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The association between diet quality and cancer incidence of the head and neck

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Abstract

The association between diet quality and head and neck cancer (HNC) was explored using a population-based case–control study of 1170 HNC cases and 1303 age-, race-, and sex-matched controls from the United States. Diet quality was assessed with three diet quality scores (DQS): (a) Healthy Eating Index 2005 (HEI-2005), (b) Mediterranean Diet Score (MDS), and (c) HNC-specific Mediterranean Diet Score (MDS-HNC), a modified MDS that we developed to be more applicable to HNC. Logistic regression models estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) representing diet quality–incident HNC associations. We examined effect measure modification (EMM) by body mass index (BMI), race, cigarette smoking, and alcohol consumption and associational heterogeneity by HPV-positivity and tumor site. A one standard deviation summary DQS decrement suggested a consistent inverse association (ORs (CIs)) for the HEI-2005, MDS, and MDS-HNC: 1.35 (1.21, 1.50), 1.13 (1.02, 1.25), and 1.17 (1.06, 1.31), respectively. This association did not vary by tumor site or tumor HPV status, though additive EMM by alcohol use and by BMI was observed. Our findings suggest the Mediterranean diet can be used to study HNC in American populations, and that poor diet quality elevates HNC incidence, particularly among alcohol users.

Keywords Mediterranean · Diet · Head and neck · Case–control

Introduction

Head and neck squamous cell carcinoma (HNC) includes cancer of the oral cavity, pharynx, and larynx. In the United States of America (USA), it is projected in 2019 that there will be 65,410 new HNC diagnoses and 14,620 HNC deaths. [1]. Generally, men have had higher incidence than women and blacks have had higher incidence than whites [2, 3]. Tobacco use and alcohol consumption are well-established risk factors for HNC [4–15], while more recent studies show that the human papillomavirus (HPV) is an important risk factor for HNC of the oropharynx [16–24].

A pooled analysis of 22 case–control studies (14,520 cases, 22,737 controls) of diet and HNC risk by the International Head and Neck Cancer Consortium (INHANCE) found that fruit and vegetable consumption reduced HNC risk, while red and processed meats increased risk [25]. INHANCE also observed that a dietary pattern of increased antioxidant vitamin and fiber consumption was inversely associated with HNC risk, while higher consumption of

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animal products, cereals, and fats was positively associated [26].

The INHANCE results suggest the importance of not only specific foods, but also the overall diet in HNC incidence. Indeed, comprehensive measures of diet may better reflect dietary exposure by accounting for synergy among dietary components, which may be missed when investigating nutrient components or food items individually. In addition, analysis of dietary patterns may yield greater statistical precision [27], as diet scores incorporate multiple potentially etiologically relevant individual exposures.

Previous investigations of the overall diet and HNC risk have characterized diet using either an a posteriori, data-driven approach [28] or an a priori hypothesis-driven approach [29–33]. The a posteriori study identified a dietary pattern characterized by fruits, vegetables, and lean protein that reduced HNC risk and a high-fat, processed meats, and sweet pattern that was positively associated with laryngeal cancer risk [28]. The a priori studies from Europe all relied on a version of the Mediterranean Diet Score (MDS), whereas the a priori study from the US used both an MDS derivative and the Healthy Eating Index 2005 (HEI-2005). These a priori studies all found that diet quality was inversely associated with HNC risk.

Previous studies that have used an a priori approach to study associations between diet quality and HNC risk have not explored heterogeneity by tumor HPV status, nor have they explored effect measure modification (EMM) by race, BMI, smoking, and alcohol, despite differential HNC risk associated with varying levels of these factors. To address these gaps, we investigated the association between diet quality and HNC incidence using a priori diet quality score (DQS) using data from a large, population-based case–control study of HNC. Bradshaw and colleagues used these same data for their study of a posteriori diet patterns, allowing a direct comparison of diet defined by an a priori approach with an a posteriori approach. We additionally evaluated whether these associations were similar across tumor sites and by tumor HPV status, and whether they differed by BMI, race, tobacco use, and alcohol consumption, and between DQSs.

