The salivary levels of metals, electrolytes, total protein, and salivary lipid oxidation did not provide a reliable measure for taste and smell changes in the cancer patients. However, since patients were not asked to report metallic taste, a possible relation between metallic taste and saliva electrolyte, metal parameters and saliva lipid oxidation remains unclear. This comparison may be relevant since differences in salivary parameters between cancer patients and healthy controls were found: cancer patients had significantly lower salivary Zn, Fe (both before and after Fe^{2+} rinse), and oral pH levels ($P < 0.05$) compared to healthy controls, whereas salivary lipid oxidation, total protein, sodium (Na), potassium (K), Cu, phosphorus (P), sulfur (S), and Mg levels were significantly higher ($P < 0.05$) as averaged across all times.

Management strategies

Several strategies have been suggested to manage metallic taste. The most commonly mentioned strategy is to use plastic utensils instead of metallic silverware [2,34]. One study showed that 26 patients with cyclophosphamide as part of their treatment reported a slight, but lingering, metallic taste. Three of these patients reported that using plastic utensils made food more palatable [33]. Not using metal utensils and consuming ice water was helpful for a pancreatic cancer patient treated with gemcitabine [21]. A study performed in patients with lymphoma, breast, lung or ovarian cancer after at least two chemotherapy cycles investigated self-care strategies to manage taste changes [12]. First, patients had to fill out a taste change questionnaire. Next, a 20-item taste change suggestion sheet of management strategies was provided to the patients. Suggestions included adding more or less seasonings, eating foods at room temperature, and using plastic utensils. Approximately two weeks later, patients had to fill out the same taste change questionnaire and a questionnaire to identify the used self-management strategies. Patients had to tick one of the following boxes: 'did not try', 'tried but did not help', 'helped a little' or 'helped a lot'. Eating cold foods was more helpful for patients who reported a metallic taste compared to patients without a metallic taste. The effectiveness of using plastic utensils was not specified. In another study, one colorectal cancer patient treated with oxaliplatin-containing chemotherapy used very strong flavors in foods, such as lots of salt, to reduce the metallic taste [17].

Furthermore, a pilot study has been carried out using the fruit *Synsepalum dulcificum*, also known as 'miracle fruit', to improve the food palatability for patients treated with chemotherapy [24]. 'Miracle fruit' has been developed as a sweetness enhancer [50]. It contains the protein miraculin, which binds to sweet receptors on the tongue, turning sour foods into sweet. Therefore, certain unpleasant tastes, like metallic, can be masked for a short duration [50]. Eight patients with various cancer types, chemotherapy regimens, and treatment phases (4–12 cycles) with taste changes received a miracle fruit supplement for two weeks following a crossover placebo design. Dietary intake was recorded using a 28-day food diary. Patients had to chew the supplement completely, swallow the substance, and had to wait for 5 min before eating. Next, patients had to report the consumed food, the portion size, and the taste of the food compared to the previous experience without using the supplement (better, same or worse). The duration of the effect of the supplement was reported as well. Five out of eight patients experienced a metallic taste and reported that this taste disappeared with the use of the supplement. The taste changes of the foods after ingesting the supplement lasted for 20–30 min. All patients reported that the taste of food improved during supplement use and an increased food intake was found in some of the patients [24].

As previously mentioned, lipid oxidation seems to play a role in the development of metallic taste. Lipid oxidation may be reduced or prevented by using antioxidants and chelating agents. One study investigated the effect of antioxidants (vitamin C and E), chelating agents (Ethylenediaminetetraacetic acid (EDTA) and lactoferrin), and water (control) on the perceived intensity of metallic taste and lipid oxidation in healthy participants (22 participants, age 19–53 years participated in various parts of the study) [35]. Participants had to sip and rinse 3 ml of an antioxidant or chelating agent solution and subsequently an 18 μmol/L ferrous iron solution. This procedure was also performed in reversed order. Next, the participants had to rate the intensity of the metallic taste on a scale from 0 to 12. A moderate to high intensity of metallic taste was reported when participants rinsed their mount with the antioxidant or chelating agent solution before ingestion of the ferrous iron solution. However, a decreased perceived intensity for metallic taste was found when lactoferrin, EDTA, rinse water, vitamin E and vitamin C (from highest to lowest difference in intensity) were ingested after the ferrous iron solution. The antioxidants vitamin C and E seemed not very effective in removing the metallic taste, since the intensity ratings for metallic taste were even lower after the reagent water rinse. The chelating agents EDTA and lactoferrin were most effective, in which lactoferrin completely eliminated the metallic taste in all participants.

Cancer patients have reported their useful management strategies on cancer patient forums. Using plastic utensils for eating and cooking, as well as eating cold or frozen foods, and chewing on (lemonade) ice blocks were frequently recommended. To overpower the metallic taste, using strong herbs and spices and strong flavored gum, mints and hard candies have been advised. Furthermore, both using sweet and sour foods, and adding sweetener or acid (like lemons, limes or oranges) to foods were helpful for patients [51–56].

Conclusion

Given the limited literature and attention to metallic taste in cancer patients treated with chemotherapy, this side effect of chemotherapy seems not to be a problem. Nevertheless, metallic taste is a frequent side effect of chemotherapy and a much discussed topic on cancer patient forums. More awareness for this side effect can result in better support for these patients.

Although taste changes have been associated with a poor appetite, a decreased energy and nutrient intake, changes in food preference, and a decreased quality of life [3–9], the impact of metallic taste on these parameters is not known. Studies specifically focused on metallic taste can yield information concerning the characteristics of this sensation and the effects on food preference, dietary intake, body weight, and quality of life.

A combination of cyclophosphamide, doxorubicin, and fluorouracil (CAF), as well as platinum based chemotherapy regimens have been reported to induce metallic taste [27,47]. However, data regarding the prevalence of metallic taste per cancer type, chemotherapy treatment, and treatment phase are scarce. These data may help to identify patients at risk for developing metallic taste. For these cancer patients, management strategies can be helpful.

The management strategies reported on cancer patients forums, can be used as guideline by health care professionals to support patients reporting a metallic taste. Furthermore, using miracle fruit and rinsing with chelating agents, such as lactoferrin and EDTA, are worthwhile to try for these cancer patients [24,35]. Nevertheless, given the limited data regarding these management strategies, their effectiveness has to be explored.

To date, no metal salt solution, solid metal or electric stimulus has been identified that reflects the metallic taste reported by cancer patients treated with chemotherapy. Such a stimulus is essential to imitate this metallic taste in healthy participants and can be used to develop suitable management strategies. Besides, such a stimulus can be useful for the food industry to develop or adapt food products to make foods more palatable for patients reporting a metallic taste.

Conflict of interest

There are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

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