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Proinflammatory diet is associated with increased risk of squamous cell head and neck cancer

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Abstract

Diets high in fruits and vegetables and low in red meat intake have been associated with decreased risk of head and neck cancer. Additionally, chronic inflammation pathways and their association with cancer have been widely described. We hypothesized a pro-inflammatory diet, as measured by the Dietary Inflammatory Index (DII®), is associated with increased risk of head and neck cancer. We used the Carolina Head and Neck Cancer (CHANCE) study, a population-based case-control study of head and neck squamous cell carcinoma. Cases were recruited from a 46-county region in central North Carolina. Controls, frequency-matched on age, race, and sex, were identified through the North Carolina Department of Motor Vehicle records. The DII score, adjusted for energy using the density approach (E-DII), was calculated from a food frequency questionnaire and split into four quartiles based on the distribution among controls. Adjusted odds ratios (ORs) were estimated with unconditional logistic regression. Cases had higher E-DII scores (i.e., a more pro-inflammatory diet) compared with controls (Mean: −0.14 versus −1.50; p-value <0.001). When compared with the lowest quartile, the OR for the highest quartile was 2.91 (95% confidence interval (CI): 2.16-3.95), followed by 1.93 (95% CI: 1.43-2.62) for the 3rd quartile, and 1.37 (95% CI: 1.00-1.89) for the 2nd quartile. Both alcohol and smoking had a significant additive interaction with E-DII (smoking relative excess risk due to interaction (RERI): 2.83; 95% CI:

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[b]**Disclosure**: J R Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counselling and dietary intervention in clinical settings. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

1.36-4.30 and alcohol RERI: 1.75; 95% CI: 0.77-2.75). These results provide additional evidence for the association between pro-inflammatory diet and head and neck cancer.

Keywords

Head and Neck Cancer; Dietary Inflammatory Index; Smoking; Alcohol

Introduction

In the United States, an estimated 50,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed every year.[1] In recent years, the decreasing rates of smoking have led to a decrease in the overall number of HNSCC cases.[2, 3] HNSCCs arise in five anatomical sites — oral cavity, hypopharynx, nasopharynx, larynx, and oropharynx. The oropharynx is the only site with increasing incidence, largely due to the rise of HPV-associated cancers.[4, 5]

In many large studies, HNSCC has been consistently associated with diet.[6–9] Individuals have a reduced risk of HNSCC with “prudent” diet patterns consisting of greater intakes of fruits and vegetables and lean proteins. Patterns described as the “Western” diet or those with high consumption of fried foods, fat, and processed meats have been associated with an elevated risk of HNSCC.[6] HNSCC also has been associated with a variety of individual foods and micronutrients.[8, 10–12]

Chronic inflammation pathways and their association with cancer have been widely described.[13–15] Chronic inflammation in the oral cavity due to gum disease or periodontitis is associated with an increased risk of HNSCC.[16, 17] In a meta-analysis, periodontal disease is associated with 2.63 times increased risk in HNSCC.[15]

Studies have demonstrated that specific dietary components can influence inflammation. The dietary inflammatory index (DII®) was created to measure the inflammation potential of a person’s diet.[18] This index was developed through an assessment of the peer-reviewed literature and standardized to dietary intake from populations around the world. The index has been associated with inflammatory biomarkers including CRP, IL-6, and homocysteine.[19–21] The DII also has been shown to be associated with cancers of head and neck in Italy,[22–24] but has never been investigated in a population-based case-control study in the United States.

The purpose of this study is to evaluate the association between DII scores and the risk of HNSCC in a large population-based case-control study in North Carolina. We also examined the interaction between smoking and alcohol and a pro-inflammatory diet.

Methods

The Carolina Head and Neck Cancer Study (CHANCE) is a North Carolina population-based case-control study of 1,389 cases (response rate: 82%) and 1,396 controls (response rate: 61%). Methods are detailed elsewhere.[25] Briefly, the cancer registrars of 54 hospitals in

the study area were contacted monthly to identify potentially eligible cases. Pathology reports and sociodemographic data were sent to the coordinating center at the University of North Carolina at Chapel Hill, usually within 4–8 weeks of diagnosis. Cases had a first primary squamous cell carcinoma of the oral cavity, hypopharynx, oropharynx, or larynx diagnosed between January 1, 2002 and February 28, 2006. Cases were between 20 to 80 years of age at diagnosis and resided in a 46-county region in central North Carolina. Since we are interested in squamous cell carcinoma, we excluded tumors of the lip, salivary glands, nasopharynx, nasal cavity, and nasal sinuses. Additionally, benign tumors, carcinomas *in situ*, thyroid papillary carcinomas, and adenocarcinomas were excluded. Controls were identified through the North Carolina Department of Motor Vehicle records. Controls must have resided in the same 46 country region in North Carolina. The controls were frequency-matched with cases on age, race, and sex. The University of North Carolina at Chapel Hill Institutional Review Board approved this present study.

