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Higher carbohydrate intake is associated with increased risk of all-cause and disease-specific mortality in head and neck cancer patients: results from a prospective cohort study

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No studies have evaluated associations between carbohydrate intake and head and neck squamous cell carcinoma (HNSCC) prognosis. We prospectively examined associations between pre- and post-treatment carbohydrate intake and recurrence, all-cause mortality, and HNSCC-specific mortality in a cohort of 414 newly diagnosed HNSCC patients. All participants completed pre- and post-treatment Food Frequency Questionnaires (FFQs) and epidemiologic surveys. Recurrence and mortality events were collected annually. Multivariable Cox Proportional Hazards models tested associations between carbohydrate intake (categorized into low, medium and high intake) and time to recurrence and mortality, adjusting for relevant covariates. During the study period, there were 70 deaths and 72 recurrences. In pretreatment analyses, high intakes of total carbohydrate (HR: 2.29; 95% CI: 1.23–4.25), total sugar (HR: 3.03; 95% CI: 1.12–3.68), glycemic load (HR: 2.10; 95% CI: 1.15–3.83) and simple carbohydrates (HR 2.26; 95% CI 1.19–4.32) were associated with significantly increased risk of all-cause mortality compared to low intake. High intakes of carbohydrate (HR 2.45; 95% CI: 1.23–4.25) and total sugar (HR 3.03; 95% CI 1.12–3.68) were associated with increased risk of HNSCC-specific mortality. In post-treatment analyses, medium fat intake was significantly associated with reduced risk of recurrence (HR 0.08; 95% CI 0.01–0.69) and all-cause mortality (HR 0.27; 95% CI 0.07–0.96). Stratification by tumor site and cancer stage in pretreatment analyses suggested effect modification by these factors. Our data suggest high pretreatment carbohydrate intake may be associated with adverse prognosis in HNSCC patients. Clinical intervention trials to further examine this hypothesis are warranted.

Introduction

Despite advances in our understanding of the biology of head and neck squamous cell carcinoma (HNSCC), 5-year survival rates of this disease have remained low (~65%) likely attributable to late detection and high rates of persistent and recurrent disease.[1,2] Previous research has suggested that a

Key words: head and neck cancer, carbohydrate, recurrence, survival, mortality, diet, nutrition, oral cancer, oropharyngeal cancer, laryngeal cancer

Abbreviations: HNSCC: head and neck squamous cell carcinoma; ; FFQ: food frequency questionnaire; GI: glycemic index; GL: glycemic load; UM HN-SPORE: University of Michigan Head and Neck Specialized Program of Research Excellence; BMI: body mass index; HR: hazard ratio; CI: confidence interval; HPV: human papillomavirus; ROS: reactive oxygen species

Additional Supporting Information may be found in the online version of this article.

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What's new?

Chowing down on carbohydrates could make things worse for those with head and neck cancer, new results show. In this prospective study, the authors collected pre- and post-treatment diet information from HNSCC patients by questionnaire, and collected recurrence and mortality data each year. They found that high pretreatment intake of total carbohydrates and total sugar were associated with increased mortality from HNSCC. Post-treatment, fat intake was associated with reduced mortality. This is the first epidemiologic study to look for an association between carbohydrate intake and HNSCC mortality.

dietary pattern characterized by high intakes of vegetables and fruits[3] and having high pretreatment serum carotenoid levels[4] are associated with more favorable HNSCC prognoses. In addition to dietary patterns and serum carotenoids, it may also be informative to investigate the associations of other aspects of diet with these outcomes in the HNSCC population. To our knowledge, macronutrient composition, carbohydrate in particular, has not yet been examined in relation to HNSCC prognosis.

The role of carbohydrate intake in cancer development and prognosis has recently become an area of interest due to a resurgence of attention on the "Warburg effect," the view that cancer cells metabolize glucose exclusively as a fuel, using aerobic glycolytic metabolism.[5] This inefficient process produces less ATP per mole of glucose than does oxidative phosphorylation.[6,7] As a result, cancer cells require high amounts of glucose to engage in mitosis and continued proliferation. The evolution of this unique metabolism may have resulted from mitochondrial damage, a universal characteristic of cancer cells that potentially renders them dependent upon glycolysis for energy production.[8] It has also been speculated that the rapid proliferation of cancer cells led to dependence upon a fuel that could double as a source of carbon for building the infrastructure of daughter cells.[6] Regardless of its origin, the dependence of cancer cells on glycolysis may make them exquisitely sensitive to an endocrine/metabolic environment that deprives them of glucose.

