UCSF UC San Francisco Previously Published Works

Title

Fatigue, Stress, and Functional Status are Associated With Taste Changes in Oncology Patients Receiving Chemotherapy

Permalink https://escholarship.org/uc/item/3vk6h3dt

Journal Journal of Pain and Symptom Management, 62(2)

ISSN 0885-3924

Authors

Joseph, Paule V Nolden, Alissa Kober, Kord M <u>et al.</u>

Publication Date

2021-08-01

DOI

10.1016/j.jpainsymman.2020.11.029

Peer reviewed



HHS Public Access

J Pain Symptom Manage. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Author manuscript

J Pain Symptom Manage. 2021 August ; 62(2): 373–382.e2. doi:10.1016/j.jpainsymman.2020.11.029.

Fatigue, Stress, and Functional Status Are Associated with Taste Changes in Oncology Patients Receiving Chemotherapy

Paule V. Joseph, CRNP, PhD¹, Alissa Nolden, PhD², Kord M. Kober, PhD³, Steven M. Paul, PhD³, Bruce A. Cooper, PhD³, Yvette P. Conley, PhD⁴, Marilyn J. Hammer, RN, PhD⁵, Fay Wright, RN, PhD⁶, Jon D. Levine, MD, PhD⁷, Christine Miaskowski, RN, PhD^{3,7}

¹Sensory Science & Metabolism Unit, Biobehavioral Branch, Division of Intramural Research, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

²Department of Food Science, College of Natural Sciences, University of Massachusetts, Amherst, MA

³Department of Physiological Nursing, School of Nursing, University of California, San Francisco, CA

⁴School of Nursing, University of Pittsburgh, Pittsburgh, PA

⁵Dana Farber Cancer Institute, Boston, MA

⁶Rory Meyers College of Nursing, New York University, New York, NY

⁷Department of Medicine, School of Medicine, University of California, San Francisco, CA

Abstract

Context: A common complaint among oncology patients receiving chemotherapy is altered taste perception. The purpose of this study was to evaluate for differences in common symptoms and stress levels in patients who reported taste changes.

Methods: Patients were receiving chemotherapy for breast, gastrointestinal, gynecological, or lung cancer. Change in the way food tastes (CFT) was assessed using the Memorial Symptom Assessment Scale prior to the patients' second or third cycle of chemotherapy. Valid and reliable instruments were used to assess for depressive symptoms, state and trait anxiety, cognitive impairment, diurnal variations in fatigue and energy, sleep disturbance, and pain. Stress was assessed using the Perceived Stress Scale and the Impact of Events Scale-Revised. Multiple logistic regression was used to evaluate for risk factors associated with CFT.

Results: Of the 1329 patients, 49.4% reported CFT. Patients in the CFT group reported higher levels of depression, anxiety, fatigue, and sleep disturbance as well as higher levels of general and

Corresponding author: Christine Miaskowski, RN, PhD, Professor, Department of Physiological Nursing, School of Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-9407 (phone), 415-476-8899 (fax), chris.miaskowski@ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: The authors have no conflicts of interest to declare.

disease specific stress. Factors associated with CFT group included: being non-White; receiving an antiemetic regimen that contained a neurokinin-1 receptor antagonist with two other antiemetics, having a lower functional status, higher levels of morning fatigue, and reporting higher scores on the hyperarousal subscale of the Impact of Event Scale-Revised.

Conclusions: This study provides new evidence on associations between taste changes and common co-occurring symptoms and stress in oncology patients receiving chemotherapy. Clinicians need to evaluate for taste changes in these patients because this symptom can effect patients' nutritional intake and quality of life.

Keywords

taste changes; chemotherapy; stress; depression; anxiety; sleep disturbance; fatigue

Introduction

Approximately 650,000 oncology patients in the United States will receive chemotherapy in 2020.¹ Prevalence rates for self-reported taste changes associated with chemotherapy range from 12% to 84%.² Despite its common occurrence and the importance of taste perception to maintain adequate nutritional status, research on the associations between taste changes and other common co-occurring symptoms associated with the administration of chemotherapy is limited.

The etiology of taste changes associated with chemotherapy is multifactorial. Preclinical evidence suggests that chemotherapy induces apoptosis of taste receptor cells and inhibits taste progenitor/stem cell proliferation.^{3,4} In addition, chemotherapy disrupts the rapidly dividing cells in the basal layer of the taste epithelium that are responsible for taste cell renewal.^{4,5} Of note, in a study of patients with head and neck cancer who received radiation therapy with (n=21) and without (n=5) cisplatin and 5-fluorouracil,⁶ changes in expression of taste receptor genes occurred particularly in patients with mild/moderate stomatitis. These changes were associated with dysgeusia for umani and sweet tastes and phantoguesia.

While not studied in oncology patients, recent evidence suggests that taste changes are associated with the occurrence and severity of common neuropsychological symptoms (e.g., depression, anxiety, fatigue, sleep disturbance, changes in cognitive function) and several studies in the general population provide insights on these relationships. For example, in two studies of patients with major depression,^{7,8} compared to healthy controls, depressed patients required significantly higher concentrations to perceive all of the basic taste modalities (i.e., sweet, salty, sour, bitter). In another study, that used data from the National Health and Nutrition Examination Survey,⁹ the prevalence rates for alterations in taste were 19.3% and 23.7% in individuals with depressive symptoms or a major depressive disorder, respectively. In another study that evaluated for associations between alterations in taste perceptions and depressive symptoms and anxiety,¹⁰ individuals with mild subclinical depression were not able to rate changes in fat taste intensities. Individuals with a normal anxiety score had decreased perceptions of both sweet and salty tastes.¹¹ Finally, in a study that examined the relationship between taste perception and mood states in female students, ¹² higher fatigue scores and low anger scores were associated with decreased sour taste

perception. Findings regarding associations between changes in taste and sleep disturbance are inconsistent.^{13–16} While in one study, no changes were found,¹³ in two studies of healthy individuals,^{14,16} preferences for sweet taste increased. In another study,¹⁵ individuals with increased sleepiness rated taste for umami and sour taste significantly higher. Given the increasing evidence on the deleterious effects of multiple co-occurring symptoms in oncology patients,¹⁷ and emerging evidence from other populations, an evaluation of the associations between taste changes and common neuropsychological symptoms in oncology patients is warranted.

