HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2019 October ; 28(10): 1652–1659. doi: 10.1158/1055-9965.EPI-19-0128.

Pre-treatment dietary patterns are associated with the presence of nutrition impact symptoms 1-year after diagnosis in patients with head and neck cancer

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Abstract

Background—Dietary inflammatory potential could impact the presence and severity of chronic adverse treatment effects among head and neck cancer (HNC) patients. The objective of this study was to determine if pre-treatment dietary patterns are associated with nutrition impact symptoms (NIS) as self-reported 1-year after diagnosis.

Methods—This was a longitudinal study of 336 newly diagnosed HNC patients enrolled in the University of Michigan Head and Neck Specialized Program of Research Excellence. Principal component analysis was utilized to derive pre-treatment dietary patterns from food frequency questionnaire (FFQ) data. Burden of seven NIS was self-reported 1-year after diagnosis. Associations between pre-treatment dietary patterns and individual symptoms and a composite NIS symptom summary score were examined with multivariable logistic regression models.

Results—Two dietary patterns emerged: Prudent and Western. After adjusting for age, smoking, BMI, tumor site, stage, calories and HPV-status, significant inverse associations were observed between the Prudent pattern and difficulty chewing (OR 0.44; 95% CI 0.21–0.93; P=0.03), dysphagia of liquids (OR 0.38; 95% CI 0.18–0.79; P=0.009), dysphagia of solid foods (OR 0.46; 95% CI 0.22–0.96; P=0.03), mucositis (OR 0.48; 95% CI 0.24–0.96; P=0.03) and the NIS summary score (OR 0.45; 95% CI 0.22–0.94; P=0.03). No significant associations were observed between the Western pattern and NIS.

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Conflict of Interest

The authors declare no potential conflicts of interest.

Conclusion—Consumption of a Prudent diet prior to treatment may help reduce the risk of chronic NIS burden among HNC survivors.

Impact—Dietary interventions are needed testing whether consumption of a Prudent dietary pattern before and during HNC treatment results in reduced NIS burden.

Keywords

symptom burden; diet; prudent; western; cancer survivors

Introduction

Head and neck cancer (HNC) accounted for an estimated 65,000 new diagnoses in men and women in the United States in 2019, resulting in roughly 14,260 deaths (https://www.cancer.net/cancer-types/head-and-neck-cancer/statistics). HNC is a heterogeneous disease typically including epithelial malignancies of the oral cavity, oropharynx, hypopharynx, and larynx of the squamous cell histologic type [1]. HNC was historically associated with extensive exposure to tobacco and alcohol consumption. However, high-risk human papillomavirus (HPV) has emerged as the primary etiologic factor for a subset of oropharyngeal tumors [2–4]. HNC patients develop severe morbidities before and/or during treatment as a result of tumor location, treatment with radiation therapy, or surgical resection of the tumor [5]. Many of these morbidities compromise food intake, and thus are termed nutrition impact symptoms (NIS).

Notably, at least 90% of HNC develop NIS during the acute phase of treatment [6, 7]. However, NIS that persist chronically (>6 months post-treatment) are understudied [5, 6, 8]. Common NIS experienced by HNC patients include trismus, xerostomia, dysphagia, difficulty chewing, taste alterations and mucositis [5]. One study conducted among HNC patients reported that aggregate burden of NIS was a significant independent predicator of reduced food intake, weight loss and survival [9]. Other consequences of NIS include poor oral hygiene, prolonged eating time, disruption of relationships and social isolation, depression and decreased quality of life [10]. Since NIS burden can result in significantly reduced dietary intake and quality of life there is an urgent need for early and effective NIS prevention and intervention.

While previous work has established that the presence of NIS is associated with decreased food intake and weight loss [8, 11–14], no studies have examined how pre-treatment dietary intake may influence the presence of NIS later in the disease trajectory. The pathogenesis of NIS are complex and differ depending on the symptom, but generally share one common mechanism—cell damage due to inflammation [15, 16]. Our research team has previously reported a whole foods pre-treatment dietary pattern, characterized by high intakes of vegetables, fruits, poultry, legumes, fish, wine, and whole grains, to be associated with lower HNC recurrence and mortality [17], as well as decreased markers of systemic inflammation, specifically TNF-α, IL-6, and IFN-γ [18]. Diet has the potential to reduce inflammation and affect biological processes involved in the pathogenesis of symptoms common in HNC patients [18]. Many nutrients and phytochemicals found in foods have been long known to have anti- or pro-inflammatory properties [19, 20]. It is possible consumption of foods

abundant in nutrients that modulate inflammation prior to treatment may influence the development and/or severity of NIS throughout the disease trajectory. Thus, the objective of this secondary analysis of a longitudinal cohort was to determine if pre-treatment dietary patterns are associated with the presence of self-reported NIS 1-year after diagnosis. The hypothesis was that a dietary pattern characterized by foods with anti-inflammatory properties (eg, fruits, vegetables, whole-grains, low-fat dairy and less saturated fat) before treatment would be associated with lower risk of self-reported chronic NIS. On the other hand, we hypothesized that a dietary pattern characterized by foods with pro-inflammatory properties (eg, red and processed meats, fried foods) before treatment would be associated with higher risk of self-reported chronic NIS.