Materials and methods

The Carolina Head and Neck Cancer Epidemiology (CHANCE) study is a population-based case–control study of HNC conducted in North Carolina, USA. The CHANCE study protocol was approved by the institutional review boards of all participating institutions [34] and this investigation was approved by the UNC Institutional Review Board (UNC IRBIS: 16-2503).

Study population

Cases ranged in age from 20 to 80 years at diagnosis, resided within a 46-country region in central and eastern North Carolina, and were diagnosed with a new first primary invasive squamous cell carcinoma of the oral cavity, pharynx, or larynx between 1 January 2002 and 28 February 2006. A rapid case ascertainment system was utilized through the North Carolina Cancer Registry and included monthly contact with the cancer registrars of 54 hospitals within the study area to identify eligible cases. Potential controls who resided in the same counties were identified through North Carolina Department of Motor Vehicles records and were frequency-matched with cases on age group (20–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–80 years), race (black; white, other), and sex (male; female) [34]. Study participants who self-reported a race other than black or white were excluded ($n=68$) as were people with missing dietary data ($n=136$).

Dietary intake assessment

A structured questionnaire was administered by trained interviewers during the in-home visit to assess information on demographic, lifestyle, and dietary behaviors. Questionnaires collected information on established risk factors for HNC, including cigarette smoking, alcohol use, anthropometric measures (self-reported), and education. Dietary intakes were collected through a modification of the National Cancer Institute's Diet History Questionnaire (DHQ) [35], a food frequency questionnaire (FFQ) designed to assess usual intakes in servings per day, week, or month of various foods consumed in the year prior to diagnosis for cases and the year prior to the interview for controls. The DHQ was modified to account for the dietary and cooking practices in North Carolina [36]. Data from the modified DHQ were processed with the Diet*Calc analysis program [37] to estimate daily intake of total energy, nutrients, and individual food items. To minimize outlier influence, we excluded subjects ($n=130$) for whom total energy intake was below the 2.5th percentile (934.9 kilocalories per day) or above the 97.5th percentile (4325.1 kilocalories per day) of the distribution for all subjects.

The Healthy Eating Index 2005 (HEI-2005) measures diet quality based on the United States Department of Agriculture (USDA)'s Dietary Guidelines for Americans [38, 39]. We specified the HEI-2005 as described by Guenther and colleagues [38]. The HEI-2005 is composed of twelve components: for nine components, higher consumption contributed positively to the HEI-2005 score (total

fruit (including juice), whole fruit, total vegetables, dark green and orange vegetables and legumes, total grains, whole grains, milk, meat and beans/legumes, and oils (vegetable, fish, nut, and seed)) and for three components, higher consumption contributed negatively to the score (saturated fats, sodium, and calories from solid fats, alcoholic beverages, and added sugars). Full specification of the HEI-2005 is detailed in Supplemental Table 1. Daily intakes for each component were standardized for energy by dividing each study participant's daily component intake by his or her total daily energy intake in kilocalories and multiplying by 1000 prior to applying the HEI-2005 scoring algorithm. Each of the 12 components of the HEI-2005 had a minimum score of zero and a maximum score ranging from 5 to 20 that reflected a pre-established level of intake (Supplemental Table 1). The summary HEI-2005 score was calculated by summation of each component score, ranging from a theoretical minimum of zero to a maximum of 100. Lower scores indicate poorer diet quality.