Similar to neuropsychological symptoms, taste changes can occur during situations of increased stress. While no studies of oncology patients were found, two studies have evaluated for associations between taste changes and laboratory induced-stress in healthy individuals.^{18,19} In one study,¹⁹ following the administration of a mental stressor, taste perceptions for sweet, bitter, and sour decreased. In another study,¹⁸ higher levels of acute stress were associated with decreases in sweet taste perceptions. Again, given the high levels of stress associated with a cancer diagnosis and its treatments,^{20,21} this relationship warrants evaluation in oncology patients.

Changes in patients' ability to taste can have a negative effect on their quality of life (QOL). ²² Across several studies of oncology patients receiving chemotherapy,^{23–26} decreased taste was associated with significant decrements in QOL. In addition, findings from several qualitative studies suggest that taste changes during chemotherapy have a negative impact on patient's social activities,^{27,28} as well as on their overall QOL.^{25,26,29}

In this study, we extended our prior analysis on associations between taste changes and gastrointestinal symptoms,² in a sample of oncology patients (n=1329) receiving chemotherapy and based on the lack of available evidence evaluate for associations between taste changes and common neuropsychological symptoms (i.e., depression, anxiety, fatigue, sleep disturbance, changes in cognitive function, decrements in energy, and pain) and stress. The purposes of this study were to evaluate for differences in the severity of common neuropsychological symptoms, perceived stress, and QOL outcomes between patients who did and did not report change in the way food tastes (CFT) in the week prior to their second or third cycle of chemotherapy. In addition, we determined which of these characteristics were associated with the occurrence of CFT.

METHODS

Study design and participants

Data for this analysis are from a larger longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy. Details on the methods used in this study are published elsewhere.^{30,31} In brief, patients were 18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy, were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. The

study was approved by the Committee on Human Research at the University of California at San Francisco and by the Institutional Review Board at each of the study sites. Of the 1343 patients who consented to participate, 1329 patients with data on CFT are included in this analysis.

Study procedures

A research staff member approached eligible patients in the infusion unit during their first or second cycle of chemotherapy and discussed participation in the study. Written informed consent was obtained from all of the patients. Data from the enrollment assessment that was completed during the week prior to the patients' second or third cycle of chemotherapy were used in this analysis. Medical records were reviewed for disease and treatment information.

Instruments

Demographic and clinical characteristics ----Patients completed a demographic questionnaire, the Karnofsky Performance Status scale,³² and the Self-Administered Comorbidity Questionnaire (SCQ).³³ The total SCQ score ranges from 0 to 39. In addition, they completed the Alcohol Use Disorders Identification Test³⁴ and a smoking history questionnaire.³⁵

Assessment of change in the way food tastes (CFT) ----CFT was measured using the Memorial Symptom Assessment Scale.³⁶ Patients were asked to indicate whether or not they had experienced CFT in the past week (i.e., symptom occurrence). If they experienced CFT, they rated its frequency, severity, and distress. Patients' assessment of CFT in the week prior to their second or third cycle of chemotherapy (i.e., enrollment assessment) was used to dichotomize the sample. Patients who provided a rating for occurrence, frequency, severity, and/or distress for the CFT were coded as having CFT. Patients who indicated "no" to the occurrence item were coded as not having CFT.

Assessment of common neuropsychological symptoms ----Associations between the occurrence of CFT and common neuropsychological symptoms were evaluated using a number of valid and reliable instruments. Diurnal variations in fatigue and decrements in energy were evaluated using the Lee Fatigue Scale.³⁷ State and trait anxiety were evaluated using the Spielberger State-Trait Anxiety Inventories.³⁸ Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale.³⁹ The quality of sleep was evaluated using the General Sleep Disturbance Scale.⁴⁰ Difficulties with executive function were assessed using the Attentional Function Index.⁴¹ Occurrence of pain was evaluated using the Brief Pain Inventory.⁴²

Assessment of stress — Stress was assessed using general (i.e., Perceived Stress Scale⁴³ and disease-specific (i.e., Impact of Event Scale-Revised (IES-R)⁴⁴) measures. Three subscales of the IES-R evaluate the level of intrusion, avoidance, and hyperarousal associated with cancer and its treatment. The Perceived Stress Scale evaluates stress due to life circumstances. For both instruments, a higher score indicates greater stress.

Assessment of QOL --QOL was evaluated using disease-specific (i.e., QOL-Patient Version (QOL-PV)⁴⁵) and generic (i.e., Medical Outcomes Study-Short Form-12 (SF-12)⁴⁶) measures. The QOL-PV assesses four domains of QOL (i.e., physical, psychological, social, and spiritual well-being) as well as a total QOL score. Higher scores indicate a better QOL. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The SF-12 is scored into physical component summary (PCS) and mental component summary (MCS) scores. Higher summary scores indicate a better QOL.