One potential and feasible means of creating an internal milieu that may be incompatible with cancer is to restrict dietary carbohydrates. Restriction of sugar and carbohydrate-containing foods not only stabilizes or lowers blood glucose, but also reduces circulating insulin. Because insulin facilitates glucose uptake by cancer cells, the decline in insulin may further deprive cancer cells of their sole source of fuel, leading to improved prognosis.[9] Herein, we examined associations between pre- and post-treatment total carbohydrate intake and recurrence, all-cause mortality, and HNSCC-specific mortality in a well-characterized, prospective cohort of newly diagnosed, previously untreated HNSCC patients. To our knowledge, this is the first epidemiological study to assess carbohydrate intake in relation to outcomes after HNSCC diagnosis. Our hypothesis was that we would observe higher rates of recurrence and mortality in HNSCC patients who reported consuming a diet high in total carbohydrates. We also explored other indices of carbohydrate intake for comparison, including total sugar, added sugar, natural sugar, glycemic index (GI), glycemic load (GL), starchy foods and simple carbohydrate foods, as well as total protein and total fat intake.

Subjects and Methods

Study population

This prospective cohort study used data collected as part of the University of Michigan Head and Neck Specialized Program of Research Excellence (UM HN-SPORE). From November, 2008 to August, 2012, the HN-SPORE study staff approached every newly-diagnosed, previously untreated HNSCC patient that presented at UM hospital clinics to participate. Subjects were screened for eligibility, with exclusion criteria including: (*i*) <18 years of age; (*ii*) pregnant; (*iii*) non-English speaking; (*iv*) diagnosed as mentally unstable; (*v*) diagnosed with another non-upper aerodigestive tract cancer; or (*vi*) diagnosed with any other primary HNSCC within the past 5 years. During the recruitment period, $N = 520$ provided written, informed consent for a response rate of 92%. Study activities were approved by the Institutional Review Board of the University of Michigan Medical School and carried out in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Consenting participants were asked to complete a detailed health behaviors survey upon entrance into the study and annually that collected data on demographics, epidemiologic characteristics and health behaviors. A medical chart review was conducted on each participant at baseline and updated annually to collect data on clinical variables including tumor site and stage, comorbidities, treatment modalities, recurrence and survival status. Dietary data were obtained at baseline and one year after diagnosis using the self-administered 2007 Harvard Food Frequency Questionnaires (FFQ).[10] Of the original 520 eligible participants, $N = 440$ (84.6%) completed the baseline (pretreatment) FFQ and $N = 303$ (58.3%) completed the 1-year (post-treatment) FFQ. Participants were excluded from analysis if they had left complete pages missing on the FFQ ($N = 17$ for pretreatment and $N = 24$ for post-treatment), had >70 missing items on the FFQ ($N = 1$ for pretreatment and $N = 4$ for post-treatment) or reported a total energy intake >5,000 kcals/day or <200 kcals/day ($N = 8$ for pretreatment and $N = 10$ for post-treatment). The final sample size was $N = 414$ for pretreatment analysis and $N = 265$ for post-treatment analysis.

Measures

Predictors: Carbohydrate, protein and fat intake. The semi-quantitative 2007 Harvard FFQ was used to estimate participants' usual pre- and post-treatment dietary intake of food, beverages and supplements over the past year. The reproducibility and validity of this FFQ has been previously reported.[11–13] Briefly, the FFQ was evaluated for reproducibility and validity in a large prospective male cohort and a large prospective female cohort separately. Study participants were administered the FFQ twice and completed four one-week diet records during a one year period. Correlation coefficients between energy-adjusted nutrients measured by diet records and the FFQ ranged from 0.28 to 0.86 and were reproducible from the first FFQ administration to the second. Indices of carbohydrate intake included total carbohydrate (g/day); glycemic index and load; and total, added, and natural sugar (g/day), fructose (g/day), starches (servings/day) and simple carbohydrates (servings/day). The nutrient database used to calculate nutrient intakes was developed by investigators at the Harvard T.H. Chan School of Public Health. Total sugar was defined as the sum of sucrose, fructose, lactose, glucose and maltose. Added sugar was added to the Harvard nutrient database in May 2009 using data from the USDA added sugar database.[14] Natural sugar was defined as total sugar minus added sugar. For the purpose of this analysis, starchy foods were defined as the number of servings per day of whole grains, potatoes, legumes, and other vegetables combined. Simple carbohydrate foods were defined as the number of servings per day of refined grains, desserts, and sugar sweetened beverages combined. Total protein and total fat intake (g/day) were examined individually. All nutrient variables were categorized into tertiles (high, medium, low) to maintain statistical power and for ease of interpretability.