The Mediterranean Diet Score (MDS) reflects adherence to the traditional Mediterranean diet, a diet associated with reduced mortality and lower chronic disease incidence [40–44, 45] The MDS was originally developed by Trichopoulou et al. [46] and was later revised to include fish intake [47]. The MDS was calculated as the sum of nine dietary components: six components were scored positively (fruit, vegetables, cereals/grains, legumes, fish, MUFA: SFA) and two components were scored negatively (dairy, meat); moderate alcohol consumption was scored positively, lower or higher alcohol consumption was scored negatively (Supplemental Table 2). For all MDS components other than alcohol, daily intakes were adjusted for energy by dividing a participant's daily component intake by his or her daily energy intake in kilocalories and multiplying by 1000 prior to applying the MDS scoring algorithm. For each non-alcohol component, participants were scored 0 or 1 based on whether his or her consumption was higher (scored 1 for positive components, 0 for negative components) or lower (scored 1 for negative components, 0 for positive components) than the median sex-specific energy-adjusted intake among controls. For alcohol, males who consumed between 10 and 50 g per day and females who consumed between 5 and 25 g per day were assigned a one. All other alcohol intakes were scored a zero. This specification for the alcohol intake component was the same specification used in the original enumeration of the MDS [47]. The summary MDS was calculated by simple summation; thus, the score ranged from a theoretical minimum of zero to a maximum of nine. As with the HEI-2005, lower scores implied poorer diet quality.

The MDS, which was originally developed to study cardiovascular disease, has a history of being modified based on new evidence [48]. Thus, we incorporated the findings from the INHANCE studies of diet and HNC [25, 49] to inform a modified MDS, the "MDS-HNC." This MDS-HNC focused on food groups identified in the INHANCE investigations to be most strongly associated (both positively and negatively) with HNC risk. For the MDS-HNC, summation of scores (0 or 1, as with the MDS) from the beneficial components (fruits, vegetables, coffee, legumes, fish, poultry), non-beneficial components (red meat, processed meat, eggs, potatoes, discretionary fat), and a component for moderate alcohol consumption defined exactly as it was for the MDS. Supplemental Table 3 illustrates how the MDS and MDS-HNC are different and similar to one another. The MDS-HNC has a theoretical range from 0 to 12, with lower scores reflecting poorer diet quality.

Laboratory assays

All case participants with oropharyngeal tumors ($n=339$) and a random sample of case participants with non-oropharyngeal tumors ($n=94$) were analyzed for the presence of HPV by p16 immunohistochemistry (IHC) and polymerase chain reaction (PCR) (total $n=433$). Cases with hypopharynx cancers, cases for whom the hospital would not release tumor blocks, and cases for whom interviews were completed by a proxy were excluded from laboratory assays [50]. To assess tumor HPV status, the International Agency for Research on Cancer performed a pathologic examination of formalin-fixed paraffin-embedded tumor tissues to confirm the presence of tumor and semi-quantitative measurement of the presence of HPV by IHC with p16 ^{IKN4a} antibody, according to the protocol provided with the CINtec Histology p16-INK4a kit (9511; MTm Laboratories Inc., Westborough, Mass). The expression of p16 was measured by applying a combined score based on both the intensity (0 to 3) and the percentage (0 to 4) of positivity. A combined score ≥ 4 was considered overexpression. DNA extraction and genotyping using Luminex-based multiplex (PCR) (TS-E7-MPG, IARC, Lyon, France) identified HPV type 6 (HPV6), HPV8, HPV11 HPV16, HPV18, HPV26, HPV31, HPV33, HPV35, HPV39, HPV58, and HPV59 [51]. Cases were designated HPV-positive (HPV+) if they were positive for HPV16 DNA (deoxyribonucleic acid) and overexpressed p16 and HPV-negative (HPV−) otherwise. Cases were designated protein16 (p16+) if they overexpressed p16, protein16-negative (p16−) otherwise.

Statistical analyses

Pearson correlation coefficients were estimated between individual components within each DQS and also between each summary DQS. Chi-square tests were used to evaluate univariate associations between categorical variables and

summary DQS quartiles separately for case and control participants and generalized linear models were used to evaluate univariate associations between continuous variables and summary DQS quartiles separately for case and control study participants.

Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between each of the three DQSs and incident HNC. Associations with individual DQS components were evaluated using two modeling strategies: (1) all DQS components were included in the same model and adjusted for potential confounders and (2) each component was examined in separate models while still adjusting for potential confounders used for the full model adjustment. For MDS and MDS-HNC individual component scores, relative odds for the individual component score analyses were based on "non-adherence" with prevailing dietary recommendations. For example, eating less versus more fruits and eating more versus less processed meat as prescribed in the MDS-HNC were considered non-adherence for the fruit and processed meats components, respectively.