Coding of the emetogenicity of the chemotherapy regimens

Using the Multinational Association of Supportive Care in Cancer guidelines,⁴⁷ each chemotherapy drug in the regimen was classified as having minimal, low, moderate, or high emetogenic potential. The emetogenicity of the regimen was categorized into one of three groups (i.e., low/minimal, moderate, high) based on the chemotherapy drug with highest emetogenic potential. An exception was made if a patient received doxorubicin and cyclophosphamide. When administered separately, doxorubicin and cyclophosphamide are listed as having moderate emetogenic potential. When given together, the combination has high emetogenic potential.

Coding of the antiemetic regimens

Each antiemetic was coded as either a neurokinin-1 receptor antagonist, a serotonin receptor antagonist, a dopamine receptor antagonist, prochlorperazine, lorazepam, or a steroid. The antiemetic regimens were coded into one of four groups: none (i.e., no antiemetics administered); steroid alone or serotonin receptor antagonist alone; serotonin receptor antagonist and steroid; or neurokinin-1 receptor antagonist and two other antiemetics.

Statistical analyses

Data were analyzed using SPSS Version 26 (IBM, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. For categorical variables, nonparametric tests were used to evaluate for differences in demographic and clinical characteristics between patients who did and did not report CFT. For continuous variables, Independent Student's t-tests were done to evaluate for differences in demographic and clinical characteristics, as well as symptom severity, perceived stress, and QOL scores between patients who did and did not report CFT. To evaluate for clinically meaningful between group differences, effect sizes were determined using Cohen's d statistic.

To evaluate for associations between select demographic, clinical, neuropsychological symptom, and stress characteristics and CFT group membership, a backwards, stepwise logistic regression analysis was performed. The initial logistic regression model included all the characteristics that differed between the two CFT groups (i.e., demographic and clinical characteristics (see Supplemental Table 1), symptom severity scores (Table 1) and stress scores Table 2)). A backwards stepwise approach was used to create a parsimonious model. Only variables with a p-value of <0.05 were retained in the final model.

RESULTS

Sample characteristics

Description of this sample was previously reported² and details are provided in Supplementary Table 1. In brief, of the 1329 patients in this study, 49.4% (n=656) reported CFT in the week prior to their second or third cycle of chemotherapy.

Differences in demographic and clinical characteristics

As noted in our previous analysis,² compared with the no CTF group, patients who reported CFT had fewer years of education; were more likely to be Black or Hispanic, mixed race, or other; and had a lower annual household income. Patients in the CFT group were less likely to be employed and less likely to exercise on a regular basis. In addition, patients in the CFT group had a higher body mass index, lower Karnofsky Performance Status scores, fewer years since their cancer diagnosis, fewer prior cancer treatments, and fewer metastatic sites. Compared to the no CFT group, patients in the CFT group were more likely to have breast cancer, received chemotherapy on a 14-day cycle, had a higher MAX2 score, received highly emetogenic chemotherapy, and were more likely to receive an antiemetic regimen that contained a neurokinin-1 receptor antagonist and two other antiemetics (Supplementary Table 1).

Differences in symptom severity

Compared to the no CFT group, patients in the CFT group had significantly higher depression, trait anxiety, state anxiety, sleep disturbance, as well as morning and evening fatigue scores, and lower attentional function and morning energy scores (Table 1).

Differences in stress scores

Compared to the no CFT group, patients in the CFT group reported a significantly higher Perceived Stress Scale score. Patients in the CFT group reported significantly higher IES-R subscale (i.e., intrusion, avoidance, and hyperarousal) and total scores (Table 2).

Differences in QOL outcomes

Compared to the no CFT group, patients in the CFT group reported significantly lower physical, psychological, and social well-being, as well as total QOL-PV scores. For the SF-12, compared to the no CFT group, patients in the CFT group had significantly lower PCS and MCS scores (Table 3).

Logistic regression analysis of factors associated with CFT group membership

As shown in Table 4, the overall logistic regression model was significant (X^2 =107.72, p<0.001). Six variables were retained in the final model, namely self-reported ethnicity, Karnofsky Performance Status score, cancer diagnosis, antiemetic regimen, morning fatigue score, and the IES-R hyperarousal subscale score. In terms of functional status, patients with higher Karnofsky Performance Status scores had a decrease in the odds of being in CFT group (OR=0.98; p=0.004). With regards to ethnicity, compared to Whites, Blacks (OR=1.89; p=0.014) had an increased odds of being in CFT group and patients of Hispanic,

Page 7

mixed race, or other (OR=1.62; p=0.018) had increased odds of being in CFT group. In terms of cancer diagnosis, compared to patients with breast cancer, patients with lung (OR=0.60; p=0.016) and gynecological (OR=0.64; p=0.014) cancers had a decrease in the odds of being in CFT group. In terms of the antiemetic regimen, compared to patients who did not receive any antiemetic, patients who received a neurokinin-1 receptor antagonist and two other antiemetics had an increased odds of being in the CFT group (OR=2.39; p=0.001). Higher morning fatigue (OR=1.10; p=0.003) and higher hyperarousal (OR=1.26; p=0.034) scores were associated with an increase in the odds of being in the CFT group.

DISCUSSION

To our knowledge, this study is the first to evaluate for associations between demographic and clinical characteristics, as well as common neuropsychological symptoms (i.e., depression, anxiety, fatigue, sleep disturbance, changes in cognitive function, decrements in energy, pain) and stress and the occurrence of CFT in oncology patients undergoing chemotherapy. In addition, this study is the first to evaluate for differences in both generic and disease-specific measures of QOL in patients who did and did not report CFT. The results of the logistic regression analysis provide new insights into risk factors associated with CFT.