Subjects and methods

Design

This secondary analysis included 336 HNC patients enrolled in the University of Michigan Head and Neck Specialized Program of Research Excellence (HN-SPORE) prospective cohort study. The independent variable of interest included dietary patterns at diagnosis. Variables controlled for (covariates) were age, tumor site, cancer stage, smoking, body mass index (BMI), calories and HPV status. The dependent variables were individual and aggregated NIS 1-year post-diagnosis.

Study population

Between November 2008 and July 2013, all patients who were newly diagnosed with a previously untreated, primary squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx were invited to participate in the University of Michigan Head and Neck Specialized Program of Research Excellence (UM HN-SPORE) prospective cohort study. Patients were recruited from UM otolaryngology, radiation oncology and dental clinics. Institutional Review Board approval was obtained from the UM Health System (Ann Arbor, MI). Exclusion criteria included: 1) less than 18 years of age; 2) pregnancy; 3) non–English speaking; 4) diagnosis of mental instability; 5) diagnosis of another non–upper aero-digestive tract cancer or 6) non-squamous cell carcinoma. All participants of the original cohort who had completed a pre-treatment (i.e., after diagnosis but prior to starting treatment) food frequency questionnaire (FFQ) matched with 1-year self-reported NIS data were included in the current analysis. No exclusions were made based on primary treatment goal or modality since any instance of being bothered by NIS is important to consider for palliative and supportive care, regardless of whether or not a patient is being treated with curative intent.

Of the original 1,031 participants enrolled, 489 had complete pre-treatment FFQ data. Participants were excluded if they were missing 1-year NIS data (n = 137) or data on key covariates planned to be used in multivariable models (n = 3 missing BMI). Participants were also excluded if they reported and estimated daily energy intake of <500 (kcals)/day or >5,000 kcals/day (n = 13). Any reported energy intake <500 or >5,000 kcals/day is considered biologically implausible and thus these observations are likely unreliable [21, 22]. The final sample size included 336 participants.

Procedures

Participants completed a self-administered epidemiologic health questionnaire at baseline (i.e., after diagnosis but prior to starting treatment) that included data on demographic, clinical and behavioral characteristics including tobacco, alcohol, physical activity, sleep, comorbidities, depression and quality of life. Dietary data were obtained at diagnosis using the self-administered 2007 Harvard FFQ [23]. An electronic medical record (EMR) review was conducted for each participant to collect data on tumor site, cancer stage and treatment modalities.

Measures

Predictor: Dietary Patterns—Usual dietary intake over the past year was estimated using the 131-item self-administered, semi-quantitative 2007 Harvard FFQ, a valid and reproducible measure of usual dietary intake [21, 24, 25]. The Harvard FFQ allows participants to choose the average frequency of consumption of food items over the past year on a Likert scale with choices ranging by individual questions. The FFQ includes standard portion sizes for each item [e.g. 1 apple, 3 oz. chicken, 2 slices bacon]. Total energy and nutrient intake was estimated by summing intakes from each food based on the selected standard portion size, reported frequency of consumption, and nutrient content of each food item [17]. Daily food group servings were estimated by summing the frequency weights of each food item based on reported daily frequencies of consumption [17, 21]. FFQs were classified *a priori* into 39 food/food groups using methods described in similar studies [17, 26, 27]. Principal component analysis (PCA) was used to derive pre-treatment dietary patterns as in previous studies of dietary patterns and cancer outcomes in this HNC cohort [2, 17].