The confounders used for full model adjustment included all matching factors (age in years (20–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–80), race (white; black), sex (male; female)) and covariates identified based on the diet and HNC literature (BMI, in kilogram per square meter [52] ($\geq 0, < 18.5; \geq 18.5, < 25; \geq 25, < 30; \geq 30$), history of loose teeth [34] (yes; no), educational attainment [34, 52] (high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes [2, 15] (0; 1–19; 20–39; ≥ 40), quartile of lifetime intake of alcohol in grams [5, 7, 8, 53] ($\geq 0, \leq 5824; > 5824, \leq 61{,}516; > 61{,}516, \leq 297{,}024; > 297{,}024$), and quartile of energy intake in kilocalories per day [28, 54] ($> 0, \leq 1517.8; > 1517.8, \leq 1909.5; > 1909.5, \leq 2359.5; > 2359.5$)).

Multinomial logistic regression was used to estimate relative odds of HNC according to (1) tumor site (oral cavity, pharynx, or larynx) and (2) tumor HPV status (HPV-positive or HPV-negative). Controls were the referent group in each analysis. Heterogeneity of effect across tumor sites and tumor HPV status was evaluated by testing equality of corresponding DQS coefficients with the likelihood ratio test, which compared the model allowing the effects to vary across the outcome categories with the model in which the effects were constrained to be the same across the outcome categories.

BMI, race, tobacco use, and alcohol consumption were explored as potential EMMs. EMM was assessed on the multiplicative scale by the likelihood ratio test (LRT) comparing models with and without product terms. Additive EMM was assessed using the Relative Excess Risk due to Interaction (RERI) estimator [55]. For the purposes of evaluating EMM, dichotomous categorizations of the summary DQS (≤ median summary DQS among controls (poor diet quality) and > median summary DQS among controls (better diet quality)), race (black, white), BMI (≥ 25 kg/m^2 (high BMI) and < 25 kg/m^2 (low BMI); smoking (never-smoker, ever-smoker), and alcohol use (never-drinker; ever-drinker) were used to reduce the imprecision caused by small strata.

Sensitivity analyses

Because tobacco use and alcohol consumption are key risk factors for HNC, the impact of residual confounding in these risk factors was assessed by restricting models to never-smokers and to never-drinkers. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The type I error rate was set to 0.05 for all statistical tests.

Results

A higher proportion of cases compared to controls had a low BMI, history of loose teeth, low educational attainment, history of smoking, high lifetime intake of alcohol, and high daily energy intake. (Table 1). Over half of cases in the study sample had tumors of the oral cavity. Among the 423 cases evaluated for tumor HPV status, 142 were classified as HPV-positive and 189 were classified as p16-positive (Table 1). Overall, there was no more than 5.5% missing data among cases and 3% missing data among controls (Table 1). Controls had higher mean summary DQSs than did cases for all three DQSs. (Table 1, Supplemental Figs. 1–3).

Pearson correlations between individual components of the HEI-2005 where generally more highly correlated with one another than were individual components of the MDS or the MDS-HNC (Supplemental Tables 4–6). As expected, the MDS and MDS-HNC summary scores correlated positively with one another. With respect to the HEI-2005, the MDS-HNC summary score was more highly positively correlated with the HEI-2005 than was the MDS summary score (Supplemental Table 7). Univariate associations between demographic variables and summary DQS quartiles and between dietary variables and summary DQS quartiles were observed for all three DQSs. Each summary DQS was found to be positively associated with the summary DQS quartiles of the other two DQSs (Supplemental Tables 8–10).