The only demographic characteristic that remained significant in the multivarible model was ethnicity. Consistent with a previous report from the general United States population that found that a higher percentage of African Americans reported taste changes,⁴⁸ patients who were Black, Hispanic, or of a mixed ethnic background were more likely report CFT. As noted in the previous study, reasons for these differences are not readily apparent.

Several clinical characteristics were associated with the occurrence of CFT. While no studies have documented an association between poorer functional status and taste changes, previous studies of oncology patients found that lower functional status scores were associated with a higher symptom burden,⁴⁹ reduced tolerance to chemotherapy,⁵⁰ and higher levels of distress.⁵¹ Consistent with our previous report,² compared to the patients with lung and gynecological cancers, patients with breast cancer had an increased risk of being in the CFT group. While previous studies described taste changes in patients with breast,^{23,26,52,53} lung,^{54,55} and gynecological^{26,56} cancers, no studies have evaluated for differences across diagnoses. Given that the various chemotherapy regimens may have differential inflammatory effects on the gastrointestinal tract, future studies are warranted that evaluate for differences in taste changes and other gastrointestinal symptoms (e.g., mucositis) within and across cancer diagnoses and chemotherapy regimens.

The type of antiemetic regimen is another characteristic that was retained in the final regression model in our previous² and current report. In the current study, being prescribed a neurokinin-1 receptor antagonist with two other antiemetics was associated with a 2.39-fold increased risk of being in the CFT group (the OR in the previous study was 2.51). As noted previously,² both the neurokinin-1 and serotonin receptor antagonists have direct effects on gastrointestinal motility and taste perceptions.^{57–62}

For patients in the taste change group, all of the symptom severity scores were near or above the clinically meaningful cut-off scores, which suggests a relatively high symptom burden. In the univariate analyses, except for evening energy, all of the other symptom severity scores were significantly higher in the patients who reported taste changes. These between group differences represent clinically meaningful differences in the severity of depressive symptoms (d=0.32), cognitive impairment (d=0.33), and morning fatigue (d=0.39).⁶³ However, morning fatigue was the only symptom that remained significant on the multivariable model with each one unit increase on the fatigue scale being associated with a 1.10 increase in the odds of being in the CFT group. Our finding is consistent with a previous report that identified taste changes as part of a fatigues/anorexia-cachexia symptom cluster in patients with advanced cancer.⁶⁴ The relationship between fatigue and taste changes warrants additional investigation given that athletes experience changes in taste sensitivity associated with profound physical fatigue following vigorous exercise.⁶⁵

Another new and emerging hypothesis for chemotherapy-induced taste changes, as well as for associations between taste changes and common neuropsychological symptoms in oncology patients is the activation of the microbiota-brain-gut axis (MBGA).^{66,67} The MBGA is a bi-directional biochemical signaling pathway between the central nervous system and the gastrointestinal system that includes the gut microbiota.⁶⁸ Like the tongue, the gastrointestinal system is capable of sensing nutrients and toxins through similar taste receptors and signaling mechanisms.^{69,70} For example, while sweet taste begins at the tongue, sugar molecules can activate sensors in the gut that send direct signals to the brain that create a preference for sugar.⁷⁰ In addition, nutrients in the intestinal lumen are detected by specific taste sensors that respond to sweet, umami, and bitter compounds, as well as both long- and short-chain fatty acids.^{71,72} Likewise, the gut microbiota plays a role in shaping neural development, brain biochemistry, and behavior.⁷³ Disruptions in these communication pathways contribute to the development of obesity,⁷⁴ psychiatric disorders, and cancer.⁷⁵

Oncology patients undergoing chemotherapy experience a significant amount of stress.²⁰ In this study, the mean Perceived Stress Scale score for the taste change group was above the clinically meaningful cut-off score of 14⁷⁶ and the mean IES-R total score approached the clinically meaningful cut-off score of 24.77,78 While all of the general and disease specific stress scores were higher in the patients with CFT, only the IES-R-hyperarousal subscale score remained significant in the logistic regression analysis. Patients who reported higher levels of hyperarousal had an increased risk of being in the CFT group. This subscale of the IES-R evaluates difficulty concentrating, anger and irritability, psychophysiologic vigilance arousal on exposure to reminders, and hypervigilance and is often used as a proxy measure for post-traumatic stress. While no studies were found that evaluated for associations between taste changes and stress in oncology patients, one of the physiologic responses to acute stress is altered food and energy intake including weight loss and weight gain.^{79,80} These stress-induced changes are modulated by the release of neurotransmitters from the hypothalamic-pituitary-adrenal axis. Of note, both noradrenaline and serotonin are involved in taste signaling.⁸¹ Serotonin and noradrenaline can effect taste cell excitability by altering the function of ion channels.^{82,83} As noted in one study,⁸⁴ taste changes are often reported by patients with chronic conditions that are characterized by changes in the release of

serotonin and noradrenaline (e.g., depression, anxiety disorder). Given that high levels of stress, depressive symptoms, and anxiety are common in oncology patients, our findings suggest that these co-occurring symptoms may contribute to the taste changes associated with the administration of chemotherapy.