Covariates

Demographic variables included age, sex and race. Body mass index (BMI; kg/m^2) at the time of 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.[3] Percent weight change in the year after diagnosis, also based on self-report, was categorized as gain or <2% loss, 2–10% loss and >10% loss. Tobacco use and alcohol consumption data were categorized as current, former or never, where "current" status reflects use in the 12 months prior to cancer diagnosis. Disease site categories included oral cavity ($N = 152$), oropharynx ($N = 166$), hypopharynx ($N = 10$) and larynx ($N = 86$). Clinical stage was categorized into two groups, stage I/II and stage III/IV. As previously described, an ultrasensitive method determined human papillomavirus (HPV)-status of the tumor was categorized as positive ($N = 80$), negative ($N = 117$) or unknown ($N = 217$). Depressive symptoms (yes or no) were assessed using the five-item Geriatric Depression Scale-Short Forms.[15] Comorbidities were recorded according to the Adult Comorbidity Evaluation-27 instrument and categorized into none or mild versus moderate to severe comorbidities.[16]

Outcomes

Recurrence and overall mortality

Study participants were followed longitudinally in accordance with the National Comprehensive Cancer Network guideline intervals. New tumor events and status, including recurrence, residual disease, persistent disease and second primary cancers were updated at each visit to UM clinics and annually via medical record review. Information on tumor events and status of participants who did not return to UM for surveillance after completing treatment was collected through self-report and contact with local physicians. Deaths were captured through the Social Security Death Index, yearly survey updates, notification from family or medical record reviews. When possible, cause of death was recorded. Survival time and recurrence/persistence-free time for pre-treatment analyses were calculated beginning at date of diagnosis. Survival time was censored to February 1, 2014 and recurrence-free time was censored to the last date of each participant's annual medical record review. Participants with persistent disease were assigned a recurrence-free time of one day. Participants lost to follow-up were censored to their date of last known status. To avoid immortal time bias in post-treatment analyses, survival and recurrence time were calculated beginning at the date the post-treatment FFQ was administered until the date of event or censoring. $N = 66$ participants who experienced a recurrence event prior to the date of the post-treatment FFQ were excluded from post-treatment recurrence analyses.

Statistical analysis

Descriptive statistics (means and frequencies) were generated for all demographic, clinic-pathologic and epidemiological characteristics and nutrient intakes. Univariate analyses were conducted to test for differences in intakes of nutrient variables of interest by demographic, clinic-pathologic and epidemiologic characteristics. All nutrient variables of interest were energy adjusted using the residual method. Survival time and recurrence/persistence-free time were calculated beginning at date of diagnosis.

Multivariable Cox proportional hazard models were built to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between each nutrient and recurrence, all-cause mortality, and HNSCC-specific mortality after adjusting for other prognostic factors that were selected for consideration *a priori*. All final multivariable models for pre-treatment analysis included age, stage, tumor site, HPV-status, smoking, total fruit and vegetable intake and total caloric intake. Final multivariable models for post-treatment analysis included the same variables with the addition of percent weight change. Covariates were chosen based on *a priori* knowledge of variables associated with head and neck cancer survival. Treatment modality was considered as a covariate, but ultimately excluded from final models because it is significantly correlated with tumor site (Spearman $r = 0.42$, $p < 0.001$). HRs and 95%

Table 1. Patient clinical and epidemiologic characteristics ($n = 414$)