Supplemental Tables 11–13 display associations between incident HNC and summary and individual component DQSs. The ORs (CI) represent a unit decrease in the summary DQS of interest. In general, a pattern of elevated ORs for incident HNC were associated with decreasing DQSs. For HEI-2005, the OR (CI) was 1.04 (1.02, 1.05). The OR for individual HEI-2005 component scores for whole fruit intake, whole grain intake, fat-derived energy intake, and SoFAAS was 1.11 (1.01, 1.21), 1.12 (1.01, 1.24), 1.07 (1.03,

Table 1 Distribution of select variables among cases with head and neck squamous cell carcinoma and controls, CHANCE Study, North Carolina, USA, 2002–2006

Variable	Cases		Controls	
	N	%	*N*	%
CHANCE participants				
Total	1170	100.0	1303	100.0
Age group, (years)				
20–49	228	19.5	145	11.1
50–54	182	15.6	151	11.6
55–59	191	16.3	200	15.3
60–64	203	17.4	197	15.1
65–69	160	13.7	232	17.8
70–74	131	11.2	220	16.9
75–80	75	6.4	158	12.1
Missing	–	–	–	–
Race				
White	896	76.6	1055	81.0
Black	274	23.4	248	19.0
Missing	–	–	–	–
Sex				
Male	899	76.8	904	69.4
Female	271	23.2	399	30.6
Missing	–	–	–	–
Body mass index (kg/m^2)				
$\geq 0, < 18.5$	37	3.2	11	0.8
$\geq 18.5, < 25$	478	40.9	438	33.6
$\geq 25, < 30$	370	31.6	498	38.2
≥ 30	285	24.4	354	27.2
Missing	0	0.0	2	0.2
History of loose teeth				
Yes	425	36.3	299	22.9
No	742	63.4	1002	76.9
Missing	3	0.3	2	0.2
Education				
High school or less	707	60.4	514	39.4
Some college	288	24.6	385	29.5
College graduation or more	175	15.0	404	31.0
Missing	–	–	–	–
Years smoking cigarettes				
0	157	13.4	498	38.2
1–19	110	9.4	280	21.5
20–39	446	38.1	314	24.1
40+	455	38.9	208	16.0
Missing	2	0.2	3	0.2
Lifetime number of standard alcoholic drinks[a]				
0	111	9.5	274	21.0
$> 0, \leq 416$	14	1.2	44	3.4
$> 416, \leq 4394$	126	10.8	314	24.1
$> 4394, \leq 21,216$	239	20.4	317	24.3
$> 21,216$	616	52.6	315	24.2
Missing	64	5.5	39	3.0
Quartile of lifetime alcohol intake, (g)				
$\geq 0, \leq 5824$	125	10.7	318	24.4
$> 5824, \leq 61,516$	126	10.8	314	24.1
$> 61,516, \leq 297,024$	239	20.4	317	24.3
$> 297,024$	616	52.6	315	24.2
Missing	64	5.5	39	3.0
Quartile of energy intake, (kcal/day)				
$> 0, \leq 1517.8$	142	12.1	326	25.0
$> 1517.8, \leq 1909.5$	178	15.2	326	25.0
$> 1909.5, \leq 2359.5$	260	22.2	326	25.0
> 2359.5	590	50.4	325	24.9
Missing	–	–	–	–
Cancer site				
Oral cavity	638	54.5	N/A	N/A
Pharynx	120	10.3	N/A	N/A
Larynx	412	35.2	N/A	N/A
Missing	–	–	N/A	N/A
Tumor HPV status[b]				
HPV−	291	24.9	N/A	N/A
HPV+	142	12.1	N/A	N/A
Missing	737	63.0	N/A	N/A
Tumor p16 status[c]				
p16−	244	20.9	N/A	N/A
p16+	189	16.2	N/A	N/A
Missing	737	63.0	N/A	N/A

To minimize bias from implausible energy intake, study participants with energy intake values less than the 2.5th percentile of energy intake (934.87 kcal/day, $N=65$) among all study participants and study participants with energy intake values greater than the 97.5th percentile of energy intake (4325.12 kcal/day, $N=65$) among all study participants were excluded. Study participants reporting a race other than black or white were excluded ($N=46$). An additional 136 study participants were excluded for missing dietary questionnaire data

CHANCE carolina head and neck cancer epidemiology study, *USA* United States of America, *N* counts, % percentage, *kg/m^2* kilogram per square meter, *kcal* kilocalorie, *HPV* human papillomavirus, *p16* protein16, *N/A* not applicable, + positive, − negative