Consistent with previous reports that found that alterations in taste perceptions were associated with decrements in oncology patients' QOL,^{85,86} patients in our study who reported taste changes had statistically significant and clinically meaningful decrements in all of the QOL-PV subscale (except spiritual well-being) and total scores (d=0.25 to 0.44).⁶³ In addition, these patients had PCS and MCS scores that were below the normative score of 50 for the United States population.⁸⁷

Several limitations warrant consideration. Given that an evaluation of taste changes was not done prior to the administration of chemotherapy, future studies need to perform this evaluation and track changes in taste over time. Because a change in taste was measured using a single item on the Memorial Symptom Assessment Scale (i.e., "change in the way food tastes") and may be interpreted by patients in a variety of ways (e.g., change in the flavor of food), future studies need to assess changes in both taste and smell using subjective and objective measures. Given the complex interactions among common neuropsychological and gastrointestinal symptoms, as well as stress, longitudinal studies are needed to assess for causal mechanisms. In addition, an evaluation of genetic and epigenetic markers may help to identify potential biological mechanisms.

Despite these limitations, findings from this study and our previous study,² suggest that the co-occurrence of gastrointestinal symptoms and common neuropsychological symptoms are associated chemotherapy-induced CFT. Clinicians need to assess for all of these symptoms and evaluate their impact on patients' nutritional intake, functional status, and QOL. Depending on the severity of their impact, patients may warrant referrals for symptom management, psychological services, dietary counseling, and/or physical therapy. These findings provide guidance for future studies that need to explore the associations among and mechanisms that underlie these multiple co-occurring symptoms in patients undergoing chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

This study was supported by a grant from the National Cancer Institute (CA134900). Dr. Miaskowski is an American Cancer Society Clinical Research Professor. Dr.Joseph is supported by the National Institute of Nursing Research (1ZIANR000035-01), the National Institutes of Health (NIH) Office of Workforce Diversity, the NIH Distinguished Scholars Award, and the Rockefeller University Heilbrunn Nurse Scholar Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

REFERENCES

 Centers for Disease Control. Preventing Infections in Cancer Patients 2019. Available from: https:// www.cdc.gov/cancer/preventinfections/providers.htm. Accessed 01/28, 2020.

- Nolden A, Joseph PV, Kober KM, et al. Co-occurring gastrointestinal symptoms are associated with taste changes in oncology patients receiving chemotherapy. J Pain Symptom Manage 2019;58:756– 765. [PubMed: 31349034]
- 3. Hovan AJ, Williams PM, Stevenson-Moore P, et al. A systematic review of dysgeusia induced by cancer therapies. Support Care Cancer 2010;18:1081–1087. [PubMed: 20495984]
- Mukherjee N, Pal Choudhuri S, Delay RJ, Delay ER. Cellular mechanisms of cyclophosphamideinduced taste loss in mice. PloS one 2017;12:e0185473–e0185473. [PubMed: 28950008]
- 5. Mukherjee N, Delay ER. Cyclophosphamide-induced disruption of umami taste functions and taste epithelium. Neuroscience 2011;192:732–745. [PubMed: 21782899]
- Tsutsumi R, Goda M, Fujimoto C, et al. Effects of chemotherapy on gene expression of lingual taste receptors in patients with head and neck cancer. Laryngoscope 2016;126:E103–109. [PubMed: 26422579]
- Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. Biol Psychiatry 1987;22:1481–1485. [PubMed: 3676376]
- Steiner JE, Rosenthal-Zifroni A, Edelstein EL. Taste perception in depressive illness. The Isr Ann Psychiatr Relat Discip 1969;7:223–232. [PubMed: 5274360]
- 9. Hur K, Choi JS, Zheng M, Shen J, Wrobel B. Association of alterations in smell and taste with depression in older adults. Laryngoscope Investig Otolaryngol 2018;3:94–99.
- Platte P, Herbert C, Pauli P, Breslin PAS. Oral perceptions of fat and taste stimuli are modulated by affect and mood induction. PLOS ONE 2013;8:e65006. [PubMed: 23755167]
- 11. Ileri-Gurel E, Pehlivanoglu B, Dogan M. Effect of acute stress on taste perception: in relation with baseline anxiety level and body weight. Chem Senses 2013;38:27–34. [PubMed: 22944612]
- Karita K, Harada M, Yoshida M, Kokaze A. Factors associated with dietary habits and mood states affecting taste sensitivity in Japanese college women. J Nutr Sci Vitaminol 2012;58:360–365. [PubMed: 23327972]
- Hogenkamp PS, Nilsson E, Chapman CD, et al. Sweet taste perception not altered after acute sleep deprivation in healthy young men. Somnologie - Schlafforschung und Schlafmedizin 2013;17:111–114.
- 14. Szczygiel EJ, Cho S, Tucker RM. Multiple dimensions of sweet taste perception altered after sleep curtailment. Nutrients 2019;11:2015.
- Lv W, Finlayson G, Dando R. Sleep, food cravings and taste. Appetite 2018;125:210–216. [PubMed: 29447996]
- Smith SL, Ludy M-J, Tucker RM. Changes in taste preference and steps taken after sleep curtailment. Physiol Behav 2016;163:228–233. [PubMed: 27184237]
- 17. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. J Natl Cancer Inst 2017;109.
- Al'Absi M, Nakajima M, Hooker S, Wittmers L, Cragin T. Exposure to acute stress is associated with attenuated sweet taste. Psychophysiology 2012;49:96–103. [PubMed: 22091733]
- Nakagawa M, Mizuma K, Inui T. Changes in taste perception following mental or physical stress. Chem Senses 1996;21:195–200. [PubMed: 8670698]
- Langford DJ, Cooper B, Paul S, et al. Distinct stress profiles among oncology patients undergoing chemotherapy. J Pain Symptom Manage 2020;59:646–657. [PubMed: 31711968]
- 21. Jakovljevic K, Kober KM, Block A, et al. Higher levels of stress are associated with a significant symptom burden in oncology outpatients receiving chemotherapy. J Pain Symptom Manage 2020.
- 22. Lindley C, McCune JS, Thomason TE, et al. Perception of chemotherapy side effects cancer versus noncancer patients. Cancer Practice 1999;7:59–65. [PubMed: 10352062]
- 23. de Vries YC, Boesveldt S, Kelfkens CS, et al. Taste and smell perception and quality of life during and after systemic therapy for breast cancer. Breast Cancer Res Treat 2018;170:27–34. [PubMed: 29476290]
- Brisbois TD, de Kock IH, Watanabe SM, Baracos VE, Wismer WV. Characterization of chemosensory alterations in advanced cancer reveals specific chemosensory phenotypes impacting dietary intake and quality of life. J Pain Symptom Manage 2011;41:673–683. [PubMed: 21276701]