Covariates—Age was modeled as a continuous variable. Smoking and drinking status was categorized as current/former vs. never smoked, where “current” status reflects use in the 12 months prior to cancer diagnosis. BMI (kg/m2) at diagnosis was calculated based on self-reported height and weight measures, which were previously reported to be well correlated (r=0.98) with clinically measured height and weight in this patient population [17]. BMI was categorized into four groups: 1) underweight (<18.5 kg/m2); 2) normal weight (18.5 – 24.9 kg/m2); 3) overweight (25.0 – 29.9 kg/m2); and 4) obese (≥30 kg/m2). Tumor site was recorded from operative notes and surgical pathology forms and categorized into four groups: 1) oral cavity; 2) oropharynx; 3) hypopharynx; and 4) larynx. Tumor, node, metastases (TNM) cancer stages were classified according to the American Joint Committee on Cancer (AJCC) VII edition and converted to stage I-IV groupings. To increase the statistical power of stage-wise comparisons, stage was categorized *a priori* for analyses as I-III vs. IV. Since NIS burden is likely to be greatest among those who receive radiotherapy, treatment modality was categorized into two groups- radiation vs. no radiation. One hundred and seventy participants had tumor tissue available for HPV testing from biopsy or surgical resection. Validated PCR methods were used to determine HPV-status, as previously described [28]. Participants with equivocal or missing HPV status were given a status of “unknown”. HPV status was categorized into three groups: 1) HPV-positive; 2) HPV-negative; or 3) unknown for statistical analyses.

Outcome variable: NIS 1-year post-diagnosis—NIS were measured using the UM Head and Neck Quality of Life questionnaire, a validated and multidimensional instrument to assess head and neck cancer-related functional status and well-being [29]. Self-reported NIS were assessed at the pre-treatment time-point and again 1-year post-diagnosis using a Likert scale ranging from "1: not at all bothered" by symptom to "5: extremely bothered". Symptom scores were dichotomized as "not at all" vs. "slightly – extremely" bothered. The research team agreed it was essential to dichotomize symptoms in this manner as sensitivity to symptoms likely varies among individuals and thus any degree of being bothered by symptoms should be considered significant. Data on seven NIS were reported, including trismus, xerostomia, dysphagia of liquids, dysphagia of solid foods, difficulty chewing, taste and mucositis. A study specific overall NIS summary score (sum of seven symptoms, range 7–34) was derived. The continuous NIS summary score was dichotomized as <13 vs. ≥13, the median and mean in the dataset. The research team selected all six symptoms from the head and neck quality of life eating domain in addition to one symptom in the pain domain (mucositis) to create the NIS summary score, as these symptoms are most likely to impact dietary intake.

Statistical analysis

Descriptive statistics (means and frequencies) were generated for all demographic, epidemiologic and clinical variables. Multivariable logistic regression models were used to examine the associations between derived dietary patterns (fit by quartiles of exposure) and each of the individual seven symptoms, as well as the dichotomous NIS summary score. Covariates were chosen *a priori* based on variables known or hypothesized to be associated with dietary intake and NIS. Covariates considered for inclusion in the final models were age, sex, pre-treatment NIS, tumor site, cancer stage, pre-treatment smoking status, pre-treatment drinking status, treatment modality, total calories, HPV status and pre-treatment BMI. Tests for collinearity were performed among all potential covariates. The final multivariable models were adjusted for age, smoking status, BMI, tumor site, cancer stage, HPV status, and total calories. As sex, drinking status, and treatment modality were found to be highly correlated with other covariates, these variables were excluded from the final model to prevent issues of collinearity. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for each quartile (Q) of dietary pattern score compared with the lowest, Q1. Additionally, a test for trend across increasing quartile of intake was performed by setting each individual's dietary pattern score to the median for that quartile and treating it as a continuous variable.

When performing sub analyses, simple models with fewer covariates (age, smoking status, cancer stage and tumor site) were used due to statistical power considerations. To assess the potential for effect measure modification, stratification analyses by smoking status (current/former and never smoked), stage (I-III and IV), treatment (radiation and no radiation), and BMI (underweight/normal weight and overweight/obese) were considered. To examine the robustness of results, sensitivity analyses were conducted in which NIS burden was modeled as a continuous variable and also dichotomized as "not at all – slightly bothered" vs. "moderately – extremely bothered". In an effort to examine the potential for reverse causation (i.e., that participants with higher NIS at diagnosis would prevent patients from

eating normally), sensitivity analyses were conducted in which the associations between pre-treatment dietary patterns and pre-treatment NIS (as opposed to 1-year NIS) were examined in multivariable models. The addition of pre-treatment NIS as a covariate in all primary multivariable models was also tested. All statistical analyses were performed in SAS 9.4 (SAS Institute Inc.) [30]. P values < 0.05 were considered statistically significant.

Results

Overall epidemiological characteristics of the study population are shown in Table 1. The mean age for study participants was 60 years. The vast majority of participants were white males. The most common tumor location was the oropharynx. HPV positive tumors were confirmed in 21% of the population in which 83% were tumors of the oropharynx. More than half the tumors were stage IV. Approximately 70% and 93% of study participants were current or formers smokers and alcohol users, respectively. Roughly 67% of the population was overweight or obese at diagnosis. Select characteristics of the study participants, according to self-reported NIS burden are shown in Table 2. Participants with a lower NIS summary score were more likely to be diagnosed with stage I-III cancers, have tumors located in the oral cavity or larynx, treated without radiation and never smokers.