[a]Standard alcoholic drinks include 12 fluid ounces (355 milliliters) of beer, 5 fluid ounces (148 milliliters) of wine, or 1.5 fluid ounces (44 milliliters) of distilled spirits

[b]Cases were designated HPV + if they were positive for both HPV16 DNA (deoxyribonucleic acid) and p16 expression, and HPV−, otherwise

[c]Cases were designated p16 + if they were overexpressing p16 protein by immunohistochemistry, and p16−, otherwise

1.10), and 0.91 (0.85, 0.98), respectively (Supplemental Table 11). For summary DQS for MDS, the OR was 1.08 (1.01, 1.14). For individual MDS component scores for fruit intake and cereals/grain intake, the OR was 1.35 (1.08,

1.68) and 1.22 (1.00, 1.49), respectively (Supplemental Table 12). The OR for MDS-HNC summary DQS was 1.08 (1.02, 1.13). The OR (CI) individual MDS-HNC component scores for fruit intake was 1.30 (1.04, 1.62) (Supplemental Table 13). When summary DQSs were rescaled to reflect a decrease of one standard deviation in the DQS, the HEI-2005 was associated with 35% greater odds of HSNCC (OR 1.35 (1.21, 1.50)). Likewise, MDS was associated with 13% greater odds of HSNCC (OR 1.13 (1.02, 1.25)), and MDS-HNC was associated with 17% greater odds of HSNCC (OR 1.17 (1.06, 1.31)) (Table 2).

For all three DQSs, the inverse association between DQS and incident HNC persisted across all tumor sites (Table 2) and regardless of tumor HPV-positivity (Table 3). For tumor sites, the test for heterogeneity suggested that the inverse association did not differ significantly by tumor site (Table 2). Similarly, tests for heterogeneity also suggested that associations between DQS scores and HNC incidence did not differ by HPV tumor status, regardless of how tumor status was specified (p16 ± or HPV ±) (Table 3).

We observed multiplicative EMM of the diet quality–incident HNC association by BMI (LRT p value < 0.05), but only for the HEI-2005 (Supplemental Fig. 4). For individuals with BMI ≥ 25, having a summary HEI-2005 DQS ≤ 51 resulted in incident HNC odds 1.74 times those of individuals with a summary HEI-2005 DQS > 51 (OR (CI) 1.74 (1.36, 2.23)). This same summary HEI-2005 DQS contrast among those with a BMI < 25 was 2.64 (1.92, 3.65). Graphical representations of the exploration of multiplicative EMM are presented in Supplemental Figs. 4–6. We did not observe EMM on the multiplicative scale by race, smoking, or alcohol use for any of the DQSs (LRT p values > 0.05) (Supplemental Figs. 4–6).

Supplemental Figs. 7–10 illustrate that, on the additive scale, BMI modified the association between diet quality and HNC risk, and did so for all three DQSs. The RERI (CI) between BMI and the HEI-2005, BMI and the MDS, and BMI and the MDS-HNC was (RERI: 0.87 (0.27, 1.48)), (RERI: 0.53 (0.06, 1.00)), and (RERI: 0.57 (0.04, 1.10)), respectively (Supplemental Fig. 7). Alcohol use also modified the association between diet quality and HNC on the additive scale, but only for the HEI-2005 and MDS-HNC. The alcohol use RERI (CIs) estimates for the HEI-2005 and MDS-HNC were 1.61 (0.65, 2.56) and 1.33 (0.61, 2.05), respectively (Supplemental Fig. 10).