Questionnaire and Clinical Assessment

After consent was received, a structured questionnaire was administered by trained nurses during the in-home visit to collect demographic, lifestyle, and other risk factors.[6] Questions of alcohol use were designed to estimate lifetime history of consumption including frequency and duration of each alcohol type. Similarly, the questionnaire asked detailed smoking history, frequency and duration. Diet — the year prior to diagnosis for cases and usual diet for controls — was assessed using a modified version of the National Cancer Institute's Diet History Questionnaire.[26] The food frequency questionnaire (FFQ) was modified to account for the dietary and cooking practices of the region. The Diet*Calc analysis program was used to calculate total energy intake per day, consumption of 72 individual food items (in g/day) and micronutrients and macronutrients.[27]

Dietary Inflammatory Index

Using data from the FFQ, estimated consumption of micronutrients, macronutrients, and single food items were integrated into the DII score. The development and validation of the DII score have been previously described.[18, 20] There are a total of 45 food parameters included in the original DII. For this study, 27 parameters were available for the DII calculation (Supplemental Table 1).

In brief, there are two steps to calculating the DII score. First, each of the food parameters' effect on inflammation was weighted to the literature robustness resulting in a "food parameter-specific inflammatory score". Second, the food and nutrient intakes in CHANCE were adjusted for total energy intake using the energy density method, where the raw nutrients values were divided by actual energy intake and then multiplied by 1000. Following this, a z score was then calculated using a world composite database including the global intake mean and standard deviation of each food parameter from 11 populations around the world. To minimize the effect of "right-skewing", this value is then converted to a centered proportion score (i.e., with values ranging from 0 to 1). These were then centered by doubling the proportion and subtracting one. The product of each food parameter's centered proportion score and "overall food parameter-specific inflammatory score" were summed across all food parameters to create the overall E-DII score.

The E-DII was split into four quartiles based on the distribution among controls (Q1: −6.25, < −3.08; Q2: −3.08, < −1.83; Q3: −1.83, < −0.16; Q4: −0.16, 3.99). Higher E-DII scores represent more pro-inflammatory diets.

Statistical Analysis

Using a directed acyclic graph (DAG) approach, we selected confounders based on their association with HNSCC, diet and inflammation.[28] Selected confounders included: education (some high school, completed high school, some college and above), annual income (>$50,000, $20,000 – $50,000, <$20,000), smoking (< 10 pack-years and ≥ 10 pack-years), and total lifetime alcohol consumption in milliliters for beer, wine, and liquor combined (Q1: 0 – <1,405.3; Q2: 1,405.3 – <67,399.3; Q3: 67,399.3 – <354,484.9; Q4: 354,484.9 – 11,797,780.0). Methods for calculating total lifetime alcohol consumption has been described previously.[29, 30]

The descriptive analysis compared the distribution of covariates in the DII quartiles within cases and controls separately. Statistical differences were calculated by chi-square test. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated with unconditional logistic regression with adjustment for the selected confounders and the cross-classification of the matching factors (age, race, and sex). We tested if the association between quartiles of E-DII quartile scores and HNSCC was linear with p for trend. P for trend was calculated by fitting E-DII quartile scores ordinally. Additionally, linear and quadratic models were fit for E-DII scores. Unconditional logistic regression was used to calculate site-specific adjusted ORs for oropharynx cases, larynx cases and oral cavity cases in comparison to all of the matched controls. Sites not otherwise specified (NOS) and hypopharynx were excluded from the site-specific analysis due to small numbers. Since smoking and alcohol are potentially important effect measure modifiers, we explored both multiplicative and additive interaction between smoking and alcohol with E-DII. The E-DII was dichotomized at the median in the controls and the relative excess risk due to interaction (RERI) was calculated to assess additive interaction. An RERI equal to 0 suggested no additive interaction. An RERI >0 suggested a positive interaction; an RERI <0 a negative additive interaction. All statistical analysis was performed in R 3.3.2. The calculation of the RERI and 95% CI was performed in SAS 9.4.