Two major dietary patterns emerged from PCA. The first pattern, termed the Prudent dietary patterns, was characterized by high intakes of fruit, vegetables, whole-grains, low-fat dairy, legumes and less saturated fat. The second pattern, termed the Western dietary pattern, was characterized by high intakes of red and processed meats, refined grains, potatoes, French fries, high-fat dairy, condiments, desserts, snacks, and sugar-sweetened beverages. The factor-loading matrix for the two dietary patterns is presented in Supplemental Table 1.

ORs and 95% CI corresponding to the magnitude of associations for the pre-treatment Prudent dietary pattern score and self-reported 1-year post-diagnosis NIS burden dichotomized as “not at all” vs. “slightly – extremely bothered” are reported in Table 3. After adjusting for age, tumor site, cancer stage, smoking, BMI, calories and HPV status, significant inverse associations were observed between pre-treatment Prudent pattern score and dysphagia of liquids, dysphagia of solid foods, difficulty chewing, and mucositis at 1-year post-diagnosis. A statistically significant inverse association was observed between the dichotomized NIS summary score and the Prudent pattern. No significant associations were observed between the Western pattern and NIS burden.

Results of sub analyses stratified by smoking status, cancer stage, and BMI for the NIS summary score are displayed in Table 4. A significant inverse association between Prudent dietary pattern score NIS was observed in never smokers, but the association for current/former smokers was not significant. A significant inverse association between Prudent dietary pattern score NIS was observed in those who were underweight or normal weight at diagnosis, but the association for those overweight or obese at diagnosis was not significant. Parameter estimates for sub analyses stratified for treatment and cancer stage were not significantly different from the estimates for the overall population.

Results of sensitivity analyses, where NIS was modeled as a continuous variable and individual NIS were dichotomized as “not at all – slightly bothered” vs. “moderately – extremely bothered” were consistent with all primary results: difficulty chewing (OR 0.44; 95% CI 0.21–0.95; *P*=0.03), dysphagia of liquids (OR 0.19; 95% CI 0.05–0.67; *P*=0.009), dysphagia of solid foods (OR 0.22; 95% CI 0.09–0.50; *P*=0.0004), dichotomized NIS summary score (OR 0.37; 95% CI 0.17–0.76; *P*=0.006), continuous NIS summary score (OR 2.52; 95% CI 1.40–4.54; *P*=0.002). The exception was mucositis, which was no longer statistically significant (Supplemental Table 2). The addition of pre-treatment NIS to the original multivariable models as a covariate did not significantly alter parameter estimates: difficulty chewing (OR 0.42; 95% CI 0.18–0.97; *P*=0.04), dysphagia of liquids (OR 0.35; 95% CI 0.15–0.79; *P*=0.01), dysphagia of solid foods (OR 0.35; 95% CI 0.15–0.80; *P*=0.01), dichotomized NIS summary score (OR 0.24; 95% CI 0.11–0.53; *P*=0.0004), continuous NIS summary score (OR 2.97; 95% CI 1.58–5.56; *P*=0.0007) (Supplemental Table 3). Sensitivity analyses examining associations between pre-treatment prudent dietary score and individual pre-treatment NIS (as opposed to 1-year NIS) yielded null results, with the exception of trismus (OR 0.33; 95% CI 0.12–0.89; *P*=0.03) (Supplemental Table 4).

Discussion

In this prospective cohort study of newly diagnosed HNC patients, high intake of a pre-treatment Prudent dietary pattern was associated with lower risk of self-reported NIS at 1-year post-diagnosis. Stratified analyses suggest possible effect modification by smoking status and BMI. While previous studies have assessed the acute relationship of NIS burden on general dietary intake [31] in HNC patients, this is the first study to prospectively examine associations between pre-treatment dietary patterns and self-reported NIS burden beyond the acute phase of treatment.

In the early 2000s, it was hypothesized that antioxidant supplementation during radiotherapy may protect normal cells from reactive oxygen species (ROS) damage, allowing for better tolerance of treatment and higher dosage without adverse toxicities [32]. Based on this hypothesis, two previous double-blind, placebo controlled randomized clinical trials (RCT) were conducted to test high-dose antioxidant supplementation with β-carotene and α-tocopherol in HNC patients during radiation [33, 34]. Both RCTs resulted in reduced treatment toxicity but one was discontinued early due to increased recurrence and mortality with supplementation while the other showed a non-significant increase in mortality with supplementation [33, 34]. The authors concluded that the high-dose antioxidant supplements may have reduced the therapeutic efficacy of radiotherapy by quenching radiation-induced ROS intended to damage cancer cells [33, 34]. On the other hand, the results of the current study suggest that a dietary pattern consisting of whole foods abundant in antioxidants and phytochemicals may offer a promising strategy for reducing treatment-related toxicities without also reducing overall prognosis. In fact, previous research from the UM HN-SPORE cohort provided evidence that the Prudent pattern may improve recurrence and survival [17, 35]. Future RCTs should be developed that test interventions focusing on soft/cooked vegetables, smoothies and other foods characterizing the Prudent pattern prepared in a way that is easier for this population to chew and swallow.