Supplemental Tables 14–16 display results from the exploration of residual confounding by smoking and alcohol consumption using restriction methods. For all three DQSs, models restricted to never-smokers and never-users of alcohol resulted in diet quality–HNC risk associations further from the null than corresponding associations observed in models in which smokers and alcohol users were included. For example, the odds ratio for the diet quality–HNC risk association for a one standard deviation decrease in the HEI-2005 summary DQS that was estimated from the model which was restricted to never-smokers and never-drinkers was 1.70 (95% CI 1.09, 2.64) ("Model4," Supplemental Table 14). In contrast, the model which included both

Table 2 Associations between HNC and HEI-2005, MDS, and MDS-HNC summary scores: overall and stratified by site, CHANCE Study, North Carolina, USA, 2002–2006

	Overall		Oral cavity		Pharynx		Larynx		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	P^a
HEI-2005									
1 SD unit change (SD = 8.0)	1.35	1.21, 1.50	1.26	1.11, 1.42	1.47	1.14, 1.91	1.53	1.30, 1.79	0.0552
MDS									
1 SD unit change (SD = 1.7)	1.13	1.02, 1.25	1.14	1.01, 1.28	1.08	0.86, 1.36	1.14	0.99, 1.32	0.8933
MDS-HNC									
1 SD unit change (SD = 2.2)	1.17	1.06, 1.31	1.16	1.03, 1.31	1.40	1.09, 1.79	1.15	0.99, 1.34	0.3126

OR represents relative odds of HNC for 1-SD unit decrease in diet quality summary score

All models were adjusted for age in years (categorical indicator: 20–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–80), race (categorical indicator: white; black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: $\geq 0, < 18.5; \geq 18.5, < 25; \geq 25, < 30; \geq 30$), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1–19; 20–39; ≥ 40), quartile of lifetime intake of alcohol in grams (categorical indictor: $\geq 0, \leq$ 5824; > 5824, ≤ 61,516; > 61,516, ≤ 297,024; > 297,024), and quartile of energy intake in kilocalories per day (categorical indicator: > 0, ≤ 1517.8; > 1517.8, ≤ 1909.5; > 1909.5, ≤ 2359.5; > 2359.5)

HNC head and neck squamous cell carcinoma, *HEI* Healthy Eating Index, *MDS* Mediterranean Diet Score, *MDS-HNC* head and neck cancer-specific MDS, *CHANCE* carolina head and neck cancer epidemiology study, *USA* United States of America, *OR* odds ratio, *95% CI* 95% confidence interval, *SD* standard deviation

[a]Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across the three tumor sites are equal

Table 3 Associations between HNC and HEI-2005, MDS, and MDS-HNC summary scores: overall and stratified by tumor HPV status and tumor p16 status, CHANCE Study, North Carolina, USA, 2002–2006

	Overall		HPV−		HPV+			P16−		P16+		
	OR	95% CI	OR	95% CI	OR	95% CI	P^a	OR	95% CI	OR	95% CI	P^b
HEI-2005												
1 SD unit change (SD = 8.0)	1.35	1.21, 1.50	1.43	1.18, 1.72	1.30	1.04, 1.64	0.5147	1.41	1.15, 1.72	1.34	1.09, 1.64	0.7127
MDS												
1 SD unit change (SD = 1.7)	1.13	1.02, 1.25	1.13	0.95, 1.34	1.04	0.84, 1.28	0.5137	1.11	0.93, 1.33	1.08	0.90, 1.31	0.8440
MDS-HNC												
1 SD unit change (SD = 2.2)	1.17	1.06, 1.31	1.25	1.05, 1.49	1.13	0.91, 1.41	0.4564	1.18	0.98, 1.43	1.23	1.01, 1.50	0.7216

All models were adjusted for age in years (categorical indicator: 20–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–80), race (categorical indicator: white; black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥ 0, < 18.5; ≥ 18.5, < 25; ≥ 25, < 30; ≥ 30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1–19; 20–39; ≥ 40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥ 0, ≤ 5,824; > 5,824, ≤ 61,516; > 61,516, ≤ 297,024; > 297,024), and quartile of energy intake in kilocalories per day (categorical indicator: > 0, ≤ 1517.8; > 1517.8, ≤ 1909.5; > 1909.5, ≤ 2359.5; > 2359.5)

OR represents relative odds of HNC for 1-SD unit decrease in diet quality summary score