Characteristic	Number (%)
Age [Mean (SD) and range]	60.9 (11), 25–95
Female	99 (24.0)
Non-Hispanic white	393 (94.9)
All-cause death events	70 (16.9)
HNSCC-specific death events	42 (10.1%)
Recurrence events	72 (17.4)
Persistent disease[1]	29 (7.0)
Median follow-up for survival	26 months
Baseline BMI (kg/m^2)	
Underweight (<18.5)	16 (3.9)
Normal (18.5–24.9)	131 (31.6)
Overweight (25–29.9)	157 (37.9)
Obese (30+)	110 (26.6)
Percent weight change[2]	
Gain or <2% loss	82 (30.9)
2–10% loss	85 (32.1)
>10% loss	98 (37.0)
Disease site	
Oral cavity	152 (36.7)
Oropharynx	166 (40.1)
Larynx	86 (20.8)
Hypopharynx	10 (2.4)
Clinical stage	
Stage I	75 (18.1)
Stage II	53 (12.8)
Stage III	55 (13.3)
Stage IV	231 (55.8)
Treatment	
Surgery alone	111 (26.8)
Radiation alone	32 (7.7)
Surgery + radiation	33 (8.0)
Radiation + chemotherapy	178 (43.0)
Surgery + radiation + chemotherapy	40 (9.7)
Unknown	20 (4.8)
HPV-positive[3]	80 (40.6)
Depressive symptoms	168 (40.5)
Comorbidities	
None/missing	116 (28.0)
Mild	197 (47.6)
Moderate	69 (16.7)
Severe	32 (7.73)
Tobacco status	
Never	115 (27.8)
Current (within 12 months)	155 (37.4)
Former (quit >12 months)	144 (34.8)
Alcohol use status	
Never/missing	30 (7.2)
Current (within 12 months)	288 (69.6)
Former (quit > 12 months)	96 (23.2)
Daily fruit and vegetable servings [mean (SD) and range]	3.9 (2.1), 0.1–12.5

[1]Disease considered persistent if patient never deemed disease-free.
[2]$N = 265$; Calculated as [(weight at one year – weight at baseline)/ weight at baseline] × 100.
[3]HPV-status available for $n = 197$ participants.

CIs were estimated for each tertile (medium and high intakes) compared with tertile 1 (low intake). A test for trend across increasing tertiles of intake was performed by setting each individual's nutrient value to the median for that tertile and treating it as a continuous variable in Cox regression models.

To assess potential effect modification by tumor site and disease stage, significant pretreatment associations were examined for the two most common sites, oral cavity and oropharynx separately, as well as for stages 1–3 and stage 4 separately. The study sample lacked the statistical power to examine HNSCC-specific survival stratified by tumor site or for post-treatment analyses. All statistical analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC). P values < 0.05 were considered statistically significant. No multiplicity adjustments were performed.

Results

During the longitudinal follow-up period, there were 72 recurrence events (17.4%), 70 death events from any cause (16.9%), 42 death events from HNSCC (10.1%), and median follow-up time of 26 months. Demographic, behavioral and clinical characteristics of the study population are displayed in Table 1. The mean age at diagnosis was 60.9 years old with a range 25–95. About one quarter (24%) of participants were female and the majority (94.9%) were non-Hispanic white. Nearly 65% of participants were classified as overweight or obese at the time of diagnosis, a slightly higher proportion than the 60% observed in our previous HNSCC cohort.[3] ~69% of the study population experienced ≥2% weight loss in the year following diagnosis. Most commonly diagnosed tumors were oropharynx (40.1) and stage III or IV (69.1%). Among participants with known tumor HPV-status (including all sites), 40.6% were positive. Depressive symptoms were reported among 40.5% of participants and ~25% were considered to have moderate to severe comorbidities. 72.2% of participants were current or former smokers and 92.8% reported current or former alcohol consumption.

Distributions of pretreatment and post-treatment intake of dietary variables are displayed in Supplementary Table 1. Select characteristics of the study participants, according to tertiles of pretreatment intake (low, medium and high) are shown in Table 2. Current drinkers were more likely to be in