No associations were found between NIS and the Western dietary pattern score. This was surprising as previous research has suggested the Western dietary pattern to be pro-inflammatory and inflammation is a common shared etiologic factor involved in the pathogenesis of these symptoms [18]. A possible explanation may be that after diagnosis, patients are motivated to change their diet to a seemingly “healthier” one consisting of fruits, vegetables, low-fat dairy and plant-based proteins, counteracting potential pro-inflammatory effects of Western pattern foods. Future research should focus on how dietary patterns may change after HNC diagnosis and the associated outcomes.

In stratified analyses, there was a suggestion of effect measure modification by smoking status and BMI. For those who have never smoked, the Prudent dietary pattern was statistically associated with decreased NIS summary score burden but the association was diminished in current and former smokers. It is possible that a high Prudent dietary pattern in current and former smokers may not offer the protective potential needed to prevent chronic NIS. Previous research suggests that cigarette smoke may result in increased metabolic turnover, with antioxidant micronutrients expended in response to increased oxidative stress. Alternatively, smoking may decrease micronutrient absorption. Regardless, ever smokers have lower levels of circulating antioxidant micronutrients and may require additional micronutrient intake than never smokers prior to observing protective benefits [36, 37].

The Prudent dietary pattern was significantly inversely associated with the NIS summary score for under/normal weight patients but not for overweight or obese patients. Patients with a lower BMI at diagnosis may experience greater NIS burden and thus be more likely to benefit from a Prudent dietary pattern. This hypothesis is consistent with Table 2, which shows that the mean NIS summary score was lower among patients diagnosed who were overweight/obesity at diagnosis as compared to those who were under/normal weight. In sub analyses stratified by treatment modality, it was surprising that radiation status did not modify the association between Prudent dietary pattern and NIS especially considering chronic radiation associated dysphagia is often a complication following HNC radiotherapy [38].

Our study is not without fault. Dietary patterns and NIS burden relied on self-report and may be vulnerable to measurement error and systematic biases. For instance, the potential presence of NIS at diagnosis may influence pre-treatment dietary intake, leading to recall bias when reporting usual diet from the past year. While there is a high prevalence of acute toxicity in HNC patients, our research team was unable to assess acute associations of dietary patterns with NIS burden; these data were only collected at pre-treatment and 1-year in this survival cohort. Lastly, while the NIS examined were from a validated quality of life questionnaire, the NIS summary score was created for this specific analysis and is not validated.

It is important to note that the observational study design does not prove causality and thus reverse causality cannot be ruled out. However, if reverse causality were present, we hypothesize a significant inverse association would have been observed for the Western dietary pattern and NIS. Observing significant inverse association with both dietary patterns

might provide stronger evidence for reverse causation- that is that a lack of NIS leads to higher reported dietary pattern scores, in general, simply because the patient is able to consume more food. Sensitivity analysis assessing pre-treatment diet and pre-treatment NIS were null. Further, results of sensitivity analyses modeling NIS burden in different ways (i.e., continuous summary score and individual NIS dichotomized as “not at all – slightly” vs. “moderately – extremely bothered”) remained statistically significant, supporting the robustness of the observed associations.

To our knowledge, this was the only study in HNC survivors to date examining the associations between pre-treatment dietary patterns and chronic NIS burden. Strengths of this analysis include the prospective, longitudinal design and ability to control for multiple confounding factors. Results of this analysis may be generalizable to other predominately non-Hispanic white HNC survivors.

In conclusion, consumption of a pre-treatment Prudent diet classified by high intakes of fruit, vegetables, whole grains, low-fat dairy, and legumes may help reduce the risk of chronic NIS such as difficulty chewing, dysphagia of liquids, dysphagia of solids foods, and mucositis 1-year after diagnosis in HNC survivors. The results may be modified by smoking status and BMI. This study provides evidence that consuming whole foods abundant in antioxidants may be an efficacious and safe alternative to reducing treatment toxicities compared to the high-dose antioxidant supplements that were tested in the early 2000s. Future research should utilized RCT designs to test whether increasing consumption of foods characterizing the Prudent pattern before and during HNC treatment results in reduced NIS and improved survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the patients, clinicians, and principal investigators of the individual projects at the UM Head and Neck SPORE program, who provided access to the longitudinal clinical database and were responsible for the recruitment, treatment, and follow-up of patients included in this report. These investigators included Avraham Eisbruch, Theodore Lawrence, Mark Prince, Jeffrey Terrell, Shaomeng Wang, and Frank Worden.

