Modifications of taste sensitivity in cancer patients: a method for the evaluations of dysgeusia

Modifications of taste sensitivity in cancer patients: a simple and inexpensive method for the evaluations of dysgeusia

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ABSTRACT

Purpose Taste changes due to chemotherapy may contribute to the high prevalence of malnutrition in cancer patients. It is believed that 50-70% of patients with cancer suffer from taste disorders, like dysgeusia. The diagnosis of dysgeusia is important in the prognosis of patients. Thus, the aim of the present study was to analyze the taste alterations in patient population compared to controls, also in relation to gender. In this way, it could open to a new approach for a personalized diet to prevent and/or reduce taste alterations and malnutrition in cancer patients.

Methods Forty-five cancer patients undergoing chemotherapy were compared to healthy controls (n = 32). Taste function test was used to determine taste sensitivity. Different concentrations for each of the 4 basic tastes (salty, sweet, sour, bitter) and also fat and water tastes were evaluated.

Results A significant difference in taste sensitivity among patients undergoing chemotherapy compared to the control group was found, in line with similar studies from literature. As in the control group, taste perception in patients was better in females than in males, suggesting interaction effect between group and gender.

Conclusions Coping strategies regarding subjective taste impairment should be provided since alterations in taste sensation influence food preferences and appetite. Clinicians could thus have the potential to underpin changes in dietary intake and consequently in nutritional status; understanding the extent of the contribution of each would help in the development of effective interventions in future. Consequently, they can adopt appropriate appetizing strategies and, based on that, change their feeding habits.

Keywords: Taste; Cancer; Malnutrition; Quality of life; Gender

Declarations of interest: none

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1. Introduction

The gustatory system is a sensory system associated with the mouth. Together with the olfactory system, it is devoted to the detection of chemicals in the environment. Taste interacts with smell, touch and other physiological cues to affect the wider perception of flavor. Taste function is defined as the perception derived when chemical molecules stimulate taste receptors in areas of the tongue, soft palate and oropharyngeal region of the oral cavity to perceive the five basic taste qualities: sweet, sour, salty, bitter and umami, and also fat recently described as basic taste (Besnard, Passilly-Degrace, & Khan, 2016; Breslin & Spector, 2008; Zocchi, Wennemuth, & Oka, 2017).

The chemoreceptors are specialized epithelial cells located in rounded structures called taste buds, each containing from 50 to 150 receptor cells, as well as immature cellular elements, the basal cells, and numerous supporting cells (Breslin & Spector, 2008). The effects of chemical stimuli are transmitted through the cranial nerves VII, IX and X, to appropriate regions of the central nervous system, insula and frontal operculum.

It's well known that cancer therapy is able to alter the chemical senses by determining ototoxicity and peripheral neuropathy (Knight, Kraemer, & Neuwelt, 2005; Quasthoff & Hartung, 2002). Chemotherapy is one of the most widely used treatment modalities, in spite of its toxicity to normal tissues, since it acts on rapidly multiplying cells: this treatment has remained the major obstacle for successful clinical use (Ruiz-Esquide, Nervi, Vargas, & Maiz, 2011).

Patients undergoing chemotherapy often report taste sensitivity alterations, even in absence of significant manifestations, such as nausea and gastroenteric symptoms (DeWys & Walters, 1975; Zabernigg et al., 2010). These alterations should be investigated at several levels, in order to elucidate if they are related to altered taste function *per se* or to changes in the oral cavity (e.g. oral dryness) that may affect mastication. Socio-cultural obstacles to communication with clinicians are frequent, with patients colloquially referring to aspects like food preferences, or appetite, using the word 'taste' (Sherry, 2002; Bartoshuk, 1990). Previous evidence showed alterations in the four basic flavors (excluding umami) in cancer patients (Welge-Lussen & Gudziol, 2004; Halyard, 2009) with acute exacerbations, especially for bitter and sweet flavor recognition, during cytotoxic drug administration (Comeau, Epstein, & Migas, 2001). However, to our knowledge no data are available on changes in fat and water recognition in chemotherapy treated cancer patients.