- 25. Zabernigg A, Gamper E-M, Giesinger JM, et al. Taste alterations in cancer patients receiving chemotherapy: a neglected side effect? Oncologist 2010;15:913–920. [PubMed: 20667968]
- 26. Gamper E-M, Giesinger JM, Oberguggenberger A, et al. Taste alterations in breast and gynaecological cancer patients receiving chemotherapy: prevalence, course of severity, and quality of life correlates. Acta Oncologica 2012;51:490–496. [PubMed: 22129358]
- 27. de Vries YC, Helmich E, Karsten MDA, et al. The impact of chemosensory and food-related changes in patients with advanced oesophagogastric cancer treated with capecitabine and oxaliplatin: a qualitative study. Support Care Cancer 2016;24:3119–3126. [PubMed: 26919988]
- Bernhardson B-M, Tishelman C, Rutqvist LE. Chemosensory changes experienced by patients undergoing cancer chemotherapy: A qualitative interview study. J Pain Symptom Manage 2007;34:403–412. [PubMed: 17616338]
- 29. Ponticelli E, Clari M, Frigerio S, et al. Dysgeusia and health-related quality of life of cancer patients receiving chemotherapy: A cross-sectional study. Eur J Cancer Care 2017;26:e12633.
- Papachristou N, Puschmann D, Barnaghi P, et al. Learning from data to predict future symptoms of oncology patients. PloS one 2018;13:e0208808. [PubMed: 30596658]
- 31. Kober KM, Cooper BA, Paul SM, et al. Subgroups of chemotherapy patients with distinct morning and evening fatigue trajectories. Supportive Care Cancer 2016;24:1473–1485.
- 32. Karnofsky D Performance scale, New York: Plenum Press, 1977.
- Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49:156–63. [PubMed: 12687505]
- 34. Babor TF, Higgins-Biddle J, Saunders J, Monteiro M. The alcohol use disorders identification test (AUDIT): Guidelines for use in primary care. In: World Health Organization, Department of Mental Health and Substance Abuse, 2001.
- Kozlowski LT, Porter CQ, Orleans CT, Pope MA, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. Drug Alcohol Depend 1994;34:211–216. [PubMed: 8033758]
- Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer 1994;30:1326–1336.
- Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991;36:291–298. [PubMed: 2062970]
- 38. Spielberger CG, Gorsuch RL, Suchene R, Vagg PR, Jacobs GA. Manual for the state-anxiety (Form Y): Self Evaluation Questionnaire, Palo Alto, CA: Consulting Psychologists Press.
- 39. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1977;1:385–401.
- 40. Lee KA. Self-reported sleep disturbances in employed women. Sleep 1992;15:493–8. [PubMed: 1475563]
- Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index--a self-report cognitive measure. Psychooncology 2011;20:194–202. [PubMed: 20213858]
- 42. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17:197–210. [PubMed: 6646795]
- 43. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385–396. [PubMed: 6668417]
- 44. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979;41:209–218. [PubMed: 472086]
- Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. Qual Life Res 1995;4:523–531. [PubMed: 8556012]
- 46. Ware J Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233. [PubMed: 8628042]
- 47. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Annals Oncol 2016;27:v119–v133.