Funding

NIH/NCI P50CA097248 was awarded to G. Wolf. USDA National Institute of Food and Agriculture, Hatch project 1011487 was awarded to Anna Arthur. SLC was supported by a Carle-Illinois Cancer Scholars for Translational and Applied Research Fellowship and an Academy of Nutrition and Dietetics Colgate Palmolive Fellowship in Nutrition and Oral Health.

Abbreviation List

(HNC)	Head and neck cancer
(NIS)	nutrition impact symptoms
(FFQ)	food frequency questionnaire

(HPV)	human papillomavirus
(HN-SPORE)	University of Michigan Head and Neck Specialized Program of Research Excellence
(BMI)	body mass index
(EMR)	electronic medical record
(PCA)	principal component analysis
(AJCC)	American Joint Committee on Cancer
(OR)	odds ratios
(CI)	confidence intervals
(Q)	quartile
(ROS)	reactive oxygen species
(RCT)	randomized clinical trials

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Table 1:

Overall demographic, behavioral and clinical characteristics (N=336)

Characteristic	N (%)	Prudent Diet Quartile 1 N=74 (%)	Prudent Diet Quartile 4 N=88 (%)	Western Diet Quartile 1 N=87 (%)	Western Diet Quartile 4 N=74 (%)
Age (y)					
Mean ± SD	60.40 ± 10.85	57.79 ± 10.68	61.04 ± 8.70	61.38 ± 11.98	60.31 ± 9.85
Range	68	52	41	68	48
Sex					
Male	260 (77.4)	62 (83.8)	64 (72.7)	58 (66.7)	59 (79.7)
Female	76 (22.6)	12 (16.2)	24 (27.3)	23 (33.3)	15 (20.3)
Marital Status					
Not married	91 (27.2)	26 (35.1)	17 (19.3)	23 (26.7)	23 (31.1)
[a]Married	244 (72.8)	48 (64.9)	71 (80.7)	63 (73.3)	51 (68.9)
Education					
High school or less	103 (30.7)	36 (48.7)	15 (17.1)	26 (30.2)	32 (43.2)
Some college or more	232 (69.25)	38 (51.3)	73 (82.9)	60 (69.8)	42 (56.8)
[b]Race					
Non-Hispanic white	322 (97.0)	70 (95.9)	86 (97.7)	82 (97.6)	72 (97.3)
Other	10 (3.0)	3 (4.1)	2(2.3)	2 (2.4)	2 (2.7)
[c]BMI (kg/m^2)					
Underweight (<18.5)	13 (3.9)	8 (10.8)	1 (1.1)	3 (3.4)	4 (5.4)
Normal weight (18.5–24.9)	97 (28.9)	20 (27.0)	28 (31.8)	22 (25.3)	20 (27.1)
Overweight (25–29.9)	132 (39.2)	23 (31.1)	33 (37.5)	38 (43.7)	22 (29.7)
Obese (30+)	94 (28.0)	23 (31.1)	26 (29.6)	24 (27.6)	28 (37.8)
Site					
Oral cavity	110 (32.7)	21 (28.4)	24 (27.3)	35 (40.2)	20 (27.0)
Oropharynx	155 (46.1)	33 (44.6)	48 (54.5)	39 (44.8)	32 (43.3)
Hypopharynx	4 (1.2)	1 (1.3)	0 (0.0)	1 (1.2)	2 (2.7)
Larynx	67 (20.0)	19 (25.7)	16 (18.2)	12 (13.8)	20 (27.0)
Stage					
I	68 (20.2)	12 (16.2)	17 (19.3)	23 (26.4)	9 (12.1)
II	40 (11.9)	9 (12.2)	6 (6.8)	11 (12.6)	7 (9.5)
III	46 (13.7)	12 (16.2)	10 (11.4)	12 (13.8)	15 (20.3)
IV	182 (54.2)	41 (55.4)	55 (62.5)	41 (47.2)	43 (58.1)
HPV Status					
HPV- negative	101 (30.0)	27 (36.5)	22 (25.0)	28 (32.2)	27 (36.5)
HPV- positive	69 (20.5)	11 (14.9)	23 (26.1)	16 (18.4)	16 (21.6)
Unknown	166 (49.5)	36 (48.6)	43 (48.9)	43 (49.4)	31 (41.9)
Treatment					