Maintenance of Quality of Life (QoL) during chemotherapy is important for patients with cancer. Taste alteration involves a series of consequences on the patients' health among which malnutrition and consequent reduction of the QoL (Huhmann & Cunningham, 2005; Muscaritoli et al., 2017). At present, it is believed that 50-70% of patients with cancer, receiving chemotherapy, radiotherapy or both, suffers from taste disorders, like dysgeusia, that can sometimes even start before the treatment and persist weeks or even months after the end of same treatment (Wickham et al., 1999). Dysgeusia is a nonlethal condition and is usually difficult and complicated to diagnose because its clinical signs are multiple and are linked to other sensory systems. However, taste alterations are critical to the pleasure of eating which is a major part of QoL, so the diagnosis of dysgeusia is important in the prognosis and treatment response of patients (Bernhardson, Tishelman, &

Rutqvist, 2009; Brisbois, Hutton, Baracos, & Wismer, 2006). Dysgeusia is associated with increased morbidity and mortality from inadequate energy and nutrient intake, weight loss and malnutrition resulting both in reduced immune response and compliance to chemotherapy (Martin et al., 2015). Cancer Anorexia Cachexia, which is characterized by muscle wasting and loss of appetite, cannot be managed adequately by nutritional supplement. Patients with this morbidity status have a poor overall QoL: they suffer from chronic pain and fatigue and if there is a 25-30% loss of total body weight, they die from respiratory failure (Muscaritoli, Molfino, Lucia, & Rossi Fanelli, 2015). Cachexia is a combination of both starvation caused by anorexia and wasting syndrome due to cachexia, so weight loss alone cannot be a prognostic factor for patients undergoing chemotherapy (Dhanapal, Saraswathi, & Govind, 2011). At present a validated methodology for the quantitative measurement of dysgeusia severity has not been established (Imai, Soeda, Komine, Otsuka, & Shibata, 2013).

Dysgeusia is clinically assessed by measuring the discovery or recognition threshold values for the seven basic tastes: bitterness, sweetness, saltiness, sourness, umami, fat and water by applying filter-paper taste strips impregnated with different concentrations of the basic tastes. However, this method does not give qualitative information on taste perception such as which basic taste perception is most influenced by cancer or its treatment but qualitative changes are reported through patient complaints, interviews, and clinical observations (Hong et al., 2009).

We focused our attention on how dysgeusia could be analyzed with a simple and inexpensive method in order to immediately intervene with a personalized diet that can prevent the patient's weight loss. This method not only allows to make a diagnosis of dysgeusia, but also to assess its degree and characteristics.

Thus, the aim of the present study was to analyze the taste alterations in cancer patient population compared to controls, also in relation to age and gender. In this way, it could open to a new approach for a personalized diet to prevent and/or reduce the taste alterations in cancer patients undergoing chemotherapy.

2. Participants and methods

2.1. Study population

Our study was carried out on 45 cancer patients undergoing chemotherapy (18 males and 27 female) whose characteristics are summarized in Table 1. Thirty-two healthy subjects (14 males and 18 female), recruited from our previous studies, were defined as historic control group (see Table 1). The 45 patients had a diagnosis of malignant neoplasia (breast, lung, pancreatic, colorectal, liver cancer). Demographic characteristics were similar in both groups. For each subject, body weight, as well as height, were determined.

Table 1. Clinical characteristics of the participants in the study presented as mean ± SD or n(%).

		Cancer Patients (N=45)	Historic Controls (N=32)
Age (years), Mean (SD)		51.4 ±13,7	48.7 ± 9.4
Sex, No. (%)			
	Men	18 (40%)	14 (44%)
	Women	27 (60%)	18 (56%)
Body mass index (kg/m2)		24.7 ± 3.1	22.9 ± 3.9
Cancer site			
	Breast	17	
	Colonrectal	10	
	Gastroesophageal	3	
	Pancreatic	5	
	Lung	3	
	Genitourinary tract	5	
	Other Cancer	2	
Treatment			
	5-Fluoruracil (5-FU)	15	
	Cisplatin	18	
	Taxame-based CT(chemotherapy)	10	
	Other CT	2	

2.2. Taste sensitivity determination

Taste sensitivity was evaluated by using the "Taste strips" test according to *Landis et al.* (Landis et al., 2009). This test consists of cotton swabs impregnated with a solution containing a substance in 4 different concentrations for each of the 4 basic tastes (salty, sweet, sour, bitter). In addition, pure rapeseed oil and deionized water were employed (Table 2).

Table 2 – Characteristics of taste stimuli.

Stimulus	Substance	Concentration
Sweet	Sucrose	• 0,05 g/ml • 0,1 g/ml • 0,2 g/ml • 0,4 g/ml
Salty	Sodium Chloride	• 0,016 g/ml • 0,04 g/ml • 0,1 g/ml • 0,25 g/ml
Bitter	Quinine hydrochloride	• 0,0004 g/ml • 0,0009 g/ml • 0,0024 g/ml • 0,006 g/ml
Sour	Citric acid	• 0,05 g/ml • 0,09 g/ml • 0,165 g/ml • 0,3 g/ml
Fat	Rape oil	Pure
Neutral	Deionized water	Pure

Rapeseed oil is a neutral oil, with little smell and flavor, unlike many other vegetable oils. Specifically, olive oil has a specific texture, making it easily recognizable, and we decided to not use it. Since gustatory stimulation also causes the activation of other sensory system (e.g. touch receptors) (Mattes & Popkin, 2009) the test should be performed in such a way as to minimize the activation of other receptors.