Table 2. Selected characteristics by pretreatment nutrient intake

	Mean age	Female (%)	≤High school/GED education (%)	Mean BMI (kg/m^2)	Stage 3/4 (%)	Depressive symptoms (%)	Never smokers (%)	Alcohol use (%)
Carbohydrate								
Low	60.2	18.9	38.7	28.3	68.8	44.4	22.6	83.2
Medium	61.8	21.0	31.4	27.1	73.9	41.2	30.4	68.8
High	60.8	31.9	33.6	27.0	64.5	41.7	29.7	57.2
p-value	0.49	0.03*	0.43	0.10	0.24	0.85	0.23	<0.0001*
Total sugar								
Low	60.1	21.2	33.6	27.8	71.7	41.5	27.0	80.3
Medium	61.7	23.9	35.5	27.7	68.1	40.1	30.4	67.4
High	61.0	26.8	34.6	26.9	67.4	45.7	25.4	61.6
p-value	0.50	0.55	0.94	0.39	0.70	0.63	0.63	0.006*
Added Sugar								
Low	62.8	22.9	21.2	26.9	68.1	35.6	31.4	86.4
Medium	60.4	23.5	40.7	28.0	69.7	39.8	31.9	63.9
High	61.7	25.2	40.7	27.6	64.7	51.4	25.2	59.7
p-value	0.18	0.91	0.001*	0.32	0.70	0.04*	0.34	<0.0001*
Natural Sugar								
Low	62.0	21.8	41.2	27.4	70.6	46.4	22.7	73.1
Medium	61.3	23.7	34.2	27.3	67.2	40.9	33.1	71.2
High	61.6	26.0	27.1	27.9	64.7	38.9	32.8	65.5
p-value	0.90	0.75	0.07	0.71	0.62	0.50	0.01*	0.38
Glycemic index								
Low	62.5	31.4	35.0	27.7	67.4	40.3	27.7	61.3
Medium	61.4	17.4	29.2	27.5	70.3	43.5	26.8	75.4
High	58.9	23.2	39.4	27.2	69.6	43.4	28.3	72.5
p-value	0.02*	0.02*	0.20	0.71	0.86	0.84	0.25	0.09
Glycemic load								
Low	61.8	24.8	38.0	27.8	68.8	44.4	22.6	75.2
Medium	60.0	20.3	32.8	27.4	72.5	39.3	31.2	74.6
High	60.9	26.7	32.8	27.3	65.9	43.7	29.0	59.4
p-value	0.43	0.43	0.59	0.76	0.50	0.65	0.28	0.02*

Table 3. Multivariable time-to-event cox proportional hazards analysis for mortality and recurrence by pretreatment nutrient intake ($n = 414$)

	Low	Medium	High	p_{trend}
All-cause mortality (70 events)				
Carbohydrate	1.0	1.79 (0.93, 3.45)	2.29 (1.23, 4.25)*	0.01*
Total sugar	1.0	1.13 (0.60, 2.14)	3.03 (1.12, 3.68)*	0.02*
Added sugar	1.0	1.17 (0.59, 2.31)	1.21 (0.61, 2.40)	0.60
Natural sugar	1.0	1.38 (0.66, 2.85)	1.66 (0.77, 3.60)	0.20
Glycemic index	1.0	1.13 (0.63, 2.13)	0.78 (0.42, 1.47)	0.43
Glycemic load	1.0	1.57 (0.81, 3.02)	2.10 (1.15, 3.83)*	0.01*
Starchy foods	1.0	0.69 (0.40, 1.19)	0.46 (0.25, 0.85)*	0.09
Simple carb foods	1.0	1.94 (1.02, 3.72)*	2.26 (1.19, 4.32)*	0.02*
Protein	1.0	0.87 (0.49, 1.54)	0.99 (0.53, 1.84)	0.96
Fat	1.0	0.60 (0.33, 1.11)	0.67 (0.38, 1.20)	0.28
HNSCC-specific mortality (42 events)				
Carbohydrate	1.0	1.40 (0.58, 3.35)	2.45 (1.14, 5.27)*	0.01*
Total sugar	1.0	0.90 (0.38, 2.11)	2.07 (0.98, 4.37)	0.04*
Added sugar	1.0	1.02 (0.40, 2.59)	1.34 (0.55, 3.29)	0.51
Natural sugar	1.0	2.21 (0.81, 6.05)	2.39 (0.83, 6.90)	0.11
Glycemic index	1.0	1.12 (0.53, 2.36)	0.58 (0.25, 1.33)	0.18
Glycemic load	1.0	0.74 (0.32, 1.71)	1.32 (0.64, 2.71)	0.40
Starchy foods	1.0	0.75 (0.44, 1.30)	0.51 (0.28, 0.95)*	0.16
Simple carb foods	1.0	1.77 (0.97, 3.26)	1.77 (0.95, 3.27)	0.20
Protein	1.0	0.69 (0.31, 1.50)	1.14 (0.54, 2.43)	0.77
Fat	1.0	0.62 (0.28, 1.37)	0.68 (0.33, 1.42)	0.45
Recurrence (72 events)				
Carbohydrate	1.0	1.04 (0.57, 1.91)	1.31 (0.74, 2.33)	0.27
Total sugar	1.0	1.04 (0.56, 1.92)	1.69 (0.95, 3.00)	0.07
Added sugar	1.0	1.40 (0.70, 2.82)	1.39 (0.69, 2.82)	0.38
Natural sugar	1.0	1.87 (0.91, 3.82)	1.40 (0.63, 3.11)	0.39
Glycemic index	1.0	1.33 (0.75, 2.34)	0.81 (0.43, 1.52)	0.48
Glycemic load	1.0	0.73 (0.39, 1.36)	1.11 (0.64, 1.92)	0.73
Starchy foods	1.0	0.75 (0.44, 1.30)	0.51 (0.28, 0.95)*	0.16
Simple carb foods	1.0	1.77 (0.97, 3.26)	1.77 (0.95, 3.27)	0.20
Protein	1.0	0.75 (0.41, 1.35)	1.18 (0.66, 2.13)	0.63
Fat	1.0	0.97 (0.52, 1.79)	1.13 (0.63, 2.01)	0.45