HNC head and neck squamous cell carcinoma, *HEI* Healthy Eating Index, *MDS* Mediterranean Diet Score, *MDS-HNC* head and neck cancer-specific MDS, *CHANCE* carolina head and neck cancer epidemiology study, *USA* United States of America, *HPV* human papillomavirus, *p16* protein-16, + positive, − negative, *OR* odds ratio, *95% CI* 95% confidence interval, *SD* standard deviation

[a]Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across HPV− and HPV + tumors are equal

[b]Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across p16− and p16+ tumors are equal

never- and ever-smokers as well as never- and ever-drinkers resulted in a diet quality–HNC risk odds ratio of 1.35 (95% CI 1.21, 1.50) ("Model1," Supplemental Table 14). Similar patterns were observed between corresponding models for the MDS (Supplemental Table 15) and MDS-HNC (Supplemental Table 16).

Discussion

Our finding that diet quality was inversely associated with HNC incidence agrees with the other studies of overall diet and HNC incidence, regardless of whether the studies [29–33] used a priori diet quality scores as we did, or an a posteriori characterization of dietary patterns as was previously done using CHANCE data [28]. The pooled analysis of 22 case–control studies of diet and head and neck cancer conducted by the INHANCE consortium identified inverse associations with HNC incidence for fruit and vegetable intake and positive associations with HNC incidence for red and processed meat intake [25]. Our findings agree with this pooled analysis as increased intakes of fruits and vegetables and decreased intakes of red and processed meats resulted in higher summary scores for all of the DQSs we studied.

Dietary micronutrients especially antioxidants found in fruits and vegetables can neutralize many of the carcinogenic tobacco and alcohol by-products [9, 10, 56–62]. It follows that fruit and vegetable intakes would be inversely associated with smoking- and alcohol-related HNC. Indeed, we observed additive EMM by alcohol use suggesting that poor diet and alcohol use amplify the risk of HNC in a super-additive fashion.

Meyer observed an inverse association with total fruit and citrus fruit consumption among HPV-seronegative individuals, but positively associated among HPV-seropositive individuals [63]. Arthur reported that dietary micronutrients are associated with HPV-positivity and suggested that some micronutrients may increase susceptibility to HPV infection [64]. We did not observe difference in the diet quality–HNC risk association by tumor HPV status. This inconsistency may be explained in part by the fact that we had a larger number of HPV-positive cases and that we explored overall diet as opposed to individual nutrients and food groups.

Previous studies which have explored BMI and HNC have suggested that BMI may simply be a consequence of the disease process as pathophysiological changes may induce weight loss [65, 66]. In addition, physical changes in the head and neck region may inhibit consumption of certain foods and calories and consequently result in weight loss [65]. Further, residual confounding by smoking has also been suggested as an explanation for the inverse BMI–HNC association as smokers tend to have lower BMIs than non-smokers and smoking is a major risk factor for HNC [52]. Taken together, these previous findings regarding BMI and HNC suggest that the EMM of the diet–HNC association by BMI observed in our data may be spurious.

The strengths of this study include the use of data from a large racially diverse population-based case–control study, the ability to explore heterogeneity by HPV status and other factors, a validated diet assessment instrument, and the utilization of the a priori approach to characterize diet quality. The high degree of correlation among individual components for all three DQSs as well as the associations between demographic and dietary variables with each DQS further support our choice to study overall diet. Our study was limited by inherent challenges of capturing comprehensive and high-quality data on usual diet through an FFQ administered after diagnosis.

Our findings further support using Mediterranean-style measures of diet quality to study health outcomes. In this American study population, the magnitude of the diet quality–HNC risk association for both the MDS and MDS-HNC mapped closely to the HEI-2005, the DQS designed for the American population in mind. This mapping was particularly good for the MDS-HNC. Thus, it appears that the MDS and its derivatives can be used to study diet quality and health outcomes in American study populations, and that the MDS-HNC, in particular, may be especially appropriate for studies of HNC in the American population.

A key takeaway from this work is that public health interventions aimed at improving diet quality, particularly those targeting alcohol consumers, have the potential to reduce the incidence of HNC.

Disclaimer The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer / World Health Organization.

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