Distilled water was used as solvent and taste solutions were freshly prepared at regular intervals. Umami was not included, because the concept of this type of taste is difficult to explain and to understand in Western Countries. Subjects were asked not to eat or drink anything other than plain water and not to chew gums or candies at least an hour before the beginning of test. The stimuli were applied just behind the anterior third of the tongue kept out of the mouth, on the left or right-side edge. Administration was randomized for each of the four levels of concentration and the side of presentation was alternated: 36 cotton swabs (18 for the left side and 18 for the right side) were used. The enrolled subjects had to identify the taste by choosing from a list that included 8 descriptions: "*sweet, salty, bitter, sour, water, fat, nothing, I do not know*" (forced multiple choice).

The current study was performed in adherence to the guidelines of the Declaration of Helsinki as revised in 2001, after the protocol was approved by the Review Board of Università Politecnica delle Marche. A written informed consent was subscribed by all subjects enrolled in the study.

2.3 Statistical analysis

Statistical analysis was performed using the SAS statistical package (Statistical Analysis System Institute, Cary, NC). Results are expressed as Means ± SD. One-way ANOVA, followed by Tukey's post hoc test, was used to analyze inter-group differences. Two-way ANOVA was used to analyze the effects of gender, type of stimulation and presence of disease on taste sensitivity. Differences were considered significant with $p < 0.05$.

3. Results

The results were analysed using appropriate statistical tests (Student's t test, linear regression analysis, ANOVA) to assess the number of correct recognitions as a function of the stimulus (taste, concentration, side of stimulation) and the other physiological (age and gender) and pathological characteristics.

A significant difference in taste sensitivity among patients undergoing chemotherapy compared to the control group was found (Fig. 1).

3.1 Historic Controls

The analysis of variance (ANOVA) on taste sensitivity tests performed on control subjects yielded significant variations among different types of stimuli [$F (5,185) = 15.306$, $p<0.001$] (Fig. 2). Post hoc Tukey test showed that identification of all 4 basic tastes was significantly better than fat ($p<0.001$) and water ($p<0.05$) recognition.

A two-way ANOVA was conducted on the percentage of correct answers among controls, with type of stimulation and gender as factors. The two-factor analysis of variance showed a significant main effect for type of stimulation, [$F (5,186) = 15,228$, $p < 0.001$] and no significant main effect for the gender factor [$F (1,186) = 1.534$, $p > 0.05$]. Significant interaction between gender and type of stimulation [$F (5,186) = 5.074$, $p < 0.001$] was found. Females showed better taste sensitivity than males in relation to 4 basic tastes (salty, sweet, sour, bitter) while, on the contrary, perception of fat and water was better in males than in females, suggesting an interaction effect between taste perception and gender (Fig. 3).

3.2 Patients

The analysis of variance (ANOVA) on taste sensitivity tests performed on oncologic patients yielded significant variations among different types of stimuli [F (5,264) = 24.656, $p<0.0001$]. Post hoc Tukey test showed a better and significant sour taste perception in oncologic patients, compared to salty perception ($p<0.001$) and not significant compared to bitter and sweet tastes perception. Identification of all 4 basic tastes was significantly better than fat ($p<0.001$) and water ($p<0.001$) recognition (Fig. 4)
A two-way ANOVA was conducted on percentage of correct answers among patients, with type of stimulation and gender as factors. The two-factor analysis of variance showed a significant main effect for type of stimulation [F (5,258) = 23.211, $p < 0.001$] and a significant main effect for the gender factor [F (1,258) = 7.004, $p < 0.01$]. Interaction between gender and type of stimulation [F (5,258) = 0.228] was not significant. Females showed better taste sensitivity than males in relation to 4 basic tastes (salty, sweet, sour, bitter) and also to fat and water, suggesting absence of interaction effect between taste perception and gender (Fig. 5).
Among patients, a simple linear regression analysis, unlike the controls, was calculated to predict taste sensitivity based on age. A significant regression equation was found [F (1,43) = 48.225, $p < 0.001$] with an R^2 of 0.529 (R = - 0.727) (Fig. 6).