Adjusted for age, tumor site, cancer stage, smoking, total fruit and vegetable intake, HPV-status and total caloric intake.
*Indicates significance at $p < 0.05$.

the low categories for carbohydrate, total sugar, added sugar and glycemic load. Females were significantly more likely to report in the high carbohydrate and low glycemic index categories compared to males. Mean age decreased across increasing categories of glycemic index. A smaller proportion of participants in the low added sugar category had $\leq$ a high school education and depressive symptoms.

Pretreatment results of multivariable time-to-event Cox proportional hazards analysis for recurrence, all-cause mortality, and HNSCC-specific survival are shown in Table 3. Unadjusted results for both pretreatment and post-treatment analyses are shown in Supplemental Table 2. Post-treatment results of multivariable time-to-event Cox proportional hazards models for recurrence and overall survival are displayed in Supplemental Table 3. There was a significant trend towards increased all-cause mortality with increasing pretreatment total carbohydrate intake, total sugar, glycemic load, and simple carbohydrate foods. A similar trend was observed for pretreatment total carbohydrate and total sugar intake with recurrence, but the HRs were smaller and did not

Table 4. Multivariable time-to-event cox proportional hazards analysis for all-cause mortality by pretreatment dietary intake and stratified by disease site[1] and cancer stage[2]

	Low	Medium	High	p_{trend}
Oral Cavity ($N = 152$)				
Carbohydrate	1.0	2.89 (1.02, 8.17)*	3.04 (1.12, 8.26)*	0.03*
Total sugar	1.0	1.23 (0.46, 3.28)	3.14 (1.21, 8.10)*	0.02*
Glycemic load	1.0	2.60 (0.84, 8.00)	3.38 (1.31, 8.72)*	0.01*
Starchy foods	1.0	1.30 (0.54, 3.14)	0.71 (0.23, 2.19)	0.56
Simple carb foods	1.0	3.20 (1.11, 9.27)*	3.91 (1.34, 11.39)*	0.01*
Oropharynx ($N = 166$)				
Carbohydrate	1.0	1.04 (0.28, 3.80)	1.69 (0.44, 6.49)	0.41
Total sugar	1.0	0.71 (0.22, 2.26)	1.22 (0.39, 3.76)	0.70
Glycemic load	1.0	1.67 (0.47, 5.95)	1.39 (0.35, 5.47)	0.72
Starchy foods	1.0	0.38 (0.11, 1.25)	0.56 (0.15, 2.12)	0.35
Simple carb foods	1.0	1.92 (0.56, 6.51)	1.47 (0.35, 6.17)	0.76
Stage 1–3 ($N = 183$)				
Carbohydrate	1.0	4.06 (0.98, 16.81)	5.11 (1.33, 19.68)*	0.02*
Total sugar	1.0	0.37 (0.10, 1.35)	1.80 (0.60, 5.41)	0.18
Glycemic load	1.0	5.44 (0.98, 30.24)	7.00 (1.51, 32.48)*	0.01*
Starchy foods	1.0	1.29 (0.44, 3.75)	0.89 (0.23, 3.45)	0.90
Simple carb foods	1.0	1.63 (0.43, 6.23)	1.18 (0.33, 4.19)	0.99
Stage 4 ($N = 231$)				
Carbohydrate	1.0	1.38 (0.64, 3.00)	1.86 (0.88, 3.92)	0.10
Total sugar	1.0	1.35 (0.62, 2.93)	2.27 (1.06, 4.88)*	0.03*
Glycemic load	1.0	1.36 (0.63, 2.95)	1.62 (0.77, 3.38)	0.20
Starchy foods	1.0	0.77 (0.38, 1.58)	0.43 (0.17, 1.11)	0.08
Simple carb foods	1.0	2.03 (0.94, 4.36)	2.06 (0.91, 4.67)	0.10

[1]Adjusted for age, cancer stage, smoking, total fruit and vegetable intake, HPV and total caloric intake.
[2]Adjusted for age, tumor site, smoking, total fruit and vegetable intake, HPV and total caloric intake.
*Indicates significance at $p < 0.05$.

reach statistical significance. Compared to low intake, high pretreatment intake of starchy foods was associated with reduced risk of all-cause mortality, HNSCC-specific mortality and recurrence. High intakes of carbohydrate and total sugar were significantly associated with increased risk of HNSCC-specific mortality compared to low. No other dietary variables assessed in pretreatment analyses were significantly associated with mortality or recurrence.