- 48. Liu G, Zong G, Doty RL, Sun QJBO. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study. BMJ Open 2016;6:e013246.
- Whitson HE, Sanders LL, Pieper CF, et al. Correlation between symptoms and function in older adults with comorbidity. J Am Geriatr Soc 2009;57:676–682. [PubMed: 19392960]
- 50. Chen H, Cantor A, Meyer J, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer 2003;97:1107–1114. [PubMed: 12569613]
- Barbaglia G, ten Have M, van Dorsselaer S, et al. Low functional status as a predictor of incidence of emotional disorders in the general population. Qual Life Res 2015;24:651–659. [PubMed: 25231202]
- 52. Steinbach S, Hummel T, Bohner C, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 2009;27:1899–905. [PubMed: 19289621]
- 53. Boltong A, Aranda S, Keast R, et al. A prospective cohort study of the effects of adjuvant breast cancer chemotherapy on taste function, food liking, appetite and associated nutritional outcomes. PLoS One 2014;9:e103512. [PubMed: 25078776]
- 54. Belqaid K, Orrevall Y, McGreevy J, et al. Self-reported taste and smell alterations in patients under investigation for lung cancer. Acta Oncol 2014;53:1405–1412. [PubMed: 24702121]
- 55. Belqaid K, Tishelman C, Orrevall Y, Månsson-Brahme E, Bernhardson BM. Dealing with taste and smell alterations-A qualitative interview study of people treated for lung cancer. PLoS One 2018;13:e0191117. [PubMed: 29360871]
- Nishijima S, Yanase T, Tsuneki I, Tamura M, Kurabayashi T. Examination of the taste disorder associated with gynecological cancer chemotherapy. Gynecol Oncol 2013;131:674–678. [PubMed: 24060414]
- Dill MJ, Shaw J, Cramer J, Sindelar DK. 5-HT1A receptor antagonists reduce food intake and body weight by reducing total meals with no conditioned taste aversion. Pharmacol Biochem Behav 2013;112:1–8. [PubMed: 24064183]
- Grant J Tachykinins stimulate a subset of mouse taste cells. PLoS One 2012;7:e31697. [PubMed: 22363709]
- 59. Huang AY, Wu SY. Substance P as a putative efferent transmitter mediates GABAergic inhibition in mouse taste buds. Br J Pharmacol 2018;175:1039–1053. [PubMed: 29328505]
- 60. Jaber L, Zhao FL, Kolli T, Herness S. A physiologic role for serotonergic transmission in adult rat taste buds. PLoS One 2014;9:e112152. [PubMed: 25386961]
- Larson ED, Vandenbeuch A, Voigt A, et al. The role of 5-HT3 receptors in signaling from taste buds to nerves. J Neurosci 2015;35:15984–15995. [PubMed: 26631478]
- 62. Onaga T Tachykinin: recent developments and novel roles in health and disease. Biomol Concepts 2014;5:225–243. [PubMed: 25372755]
- Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:371–383. [PubMed: 11936935]
- Walsh D, Rybicki L. Symptom clustering in advanced cancer. Support Care Cancer 2006;14:831– 836. [PubMed: 16482450]
- 65. Narukawa M, Ue H, Morita K, et al. Change in taste sensitivity to sucrose due to physical fatigue. Food SciTechn Res 2009;15:195–198.
- Bajic JE, Johnston IN, Howarth GS, Hutchinson MR. From the bottom-up: chemotherapy and gutbrain axis dysregulation. Front Behav Neurosci 2018;12:104. [PubMed: 29872383]
- Jordan KR, Loman BR, Bailey MT, Pyter LM. Gut microbiota-immune-brain interactions in chemotherapy-associated behavioral comorbidities. Cancer 2018;124:3990–3999. [PubMed: 29975400]
- Wang H-X, Wang Y-P. Gut Microbiota-brain Axis. Chinese Medical Journal 2016;129:2373–2380. [PubMed: 27647198]
- 69. McIntyre JC, Thiebaud N, McGann JP, Komiyama T, Rothermel M. Neuromodulation in chemosensory pathways. Chem Senses 2017;42:375–379. [PubMed: 28379355]
- 70. Tan H-E, Sisti AC, Jin H, et al. The gut-brain axis mediates sugar preference. Nature 2020.

- Raka F, Farr S, Kelly J, Stoianov A, Adeli K. Metabolic control via nutrient-sensing mechanisms: role of taste receptors and the gut-brain neuroendocrine axis. Am J Physiol Endocrinol Metab 2019;317:E559–E572. [PubMed: 31310579]
- 72. Baj A, Moro E, Bistoletti M, et al. Glutamatergic signaling along the microbiota-gut-brain axis. Int J Mol Sci 2019;20.
- 73. Shen HH. News Feature: Microbes on the mind. PNAS 2015;112:9143. [PubMed: 26221006]
- 74. Gutierrez R, Fonseca E, Simon SA. The neuroscience of sugars in taste, gut-reward, feeding circuits, and obesity. Cell Mol Life Sci 2020;77:3469–3502. [PubMed: 32006052]
- 75. Di Y-Z, Han B-S, Di J-M, Liu W-Y, Tang Q. Role of the brain-gut axis in gastrointestinal cancer. World J Clin Cases 2019;7:1554–1570. [PubMed: 31367615]
- Hewitt PL, Flett GL, Mosher SW. The Perceived Stress Scale Factor structure and relation to depression symptoms in a psychiatric sample. J Psychopathol Behav Assess 1992;14:247–257.
- 77. Asukai N, Kato H, Kawamura N, et al. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. J Nerv Ment Dis 2002;190:175–182. [PubMed: 11923652]
- 78. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale Revised. Behav Res Ther 2003;41:1489–1496. [PubMed: 14705607]
- 79. Godos J, Currenti W, Angelino D, et al. Diet and mental health: Review of the recent updates on molecular mechanisms. Antioxidants (Basel) 2020;9.
- Steiger H, Booij L. Eating disorders, heredity and environmental activation: Getting epigenetic concepts into practice. J Clin Med 2020;9.
- Roper SD. Taste buds as peripheral chemosensory processors. Semin Cell Dev Biol 2013;24:71– 79. [PubMed: 23261954]
- Herness S, Zhao FL, Kaya N, et al. Adrenergic signalling between rat taste receptor cells. J Physiol 2002;543:601–614. [PubMed: 12205193]
- Huang YA, Maruyama Y, Roper SD. Norepinephrine is coreleased with serotonin in mouse taste buds. J Neurosci 2008;28:13088–13093. [PubMed: 19052199]
- 84. Heath TP, Melichar JK, Nutt DJ, Donaldson LF. Human taste thresholds are modulated by serotonin and noradrenaline. J Neurosci 2006;26:12664–12671. [PubMed: 17151269]
- Epstein JB, Phillips N, Parry J, et al. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplantation 2002;30:785–792. [PubMed: 12439702]
- Alvarez-Camacho M, Gonella S, Ghosh S, et al. The impact of taste and smell alterations on quality of life in head and neck cancer patients. Qual Life Res 2016;25:1495–1504. [PubMed: 26589527]
- Ware JE Jr., Kosinski M, Bayliss MS, et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33:AS264–279. [PubMed: 7723455]

Table 1.

