Author’s response to reviews

Title: The influence of taste disorders on dietary behaviors in patients with cancer under chemotherapy treatment

Authors:

Karla Sánchez Miss (ksanchez@medicasur.org.mx)
Ricardo Sosa Dr (drrsosa@hotmail.com)
Dan Green Dr (dgreen@medicasur.org.mx)
Cindy Rodriguez (zymaro_rodpach@hotmail.com)
Daniel Motola (dmotola@yahoo.com)
Susana Torres Miss (susana.araiza@hotmail.com)
Oscar Arrieta (ogar@servidor.unam.mx)

Version: 3 Date: 10 November 2009

Author’s response to reviews: see over
Second VERSION: manuscript 2123106711298952

Title: The influence of taste disorders on dietary behaviors in patients with cancer under chemotherapy treatment

Dear Dr. Nehme Gabriel:

We appreciate the comments made to our manuscript; undoubtedly they have increased the quality of our paper. Enclosed please find the revised manuscript and a detailed description point by point addressing the reviewers’ comments.

All authors have read and approved the final version of this manuscript, and concur with the submission.

Waiting your reply, I remain.

Yours sincerely,

Karla Sánchez Lara

Oncology Center Diana Laura Riojas de Colosio, Médica Sur Clinic and Foundation,
Mexico. Puente de piedra 150, Toriello Guerra, Tlalpan CP 14050. Mexico City.
Telephone: (55) 54 24 72 00 ext 4216. Fax (55) 54 24 72 10.
ksanchez@medicasur.org.mx
**Reviewer’s report:**

In my opinion the article would benefit if the authors could clarify on the issues below:

1. If there is an approval for the study from the Ethics Committee I would suggest that it is pointed out in the text. The authors wrote that the study protocol was approved by the Institutional Review Board at the participating center. Is that corresponding to the Ethics Committee?

   Protocol was approved by the Institutional Ethics Committee (Number 238-C, date: 21st November 2008). This have been added at the Patients and methods section (Page 4, paragraph 2, line 11) “The study protocol was approved by the Institutional Ethics Committee. All subjects provided written informed consent”

2. In my opinion there are not sufficient details provided to replicate the work. I suggest that the authors clarify what umami testing substance that was used. I presume it was Sodium glutamate. My suggestion is that the authors provide information about the highest and lowest concentration in mmol/L of the testing substances.

   We described the substance used for umami taste, and lowest and highest concentration of testing substances in the Test evaluation section (Page 5, paragraph 3, line 1). “Five concentrations were dissolved in distilled water from each of the three taste study substances, including sucrose (3.5-15.5 µmol/ml), urea (91-115 µmol/ml), and sodium glutamate (0.3-2.7 µmol/ml).”

3. The authors found that patients with sweet and bitter taste disturbances had a lower energy intake. The finding raise the question: Did this result in loss of body weight?

   We made a new analysis, added in results (Page 7, paragraph 2, line 1): “We calculated total metabolic rate (TMR) and protein requirement from all patients, and compared this results with calories and protein consumption. The proportion of patients that were not able to complete their daily energy requirements was higher in those with values of sweet DT, sweet RT, and bitter RT above the median compared to patients with normal taste thresholds (Tabla 6). Lower daily caloric intake was found in patients with higher values of sweet DT (-632±361 vs -32±162 kcal/day, p=0.05), sweet RT (-428±2.58 vs 14.7±8.2 kcal/day, p=0.06) and bitter RT (-487.4 vs 66 kcal/day, p=0.031). The percentage of subjects with weight loss was higher in patients with bitter RT above the median (100% vs 67%, p=0.03)”.

4. My suggestion is that the authors calculate the individual energy and protein requirement. Basal metabolic rate, BMR, can be calculated by for example Harris-Benedict energy estimation. The physical activity level, PAL, could be approximately defined. The basal energy requirement is approximately 20 kcal per kilogram body weight per day and protein requirement of an healthy individual is approximately 0,8 gram per kilogram body weight. However, the actual protein requirement of an individual with cancer is not known, it might be 1,0 to 1,5 gram per kilo and day. The consumed energy and protein could be calculated and put in relation to the calculated needs. This would show weather the cancer patients were able to meet their nutritional needs or not. It would say more than just energy intake in kcal.