Results

Overall, cases were more likely to have a pro-inflammatory diet (E-DII mean: −0.14) compared with controls (E-DII mean: −1.50). Distributions of demographic and socioeconomic variables for cases and controls are detailed in Table 1 by E-DII quartile. Controls within the E-DII quartile 1 (Q1) or having a more anti-inflammatory diet were more likely to have high socioeconomic status (income greater than $50,000; 45.3%), be White American (86.3%), and have education beyond high school (73.1%) compared to other quartiles. Similar results also were seen for the cases. Additionally, there appeared to be little difference in E-DII by tumor site.

We observed a monotonic increase in the odds ratios for each increasing quartile of E-DII score (Table 2). When compared with the lowest quartile (Q1), the OR for the highest quartile (Q4) was 2.91 (95% CI: 2.16, 3.95), followed by 1.93 (95% CI: 1.43, 2.62) for the

3rd quartile (Q3) and 1.37 (95% CI: 1.00, 1.89) for the 2nd quartile (Q2) (p for trend < 0.001). When E-DII score was modeled continuously, the OR for every 1-unit increase in E-DII score was 1.22 (95% CI: 1.17, 1.28). The quadratic for the continuous score was non-significant, further suggesting a linear relationship (p = 0.750).

There was little difference in the association of E-DII with each tumor site (Table 2). Overall, laryngeal cancer had the largest magnitude of association (Q4 versus Q1 OR: 3.49, 95% CI: 2.17, 5.77) followed by oropharyngeal cancer (OR: 2.92; 95% CI: 1.86, 4.70) and oral cavity cancer (OR: 2.47; 95% CI: 1.34, 4.75).

To increase power for the evaluation of interaction with alcohol and smoking, we dichotomized the E-DII score at the median based on controls (-1.83). (Table 3 and 4). There is no significant multiplicative interaction for either smoking (p-value: 0.68) or alcohol (p-value: 0.53). However, there was a positive additive interaction between smoking and E-DII and the risk of HNSCC (RERI: 2.83; 95% CI: 1.36, 4.30). For interaction with alcohol consumption, we also dichotomized alcohol at the median (67399 milliliters ethanol) based on controls. There was a significant positive additive interaction between alcohol and E-DII score (RERI: 1.75; 95% CI: 0.77, 2.75).

Discussion

The results from this study provide additional evidence for the association between a pro-inflammatory diet and HNSCC. We demonstrated a monotonic and linear association between quartiles of E-DII and risk of HNSCC. There appears to be little difference in the magnitude of association by anatomic site. Lastly, there is a positive additive interaction between both smoking and alcohol with E-DII, suggesting these subgroups may benefit the most from diet intervention.

Previous studies conducted in Italy reported associations between a pro-inflammatory diet and increased HNSCC risk. Our results replicate a previous Italian case-control study of 460 laryngeal cases and 1088 hospital-based controls, which found that individuals in E-DII Q4 had 3.30 (95% CI: 2.06-5.28) times the risk of laryngeal cancer compared with those in Q1.[23] Similar to our findings, Shivappa et al. noted a borderline significant additive interaction with smoking in that study.[23] In another study from Italy of 946 oral and pharyngeal cancer cases and 2492 controls, higher DII scores (i.e., with a more pro-inflammatory diet) had a higher risk of oral and pharyngeal cancer (Q4 versus Q1 OR: 1.80; 95% CI 1.36-2.38 and one-unit increase OR: 1.17; 95% CI 1.10-1.25).[22] In this same study, strong combined effects of higher DII score and tobacco smoking or alcohol consumption on oral and pharyngeal cancer were observed.

There are many different pathways through which a pro-inflammatory diet can influence the risk of HNSCC. Diet directly contributes to the excessive production of pro-inflammatory biomarkers such as CRP, IL-6, white blood cell count, and homocysteine.[31–33] Inflammation contributes to the “hallmarks of cancer” by supplying bioactive molecules to the tumor microenvironment.[34] Additionally, inflammatory transcription factors can be activated by inflammatory cytokines and other inflammatory biomarkers, which play a key role in both

cancer initiation and promotion. Inflammatory cytokines can change the oral microbiota, which in turn can cause an increased risk of periodontitis and cancer.[35, 36]