3.3 Historic Controls and patients

A two-way ANOVA analysis was conducted on the percentage of correct answers, with type of stimulation, subject's group (cases, controls) and gender as factors. The two-factor analysis of variance showed a significant main effect for both the group factor [F (1,432) = 49,246, $p < 0.001$] and type of stimulation [F (5,432) = 33,699, $p < 0.001$], and no significant main effect for the gender factor [F (1,1) = 0.616, $p > 0.05$]. Significant interactions between group and type of stimulation [F (5,432) = 3,119, $p < 0.01$] and group and gender [F (1,432) = 7,033, $p < 0.01$] were found. Cumulative interaction between groups, type of stimulation and gender was significant [F (5,432) = 2,650, $p<0.05$].
At variance with control group (where males and females showed similar taste sensitivity), taste perception in the patient group was better in females than in males, suggesting interaction effect between group and gender (Fig. 1 and Fig. 7).

4. Discussion

The physio-pathological mechanisms determining the onset of dysgeusia during chemotherapy are linked to neurological damage to cranial nerves (VII, IX and X), taste buds and oral mucosa (Comeau et al., 2001). Furthermore, anticancer drugs can access the oral cavity through diffusion from plasma into the capillaries, producing an unpleasant taste (Mosel, Bauer, Lynch, & Hwang, 2011). Dysgeusia can also be related to modifications of the concentrations of sodium, potassium and calcium in the cells of taste receptors (Cowart, 2011), to candidiasis, viral infections and gingivitis. As reported in various studies, different chemotherapy drugs, among which cisplatin, doxorubicin, 5-fluorouracil (5-FU), docetaxel and paclitaxel, induce changes in taste sensitivity (Ackerman & Kasbekar, 1997). Consistently with the literature on patients with various cancer types (Coa et al., 2015), in the present study we showed that subjects treated with these anticancer drugs - 5-FU and paclitaxel - showed weight loss from the beginning of treatment and reported an increased sensitivity to metallic taste. As a consequence, inadequate energy and nutrient intake, weight loss and malnutrition are often reported (Schiffman, 2007), with subsequent reduced compliance with treatment regimens (Doty, Shah, & Bromley, 2008), immunodepression (Schiffman, 2007; Schiffman et al., 2007), emotional distress and interference with daily life activities (Bernhardson, Tishelman, & Rutqvist, 2007).

Our study, in accordance with the literature, shows that patients with cancer reported abnormalities in taste recognition (Nakazato, Imai, Abe, Tamura, & Shimazu, 2006; Schiffman, 1983). However, to our knowledge no data are available on changes in fat and water recognition, recently described as basic tastes (Besnard et al., 2016; Zocchi et al., 2017), in chemotherapy treated cancer patients.

For the evaluation of taste sensitivity, we used a simple and inexpensive method, with fat and water taste perception analysis as well. A significant difference in taste sensitivity among patients undergoing chemotherapy compared to the control group was found. In patients, we observed a better and significant sour taste perception in comparison to salty perception and not significant in comparison to bitter and sweet taste perception. In both control and patient groups, the identification of all 4 basic tastes was significantly better than fat and water recognition. Specifically, fat stimuli were less perceived by both groups. Patients reporting metallic taste often reported that they were annoyed by fatty foods - especially animal proteins sources, such as red meat - but this relationship is still not well interpreted (I, Timmermans, Renken, Ter Horst, & Reyners, 2017). Moreover, a reduced response profile for salty stimuli in cancer patients compared to controls was found, while less differences between the two groups for sour stimuli were detected.

Taste alterations in cancer patient population, compared to controls, were analyzed also in relation to age and gender. An interaction effect between group and gender was found. Among controls, males showed better taste sensitivity than females while, on the contrary, taste perception in patients was better in females than in males. Many studies indicate that taste changes are more prevalent in females compared to males (Bernhardson, Tishelman, & Rutqvist, 2008; Coa et al., 2015; Zabernigg et al., 2010), while other papers found no gender difference (Brisbois, de Kock, Watanabe, Baracos, & Wismer, 2011). IJpma *et al.* (I et al., 2017) showed that females perceived metallic taste better than men. This sensation of metallic taste seems to be related with bitter taste, as supported by IJpma's observations [38]. Even in the present study, we realized how common this experience is in patients undergoing chemotherapy but we did not observe gender differences. Similarly to our study, a previous work on taste and smell alterations in patients with lung cancer (McGreevy et al., 2014) showed that females more often report stronger sensations than males. Although the reasons of gender differences in taste alterations are still unknown, we can speculate that women's cognitive or emotional superiority plays a role in sensorial behavior. However, as a general rule, females have greater taste and olfactory sensitivity than men (Doty & Cameron, 2009; Soter et al., 2008).