By reviewer suggestion, we calculated total metabolic rate (TMR) and protein requirement from all patients, and compared this results with calories and protein consumption. Patients with cancer diagnosis (cases) were classified in subjects that completed their calculated needs and subjects who did not. Each of this groups was compared for alteration in taste perception (sweet and bitter DT and RT). Results were described in table 6 and Results section (Page 7, paragraph 2, line 3) The proportion of patients that were not able to complete their daily energy requirements was higher in those with values of sweet DT, sweet RT, and bitter RT above the median compared to patients with normal taste thresholds (Tabla 6). Lower daily caloric intake was found in patients with higher values of sweet DT (-632±361 vs -32±162 kcal/day, p=0.05), sweet RT (-428±2.58 vs 14.7±8.2 kcal/day, p=0.06) and bitter RT (-487.4 vs 66 kcal/day, p=0.031). We also added table number 6. Page 20

5. In Table 1 p-values for gender and age are presented. I don’t find it useful to test p-values on that kind of data.

It’s well known that age is an independent factor associated for taste disorders. We think that is important to show that cases and controls in our study have no significant difference in age.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being Published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer: Barbara Stewart-Knox

Reviewer's report:
General Points
Replace ‘perception’ threshold with ‘detection’ threshold throughout.
Correct grammar throughout.
Pages are not numbered.

Corrections are done

Abstract
Remove ‘dietary nutrient’ consumption and replace with ‘food habits’ (since an FFQ was used).
Insert ‘(sweet)’ after sucrose.
Replace ‘perception’ threshold with ‘detection’ threshold.

Corrections are done (Page 2, paragraph 1, line 7, 9, 11,12,13, 16, 17)

Introduction
Reference all background statements.

Corrections are done, we added bibliography:

41. Henkin RI, Schecter PJ, Friedewald WT, Demets DL, Raff M: A double blind study of the effects of zinc sulfate on taste and smell
Method
Sampling
How were the sample/s recruited?

We added more description about the samples recruited at Patients and methods section (Page 4, paragraph 2, line 1) “We conducted a cross-sectional study of flavor test evaluations at the Oncology Center of a University hospital in Mexico City; our sample population consisted of 60 subjects who agreed to participate. They had no history of infections of the oral/nasal cavity, brain disease, acute respiratory illness or gastroesophageal reflux. Study participants included 30 subjects with a histological diagnosis of a malignant neoplasia (breast, lung, prostate, multiple myeloma and lymphoma) while in their second chemotherapy cycle. Subjects with central nervous system metastasis, gastrointestinal and head and neck cancer and oral, nasal disease or infections were excluded. We included 30 control-group subjects with no evidence of cancer. Eligible patients had biopsy proved diagnosis of cancer on clinical stages II and III with an Eastern Cooperative Group performance status (ECOG) of 0 or 1, with adequate hematologic, hepatic, and renal functions”
Were the cancer and non-cancer groups matched in any way (eg demographically)?

No, there are no matched analysis. But there are no differences in age, demographic and gender between cases and controls.

What sort of cancer (also prognosis) did the patient group have? This is important as cancer of the head and neck or GI tract may have a direct influence on the outcome variables over and above that of the chemotherapy.

We reviewed that point in patients and methods section. (Page 4, paragraph 2, line 6) “Study participants included 30 subjects with a histological diagnosis of a malignant neoplasia (breast, lung, prostate, multiple myeloma and lymphoma) while in their second chemotherapy cycle. Subjects with central nervous system metastasis, gastrointestinal and head and neck cancer and oral, nasal disease or infections were excluded”.

Dietary assessment
It is unclear if a dietary history was taken in addition to using an FFQ or were both used? More detail as to the structure, format and outcome measures of the FFQ is required.

For this purpose we search for a validated FFQ in our population. The only validated FFQ is the one we used. Information about structure and format of this FFQ is detailed in Dietary history questionnaire (Page 5, paragraph 2, line 2) “Nutrients intake was evaluated using the “SNUT” program. This food frequency questionnaire (FFQ) was developed and validated for Mexican population by the National Institute of Public Health Mexico [28] SNUT is composed of a matrix listing 116 food items and 10 frequencies of consumption with specified size portion; the program also included information concerning the frequency of ingestion and the brand of vitamin supplements. SNUT software is useful to calculate daily intake of: calories, proteins, carbohydrates, saturated, polyunsaturated and monounsaturated fat; vitamins and zinc intake”

Taste threshold assessment
Where any tests carried out at baseline, before the chemotherapy?

The aim of this study was to determine the existence of taste disorders in cancer patients treated with chemotherapy. Baseline taste were not made in this first study. As said in discussion (Page 10, paragraph 4, line 1) “Methodological weaknesses of this research include: Variability in cancer types and chemotherapy drugs used; and the absence of basal taste
disorder evaluation before chemotherapy treatment, and for establishing a causal association between chemotherapy and taste disorders. Continuing research is required to develop an understanding of the nature, frequency, severity, and duration of taste alterations and their significance in food consumption and malnutrition in patients with cancer under chemotherapy treatment.