Differences in Symptom Severity Scores Between Patients With and Without Change in the Way Food Tastes

Symptom	Clinically Meaningful Cut-off Scores	No Taste Changes With Taste Changes 50.6% (n = 673) 49.4% (n = 65			
		Mean (SD)	Mean (SD)		
CES-D score	16.0	11.3 (9.1)	14.4 (10.0)	t = -5.95, p < 0.001	
Trait Anxiety Inventory score	32.2	34.0 (10.2)	36.3 (10.7)	t = -4.01, p < 0.001	
State Anxiety Inventory score	31.8	32.6 (11.6)	35.1 (13.0)	t = -3.64, p < 0.001	
Attentional Function Index score	<5 Low 5 – 7.5 Moderate >7.5 High	6.7 (1.7)	6.1 (1.8)	t = 5.56, p < 0.001	
General Sleep Disturbance Scale	43.0	50.1 (20.4)	55.0 (19.7)	t = -4.37, p < 0.001	
Morning fatigue score (LFS)	3.2	2.7 (2.1)	3.6 (2.3)	t = -7.28, p < 0.001	
Evening fatigue score (LFS)	5.6	5.1 (2.1)	5.6 (2.1)	t = -4.43, p < 0.001	
Morning energy score (LFS)	6.2	4.6 (2.2)	4.2 (2.2)	t = 3.03, p = .003	
Evening energy score (LFS)	3.5	3.6 (2.0)	3.5 (2.1)	t = 1.74, p = 0.082	
Percentage of patients with pain (%, n)		70.6 (471)	75.1 (488)	FE, p = 0.073	

Abbreviations: CES-D = Center for Epidemiological Studies-Depression Scale, FE = Fisher's Exact, LFS = Lee Fatigue Scale, SD = standard deviation

Table 2.

Differences in Stress Scores Between Patients With and Without Change in the Way Food Tastes

Instrument	No Taste Changes 50.6% (n = 673)	With Taste Changes 49.4% (n = 656)	Statistics
	Mean (SD)	Mean (SD)	Staustics
Perceived Stress Scale score	17.67 (8.06)	19.30 (8.23)	t = -3.60, p < 0.001
IES-R subscale scores			
Intrusion	0.83 (0.68)	0.98 (0.74)	t = -3.78, p < 0.001
Avoidance	0.88 (0.63)	1.01 (0.71)	t = -3.22, p < 0.001
Hyperarousal	0.56 (0.61)	0.75 (0.70)	t = -5.09, p < 0.001
IES-R total score	17.15 (12.01)	20.47 (13.95)	t = -4.54, p < 0.001

Abbreviations: IES-R = Impact of Event Scale-Revised, SD = standard deviation

Table 3.

Differences in Quality of Life Scores Between Patients With and Without Change in the Way Food Tastes

Instrument	No Taste Changes 50.6% (n = 673)	With Taste Changes 49.4% (n = 656)	Start and an
	Mean (SD)	Mean (SD)	Statistics
Quality of Life – Patient Version			
Physical well-being	7.0 (1.7)	6.2 (1.8)	t = 8.91, p < 0.001
Psychological well-being	5.7 (1.8)	5.2 (1.8)	t = 5.26, p < 0.001
Social well-being	6.0 (2.0)	5.5 (2.0)	t = 4.75, p < 0.001
Spiritual well-being	5.4 (2.1)	5.5 (2.0)	t = -1.58, p = 0.114
Total QOL score	6.0 (1.4)	5.5 (1.4)	t = 5.89, p < 0.001
Short Form 12 Health Survey			
PCS score	42.4 (10.7)	40.0 (10.3)	t = 4.12, p < 0.001
MCS score	50.4 (9.9)	47.5 (10.8)	t = 4.86, p < 0.001

Abbreviations: MCS = Mental Component Summary, PCS = physical component summary, QOL = quality of life, SD = standard deviation

Table 4.

Multiple Logistic Regression Analysis Predicting Change in the Way Food Tastes Group Membership

Predictor	Odds Ratio (95% CI)	p-value
Karnofsky Performance Status score	0.98 (0.97, 0.99)	0.004
Ethnicity		
Asian or Pacific Islander vs. White	1.43 (0.98, 2.08)	0.065
Black vs. White	1.89 (1.14, 3.15)	0.014
Hispanic, Mixed Race, or Other vs White	1.62 (1.09, 2.41)	0.018
Cancer diagnosis		
Gastrointestinal vs. breast	0.99 (0.74, 1.34)	0.971
Gynecological vs. breast	0.64 (0.45, 0.92)	0.014
Lung vs. breast	0.60 (0.39, 0.91)	0.016
Antiemetic regimen		
Steroid alone or serotonin receptor antagonist alone vs. none	1.24 (0.73, 2.10)	0.425
Serotonin receptor antagonist and steroid vs. none	1.34 (0.82, 2.20)	0.247
NK-1 receptor antagonist and two other antiemetics vs. none	2.39 (1.41, 4.05)	0.001
Morning fatigue score	1.10 (1.03, 1.18)	0.003
Impact of Event Scale-Revised - Hyperarousal subscale score	1.26 (1.02, 1.57)	0.034
Overall model fit: degrees of freedom = 12; $X^2 = 107.72$, p < 0.0	01	