No dietary variables assessed in post-treatment analyses were significantly associated with mortality or recurrence and thus results are displayed in Supplemental Table 3. The exception was that compared to Low intake, Medium post-treatment intake of total fat was significantly associated with a reduction in risk of both mortality (HR 0.27; 95% CI 0.07–0.96) and recurrence (HR 0.08; 95% CI 0.01–0.69).

Results of pretreatment subanalyses that stratified by tumor site and cancer stage for significant variables are displayed in Table 4. Interestingly, statistically significant associations remained for oral cavity cancers but not for oropharyngeal cancers. Similarly, significant associations remained for stage 1–3 cancers but not stage 4 cancers. The exception was for total sugar, which was not statistically significant for stage 1–3 cases, but was significant for stage 4 cases.

Discussion

In this prospective cohort study of newly diagnosed, previously untreated HNSCC patients, we found that high pretreatment intakes of carbohydrate, total sugar, glycemic load, and simple carbohydrate foods were significantly associated with increased risk of all-cause mortality after adjusting for other known prognostic variables. Significant associations remained for pretreatment intakes of carbohydrate and total sugar when examining these variables in relation to HNSCC-specific mortality. Stratified analyses of statistically significant associations suggest potential effect modification by tumor site and cancer stage. In post-treatment analysis, medium fat intake was significantly associated with a greater reduction in risk for both mortality and recurrence. To our knowledge this is the first study to prospectively examine associations between carbohydrate intake and HNSCC recurrence and mortality.

In this study, intakes of carbohydrate and fat were independently associated with cancer outcomes. Looking across both phases (pre- and post-treatment), higher intakes of carbohydrate, total sugar, glycemic load, and simple carbohydrate foods were variably associated with greater recurrence and mortality, whereas post-treatment medium fat intake was associated with lower recurrence and mortality. These observations suggest that both restriction of dietary carbohydrate and a moderate increase in dietary fat may have independent effects, and suggest that overall macronutrient composition, rather than foods or macronutrients individually, may be relevant in determining cancer outcomes. The theoretical basis through which alteration in dietary carbohydrate or fat intake could affect cancer-related outcomes has been reviewed.[6,9] In general, higher dietary carbohydrate could provide the glucose necessary to support metabolism of cancer cells, which are obligately glycolytic. Higher carbohydrate intake also stimulates insulin secretion, which not only accelerates glucose uptake by cancer cells, but also stimulates mitogenesis. Higher fat intake could impair metabolism of cancer cells, which cannot use fat as a fuel, and would increase production of ketones, which appear to interfere with cancer cell glycolysis.[7,9]

Based on these concepts, in previous studies, a carbohydrate-restricted (ketogenic) diet was developed and tested in cancer patients and model systems.[17–20] Preclinical data support the ability of a low carbohydrate, ketogenic diet to improve survival and decrease tumor burden. In a mouse model of astrocytoma, the ketogenic diet increased apoptosis, inhibited angiogenesis, and extended survival.[21–24] In a mouse model of malignant glioma, consumption of a ketogenic diet slowed tumor growth, prevented increases in reactive oxygen species (ROS) associated with tumor growth, and shifted gene expression patterns in tumor tissue to more closely resemble those of healthy tissue.[25] These results suggest that reduced production of ROS in the tumor may limit growth and angiogenesis, processes that depend upon ROS signaling, while at the same time, promote apoptosis. The effect of the diet on gene expression in both healthy and cancerous brain tissue suggests that the anti-cancer effects of the ketogenic diet are far more extensive than simply lowering glucose.