Our study showed a significant main effect for both the group factor and type of stimulation and no significant main effect for the gender factor. Significant interactions between group and type of stimulation and group and gender were found. A significant cumulative interaction effect between groups, type of stimulation and gender was reported. To our knowledge, there is no evidence regarding this type of effect.

A simple linear regression analysis was calculated to predict taste sensitivity based on age among patients and a significant regression equation was found, suggesting interaction effect between group and age. Our results are in line with observations by de Ruiter *et al.* (de Ruiter et al., 2011) indicating that chemotherapy is associated with a long-term impairment in cognitive function and brain activity alterations in regions involved with executive function (i.e. dorsolateral prefrontal cortex) and memory encoding (i.e. hippocampal regions). This may result in lower attention capacities and underlie the diffuse pattern of cognitive dysfunction observed in these patients, thus contributing to the progression of dysgeusia in older chemotherapy patients.

Cancer treatments -chemotherapy and radiotherapy- are the main causes of dysgeusia in patients because of their action on oral epithelial cell turnover (direct stomatological toxicity) (Lopez-Galindo, Bagan, Jimenez-Soriano, Alpiste, & Camps, 2006). Other common side-effects of chemotherapy is myelosuppression (indirect stomatological toxicity), alopecia, and effects on nerves, taste buds and olfactory receptors (Epstein, Tsang, Warkentin, & Ship, 2002).

Although there are a variety of causes of dysgeusia, treatment still relies on simple approaches, including dose reduction of certain chemotherapeutic drugs (e.g., histone deacetylase inhibitors), treatment of oral infections, and dietetic counseling (Mosel et al., 2011). In relation to this latter aspect, it is advisable to increase liquid intake with meals, and chew food slowly - thereby unleashing more flavors and especially increasing saliva production. In addition, food and nutrient variety should be encouraged, to prevent taste bud adaptation to flavors.

Thus, we would have a personalized therapy of dysgeusia resulting in an increased protein-energy intake and reduced malnutrition associated with the disease. Considerable importance will also be placed on palatability of foods, including not only the taste but also the colour, the smell and the combinations that best fit the individual patient. Sometimes cancer patients have difficulty chewing and swallowing and tend to prefer liquid preparations; other times they suffer from nausea and prefer powder preparations.

Dysgeusia can be fought by means of prevention of malnutrition, combating the devastating effects of anticancer therapy and thus allowing to maintain a good nutritional status and thus a good QoL.

Our study has a series of limitations which need to be addressed. First, our research was carried out in a heterogeneous cancer patient population, with wide variations in type of complaints and their severity. Given the large variations in symptoms among these patients, drawing of correlations between sensory alterations and specific biologic markers is still difficult. Furthermore, metabolism in cancer patients is influenced by many interconnected endogenous and exogenous factors, without identifying a certain single factor accountable for taste alterations. There is agreement, however, that abnormal neuronal activities and damage to sensory receptor cells are independent causes of taste alterations in these patients, but the etiology of these disorders is likely multifactorial.

5. Conclusions

The oral cavity is very sensitive to the direct and indirect toxic effects of chemotherapy (Bernhardson et al., 2009). The pathogenesis of dysgeusia is not completely understood but it is thought to be somehow related to weight loss (Bertoli et al., 2014).

The present study provides a significant difference in taste sensitivity among patients undergoing chemotherapy compared to the control group, in line with similar studies from literature (Cohen, Wakefield, & Laing, 2016; I et al., 2016).

Our study confirms that taste disorders involves food intake modifications in terms of quantity and quality in patients, leading them to unhealthy eating habits affecting dietary intake, nutritional status and overall QoL (McQuestion, Fitch, & Howell, 2011). Since alterations in taste sensation influence food preferences and appetite, they all have the potential to underpin changes in dietary intake and consequently in nutritional status; understanding the extent of the contribution of each would help in the development of effective interventions in future. Obviously, more research is needed to clarify the character, frequency and duration of taste modifications and their healthy implications and the correlations between taste alterations, food consumption and malnutrition in cancer patients undergoing chemotherapy. To this purpose, our future perspectives are to evaluate several homogenous patient populations regarding type of cancer and treatment, performing a complete nutritional management of individuals with chemosensory disorders, through clinical evaluation and recommendation of appropriate dietary-intake measurement. This type of analysis can allow the patients themselves to evaluate the changes in thresholds for different taste modalities. Consequently, they can adopt appropriate appetizing strategies and, based on that, change their feeding habits.

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