Characteristic	N (%)	Prudent Diet Quartile 1 N=74 (%)	Prudent Diet Quartile 4 N=88 (%)	Western Diet Quartile 1 N=87 (%)	Western Diet Quartile 4 N=74 (%)
Surgery only	82 (24.4)	16 (21.6)	22 (25.0)	23 (26.5)	15 (20.2)
Radiation only	28 (8.3)	6 (8.1)	7 (8.0)	9 (10.3)	4 (5.4)
Surgery + radiation or chemoradiation	58 (17.3)	16 (21.6)	9 (10.2)	13 (14.9)	17 (23.0)
Chemoradiation only	150 (44.6)	32 (43.2)	45 (51.1)	38 (43.7)	34 (46.0)
Chemotherapy only	7 (2.1)	1 (1.4)	3 (3.4)	0 (0.0)	3 (4.1)
Palliative or unknown	11 (3.3)	3 (4.1)	2 (2.3)	4 (4.6)	1 (1.3)
[c]Smoking Status					
Current	112 (33.3)	39 (52.7)	26 (29.5)	17 (19.5)	33 (44.6)
Former	123 (36.6)	19 (25.7)	36(40.9)	31 (35.6)	29 (39.2)
Never	101 (30.1)	16 (21.6)	26 (29.5)	39 (44.8)	12 (16.2)
[c]Drinking Status					
Current	239 (71.1)	54 (73.0)	67 (76.1)	61 (70.1)	52 (70.3)
Former	74 (22.0)	17 (22.9)	15 (17.1)	16 (18.4)	18 (24.3)
Never	23 (6.9)	3 (4.1)	6 (6.8)	10 (11.5)	4 (5.4)

[a]n=1 missing

[b]n=4 missing

[c]pre-treatment measure

Table 2:

Select characteristics by 1-year NIS Summary Score (N=336)

	NIS Summary Score (7–34)	
Characteristic	**Mean (SD)**	**P-Value[a]**
Age		0.10
< 65 years	14.41 (6.06)	
≥ 65 years	13.28 (5.84)	
Sex		0.20
Male	13.78 (5.67)	
Female	14.78 (6.96)	
[b] *Marital Status*		0.002
Married	13.41 (5.59)	
Not Married	15.64 (6.75)	
Education		0.0004
High school or less	15.76 (6.39)	
Some college or more	13.25 (5.67)	
Site		0.03
Oral cavity	12.23 (5.5)	
Oropharynx	14.83 (5.75)	
Hypopharynx	13.25 (3.77)	
Larynx	12.23 (5.54)	
Stage		0.001
Stage I-III	12.86 (6.07)	
Stage IV	14.98 (5.76)	
[c] *BMI*		0.11
Underweight	16.31 (5.62)	
Normal weight	14.75 (6.65)	
Overweight	13.18 (5.22)	
Obese	14.10 (6.25)	
HPV Status		0.35
HPV Negative	14.67 (6.54)	
HPV Positive	14.09 (5.67)	
HPV Unknown	13.58 (5.78)	
Treatment		0.0009
No Radiation	12.36 (5.96)	
Radiation	14.71 (5.89)	
[c] *Smoking Status*		0.01
Current Smoker	15.31 (6.60)	

	NIS Summary Score (7–34)	
Characteristic	**Mean (SD)**	**P-Value**[a]
Former Smoker	13.82 (5.80)	
Never Smoked	12.80 (5.27)	
[c]*Drinking Status*		0.12
Current Drinker	13.62 (5.80)	
Former Drinker	15.24 (5.92)	
Never Drank	14.17 (7.81)	
Prudent Dietary Pattern		0.01
Q1	16.09 (6.37)	
Q2	13.67 (5.59)	
Q3	13.20 (6.11)	
Q4	13.41 (5.64)	
Western Dietary Pattern		0.32
Q1	13.68 (6.17)	
Q2	13.49 (5.62)	
Q3	13.94 (5.93)	
Q4	15.12 (6.29)	

[a]ANOVA with continuous NIS summary score

[b]n=1 missing

[c]pre-treatment measure

Table 3:

Multivariable[a] odds ratios and 95% CI for association between pre-treatment dietary pattern scores with being **slightly to extremely** bothered by NIS at 1-year post-diagnosis