Only three threshold concentrations were used. Was this method sensitive enough?

In taste and evaluation section is corrected the mistake, there was not 3 but 5 concentration threshold. (Page 5, paragraph 3, line 1) “Five concentrations were dissolved in distilled water from each of the three taste study substances, including sucrose (3.5-15.5 µmol/ml), urea (91-115 µmol/ml), and sodium glutamate (0.3-2.7 µmol/ml”).

What is meant by ‘hedonic responses’ and how were they measured?

We discarded information about hedonic responses in order to avoid confusion in results.

Data Analysis
Specify which variables were analysed by which method?

We completed Data analysis section (Page 6, paragraph 2, line 1) “Student t test was employed for continuous variables, the Mann-Whitney U test and Fisher’s exact test was employed for non-parametric variables, while the chi square test was utilized for nominal variables. All statistical analyses were carried out with SPSS/PC v. 15.0 program software (SPSS, Inc., Chicago, IL, USA)”.

Results
That ‘some subjects had no perception or recognition threshold at any concentration’ suggests a floor effect and a major methodological flaw (see above)!

Unami taste is difficult to recognize and to be described. People are not used to identify this new flavor as the basic ones (bitter, sweet, salty and acid). This is why some subjects had no perception or recognition threshold at any concentration (we added this paragraph in discussion) (Page 8, paragraph 3, line 1) “This novel substance is difficult to recognize and to be described; people mentioned it as a different unrecognizable flavor, different from water, and were not able to identify this new perception as a basic taste one. This is why some subjects had no
detection or recognition threshold at any concentration.”. We also eliminated table that used to be number 3 that describe this differences.

Where there any baseline dietary or sensory measures taken prior to chemotherapy?

The aim of this study was to determine the existence of taste disorders in cancer patients treated with chemotherapy. Baseline taste were not made in this first study. As said in discussion more studies are required to determine the cause of this disorders, in whom baseline characteristics are going to be important.

Strange that there were no differences in dietary intakes at baseline, unless these measures were taken prior to chemotherapy?

In studied population there were no statistical differences between cases and controls in calories and nutriments intake, this could be secondary to the good performance status in included patients (ECOG 0-1) and the exclusion of gastrointestinal cancer. Nutriments and calories patients intake is affected by taste disorders as showed in tables 4 and 5. This concludes that taste disorders are important adverse factors for diet consumption. This explanation was added to discussion section . (Page 9, paragraph 3, line1) “Calories and nutrient intake did not show statistical differences between cases and controls in our studied population, this could be due to a good performance status in included patients (ECOG 0-1) and the exclusion of individuals with gastrointestinal cancer”.

Tables need more information as to when (what stage in the research process) the data were collected.
Tables 2, 3, 4, 5 and 6: What test/s were used?

Corrections are done. (Pages 15-20)

Discussion
Explore the significance of lower zinc intake among the cancer group?

We added a possible explanation in discussion section (Page 10, paragraph 2, line 1) “Zinc deficiency have been associated in some studies with taste Zinc deficiency has been associated with taste disorders in some experiences [41-46], but other studies have not confirmed this findings [47, 48]. A possible explanation has been described: Drugs that cause hypogeusia have a sulphydryl group in their structures; this component is known to bind and chelate heavy metal ions like zinc [16]. In the present
study, zinc consumption was not significantly different between cases and controls. However, cases with higher sweet RT exhibited significantly less zinc consumption than patients with lower thresholds; these data might suggest some relationship between high sweet RT and low zinc intake.

Was the cancer the problem or the chemotherapy?

The aim of this study was to determine the existence of a relationship between energy and nutrient consumption with chemosensory changes in cancer patients under chemotherapy treatment, so, it doesn’t answer that question. More prospective studies are needed including basal information about taste disorders and same information after chemotherapy.

The methodological weaknesses of the research do not appear to be addressed in the discussion.

We included in discussion (Page 10, paragraph 4, line1) “Methodological weaknesses of this research include: Variability in cancer types and chemotherapy drugs used; and the absence of basal taste disorder evaluation before chemotherapy treatment, and for establishing a causal association between chemotherapy and taste disorders. Continuing research is required to develop better understanding of the nature, frequency, severity, and duration of taste alterations and their significance in food consumption and malnutrition in those patients with cancer under chemotherapy”.