While our data supports a potential benefit to HNSCC patients avoiding higher levels of carbohydrate intake, it cannot be used to draw conclusions related to the benefits of a ketogenic diet. In our study population the median for the low carbohydrate group was 199 g/day for pretreatment intake and 189 g/day for post-treatment intake—much higher than what is considered ketogenic ($\leq$20 g/day). However, there may be biological plausibility for benefits of the ketogenic diet in HNSCC patients in particular, since HNSCC is a highly glycolytic form of cancer.[9] The therapeutic potential of the ketogenic diet for this population has recently been reviewed.[9] In theory, the high fat (energy) content of the ketogenic would help preserve lean muscle mass in patients who have difficulty eating.[26–28] At the same time, the combination of medium fat and low sugar/carbohydrate would minimize fuel availability to the cancer cells, which are highly dependent upon glucose, and potentially inhibit cancer cell growth. While the optimal amount of carbohydrate intake requires further exploration, our results may be the first observational data in humans to support the therapeutic potential of a diet characterized by carbohydrate restriction and elevated fat intake within a population of HNSCC patients.

Associations of all post-treatment dietary variables, with the exception of medium fat intake, were null. This could be due to a lack of statistical power as a result of shorter follow-up time, smaller sample size, and fewer recurrence and mortality events. Another possible explanation is that dietary intake of carbohydrates has the greatest effect on outcomes prior to or during active oncological treatment. Further research should assess how timing of carbohydrate intake across the cancer continuum influences cancer outcomes.

In stratified analyses of statistically significant pretreatment dietary variables, there was a suggestion of effect modification by tumor site and cancer stage. Specifically, high intake of total carbohydrate, total sugar, glycemic load and simple carbohydrate foods were significantly associated with increased risk of all-cause mortality in oral cavity cancer cases but not in oropharyngeal cases. In stratified analyses by stage, high carbohydrate and glycemic load was significantly associated with increased risk of all-cause mortality in stage 1–3 cancers but not stage 4. High total sugar intake was significantly associated with higher mortality in stage 4 cancers but not stage 1–3. An explanation for these results is unclear; since the majority of oral cavity cancers are diagnosed in earlier stages, and the opposite is true for oropharyngeal cancers, it is possible that carbohydrate intake has a greater effect on the progression of earlier stage cancers than on late stage cancers. Future studies should address potential differences of the effect of carbohydrate intake on HNSCC outcomes across different tumor site and cancer stages.

Strengths of this analysis include the prospective, longitudinal design, the examination of both pre-and post-treatment dietary intake, uniform treatment regimens, the ability to investigate both all-cause mortality and HNSCC-specific mortality, and the adjustment for multiple prognostic variables, including HPV-status. Results of this analysis can be generalized to other predominately non-Hispanic White HNSCC patient populations but the generalizability to more diverse HNSCC populations is limited.

Results do need to be considered cautiously in light of some limitations. Swallowing difficulties prior to and following treatment for head and neck cancers are common and could lead to dietary alterations favoring carbohydrate and sugar intake. This would be particularly true for patients with advanced disease which comprised the majority of our cohort. Radiation therapy which is commonly used for oropharyngeal cancer treatment and as part of multimodality treatment for patients with advanced disease also significantly affects swallowing function. Additionally, it is likely a large number of patients in the study population received nutrition support in the form of liquid oral or enteral nutrition during the study period but this was not well captured by the FFQ and thus we were not able to separately analyze for liquid nutritional

supplementation in this analysis. Although results suggest reduction in risk of recurrence and mortality with medium post-treatment fat intake, the current study only investigated total fat. Future research should examine differences in association by subcategories of fat, including saturated, unsaturated, omega-3, and omega-6 fat intake. Also, the shorter follow-up time, smaller sample size, and decreased number of recurrence and survival events is a limitation of our post-treatment analyses. Finally, the FFQ is vulnerable to potential systematic biases and measurement error and the observational study design does not prove causality but merely an association between the predictors and outcomes.

In summary, this is the first epidemiologic study examining associations between carbohydrate intake and survival outcomes in HNSCC. Our findings suggest that high pretreatment intakes of total carbohydrate and total sugar may be associated with increased all-cause mortality and HNSCC-specific mortality in HNSCC patients. These associations may be modified by tumor site and cancer stage. While these results need to be interpreted with caution, these data support the development of randomized controlled trials that test the effect of limiting carbohydrate intake and/or adjusting the macronutrient composition of HNSCC patients and the magnitude of restriction/control that optimally balances patient adherence, quality of life and cancer outcomes requires further study. Prior to developing new medical nutrition therapy recommendations for HNSCC patients, translational dietary intervention research should be conducted to further elucidate the potential role of carbohydrate restriction and/or macronutrient composition on prognostic outcomes in this patient population.

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