Prudent Pattern						
Symptom	**Q1**	**Q2**	**Q3**	**Q4**	**P trend**	**P_{Q4-Q1}**
Trismus	1.00	0.64 (0.32 – 1.32)	0.76 (0.37 – 1.55)	0.55 (0.26 – 1.16)	0.18	0.12
Xerostomia	1.00	0.57 (0.24 – 1.36)	0.61 (0.26 – 1.45)	0.65 (0.26 – 1.61)	0.51	0.34
Difficulty Chewing	1.00	0.81 (0.39 – 1.70)	0.68 (0.33 – 1.44)	0.44 (0.21 – 0.93)	**0.02**[b]	**0.03**[b]
Dysphagia Liquids	1.00	0.58 (0.29 – 1.15)	0.47 (0.23 – 0.96)	0.38 (0.18 – 0.79)	**0.01**[b]	**0.009**[b]
Dysphagia Solids	1.00	0.75 (0.37 – 1.51)	0.50 (0.25 – 1.01)	0.46 (0.22 – 0.96)	**0.02**[b]	**0.03**[b]
Taste	1.00	0.46 (0.21 – 0.99)	0.43 (0.20 – 0.92)	0.52 (0.23 – 1.16)	0.27	0.11
Mucositis	1.00	0.72 (0.37 – 1.41)	0.56 (0.28 – 1.11)	0.48 (0.24 – 0.96)	**0.03**[b]	**0.03**[b]
NIS Summary Score	1.00	0.60 (0.29 – 1.22)	0.39 (0.19 – 0.77)	0.45 (0.22 – 0.94)	**0.04**[b]	**0.03**[b]
Western Pattern						
Symptom	**Q1**	**Q2**	**Q3**	**Q4**	**P trend**	**P_{Q4-Q1}**
Trismus	1.00	0.77 (0.38 – 1.54)	0.69 (0.32 – 1.50)	0.67 (0.26 – 1.79)	0.48	0.42
Xerostomia	1.00	0.76 (0.34 – 1.71)	0.83 (0.33 – 2.13)	1.60 (0.44 – 5.82)	0.39	0.48
Difficulty Chewing	1.00	0.62 (0.31 – 1.23)	0.87 (0.40 – 1.90)	0.94 (0.34 – 2.60)	0.83	0.91
Dysphagia Liquids	1.00	0.98 (0.49 – 1.97)	0.93 (0.42 – 2.06)	0.40 (0.14 – 1.15)	0.07	0.09
Dysphagia Solids	1.00	0.90 (0.46 – 1.75)	0.79 (0.37 – 1.67)	0.56 (0.21 – 1.45)	0.22	0.23
Taste	1.00	0.79 (0.38 – 1.61)	0.64 (0.29 – 1.43)	0.81 (0.29 – 2.29)	0.74	0.69
Mucositis	1.00	0.55 (0.28 – 1.07)	0.73 (0.35 – 1.53)	1.39 (0.54 – 3.57)	0.24	0.49
NIS Summary Score	1.00	0.66 (0.33 – 1.31)	0.82 (0.38 – 1.73)	1.07 (0.41 – 2.77)	0.65	0.89

[a] Adjusted for age, tumor site, cancer stage, smoking status, calories, HPV status and BMI

[b] Indicates statistical significance <0.05

Table 4:

Covariate-stratified odds ratios and 95% CIs for associations between quartiles of pre-treatment prudent dietary pattern score with being slightly to extremely bothered by NIS at 1-year (N=336)

Smoking Status[a]					
Current/Former Smokers (n=235)					
Q1 (n=58)	**Q2 (n=62)**	**Q3 (n=53)**	**Q4 (n=62)**	**P_{trend}**	**P_{Q4-Q1}**
1.00	0.57 (0.27–1.24)	0.46 (0.21–1.03)	0.56 (0.26–1.24)	0.21	0.15
Non-Smokers (n=101)					
Q1 (n=16)	**Q2 (n=25)**	**Q3 (n=34)**	**Q4 (n=26)**	**P_{trend}**	**P_{Q4-Q1}**
1.00	0.28 (0.06–1.28)	0.23 (0.03–0.55)	0.14 (0.03–0.69)	**0.02**[b]	**0.01**[b]
BMI[c]					
Underweight/Normal Weight (n=110)					
Q1 (n=28)	**Q2 (n=26)**	**Q3 (n=27)**	**Q4 (n=29)**	**P_{trend}**	**P_{Q4-Q1}**
1.00	0.25 (0.07–0.96)	0.09 (0.02–0.38)	0.12 (0.02–0.51)	**0.005**[b]	**0.003**[b]
Overweight/Obese (n=226)					
Q1 (n=46)	**Q2 (n=61)**	**Q3 (n=60)**	**Q4 (n=59)**	**P_{trend}**	**P_{Q4-Q1}**
1.00	0.88 (0.37–2.05)	0.65 (0.28–1.53)	0.64 (0.27–1.50)	0.26	0.31

[a] Adjusted for age, cancer stage, tumor site

[b] Indicates statistical significance <0.05

[c] Adjusted for age, smoking status, cancer stage, tumor site