Another mechanism may be that diet directly modifies the microbiota of the mouth. The most common example is carbohydrate consumption, which readily provides sugars for oral microorganisms leading to increased populations of *lactobacilli* bacteria.[37] Additionally, saturated fatty acids and vitamin C are associated with diversity in the oral microbiome. Interestingly, when catalyzed by oral bacterial enzymes, saturated fatty acids and vitamin C produce carcinogenic enzymes.[38] Additionally, the oral cavity, pharynx and larynx are all connected anatomical sites, therefore dysbiosis in one site can lead to dysbiosis in another.[39] Although the exact mechanism has yet to be elucidated, dysbiosis microbiota has been linked to head and neck cancer.[35, 40–42]

Smoking and alcohol have both been linked with increased systemic inflammation.[43, 44] The International Head and Neck Cancer Epidemiology (INHANCE) consortium found that individuals consuming a diet low in carotenoids – organic pigments associated with decreased inflammation – and with high exposure to smoking have over 30 times the risk of HNSCC compared to non-smokers with high carotenoid intake. Folate deficiencies can lead to elevated homocysteine levels. Elevated homocysteine levels are linked with increased inflammation.[45, 46] Similar results were seen with folate; it was observed that 10% of head and neck cancers were due to the interaction between low folate and smoking.[8] The same study found that those with high alcohol consumption and low folate intake had over 4 times the odds of head and neck cancer compared to those with low alcohol and high folate intake. Flavonoids are a well-known anti-oxidant and recently implicated with anti-inflammatory properties as well.[47] Studies also have found that flavonoid intake is associated with a decreased risk of cancer, especially among smokers.[48] Smokers and people who drink large amounts of alcohol have higher levels of inflammation markers,[49–51] thus the role of an anti-inflammatory diet may be more pronounced among these individuals.

There are several limitations to our present study. The E-DII was calculated from an FFQ, which could lead to biased recall by case-control status. Although the nurses conducting the in-home questionnaire were able to reference date for cases, cases still may recall dietary behaviors differently. We have identified patterns of association with diet, tobacco, and alcohol consistent with other studies of HNSCC including cohort studies. This leads us to believe that any misclassification would be non-differential which, on average, would bias the odds ratios towards the null. However, given the retrospective nature of the study, we cannot definitively rule out differential misclassification. Another limitation is the non-availability of the remaining 18 food parameters to calculate the DII. Previously, we showed that there was no drop in the ability to predict high sensitive-CRP >3mg/l when DII was calculated with 27 food parameters as compared to the predictive ability when DII was calculated using 44 food parameters.[20] Part of the reason could be that some of the food parameters that are missing include components such as ginger, turmeric, saffron, thyme, eugenol, which are not consumed in high amounts in this population. However, presence of some missing parameters like various flavonoids, which are consumed regularly, could have influenced the results. Lastly, we were not able to further stratify oropharyngeal cancer by HPV-status due to the limited number of HPV-negative oropharyngeal cases (N = 61).

However, when stratified by HPV-status, the point estimates for quartile of DII between HPV-positive and HPV-negative oropharyngeal cancer are similar (data not shown).

This study has several noteworthy strengths. CHANCE is a population-based case-control study, making these results generalizable and less prone to selection bias that may arise from hospital-based case-control studies. Additionally, the E-DII is a combined metric describing the overall inflammatory potential of diet.

Conclusion

The E-DII was associated with increased risk of HNSCC and had a positive additive association with smoking and alcohol. This study, along with the other studies, further emphasizes the importance of inflammation and diet on cancer development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HNSCC	Head and neck squamous cell carcinoma
DII	Dietary Inflammatory Index
CHANCE	Carolina Head and Neck Cancer Study
FFQ	Food frequency questionnaire
DAG	Directed acyclic graph
E-DII	Energy-adjusted Dietary Inflammatory Index
OR	Odds ratio
NOS	Not otherwise specified
RERI	Relative excess risk due to interaction
CI	Confidence interval
Q1	First quartile
Q2	Second quartile
Q3	Third quartile
Q4	Fourth quartile

INHANCE The International Head and Neck Cancer Epidemiology Consortium

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Novelty & Impact Statements

Diets high in fruits and vegetables and low in red meat intake decrease the risk of head and neck cancer. Additionally, inflammation is widely considered to be a hallmark of cancer. The dietary inflammatory index measures the inflammatory potential of diet. This is the first study to find an association between pro-inflammatory diets on head and neck cancer in population-based case-control study in the United States.

Table 1

Descriptive statistics of cases by energy-adjusted dietary inflammatory index quartile, Carolina Head and Neck Cancer (CHANCE) Study, 2001 to 2007.

	Cases					Control				
	Q1 N = 116	Q2 N =187	Q3 N = 399	Q4 N = 566		Q1 N = 342	Q2 N =344	Q3 N = 343	Q4 N = 343	
	N (%)	N (%)	N (%)	N (%)	p-value*	N (%)	N (%)	N (%)	N (%)	p-value*
Age										
≤ 50	16 (13.8)	25 (13.4)	79 (23.5)	162 (25.8)	<0.001	23 (6.7)	43 (12.5)	54 (15.7)	66 (19.2)	<0.001
51 – 65	50 (43.1)	101 (54.0)	165 (49.1)	324 (51.5)		134 (39.2)	140 (40.7)	137 (39.9)	162 (47.2)	
66+	50 (43.1)	61 (32.6)	92 (27.4)	143 (22.7)		185 (54.1)	161 (46.8)	152 (44.3)	115 (33.5)	
Sex										
Male	70 (60.3)	120 (64.2)	247 (73.5)	529 (84.1)	<0.001	196 (57.3)	228 (66.3)	244 (71.1)	277 (80.8)	<0.001
Female	46 (39.7)	67 (35.8)	89 (26.5)	100 (15.9)		146 (42.7)	116 (33.7)	99 (28.9)	66 (19.2)	
Race										
White	105 (90.5)	150 (80.2)	255 (75.9)	432 (68.7)	<0.001	295 (86.3)	291 (84.6)	270 (78.7)	240 (70.0)	<0.001
Black	8 (6.9)	35 (18.7)	70 (20.8)	188 (29.9)		39 (11.4)	49 (14.2)	69 (20.1)	102 (29.7)	
Other	3 (2.6)	2 (1.1)	11 (3.3)	9 (1.4)		8 (2.3)	4 (1.2)	4 (1.2)	1 (0.3)	
Smoking										
< 10 pack-years	45 (39.1)	50 (26.9)	69 (20.6)	110 (17.5)	<0.001	228 (66.7)	211 (61.3)	166 (48.4)	156 (45.5)	<0.001
≥ 10 pack-years	70 (60.9)	136 (73.1)	266 (79.4)	518 (82.5)		114 (33.3)	131 (38.1)	177 (51.6)	186 (54.2)	
Missing	1	1	1	1		0	2	0	1	
Income										
>$50,000	53 (49.5)	61 (34.7)	101 (30.8)	142 (23.3)	<0.001	155 (45.3)	166 (48.3)	146 (42.6)	118 (34.4)	<0.001
$20,000 – $50,000	38 (35.5)	55 (31.2)	122 (37.2)	220 (36.1)		125 (36.5)	113 (32.8)	115 (33.5)	130 (37.9)	
<$20,000	16 (15.0)	60 (34.1)	105 (32.0)	248 (40.7)		42 (12.3)	53 (15.4)	69 (20.1)	90 (26.2)	
Missing	9	11	8	19		20	12	13	5	
Education										
Less than high school	15 (12.9)	40 (21.4)	91 (27.1)	270 (42.9)	<0.001	31 (9.1)	32 (9.3)	60 (17.5)	89 (25.9)	<0.001
High school	26 (22.4)	44 (23.5)	92 (27.4)	199 (31.6)		61 (17.8)	77 (22.4)	83 (24.2)	106 (30.9)	
Greater than high school	75 (64.7)	103 (55.1)	153 (45.5)	160 (25.4)		250 (73.1)	235 (68.3)	200 (58.3)	148 (43.1)	
Site										

	Cases					Control				
	Q1 N = 116	Q2 N =187	Q3 N = 399	Q4 N = 566		Q1 N = 342	Q2 N =344	Q3 N = 343	Q4 N = 343	
	N (%)	N (%)	N (%)	N (%)	p-value*	N (%)	N (%)	N (%)	N (%)	p-value*
Hypopharynx	2 (1.7)	8 (4.3)	18 (5.4)	27 (4.3)	0.06	—	—	—	—	—
Larynx	29 (25.0)	65 (34.8)	112 (33.3)	239 (38.0)		—	—	—	—	
Oral cavity	19 (16.4)	39 (20.9)	50 (14.9)	87 (13.8)		—	—	—	—	
Oropharynx	36 (31.0)	40 (21.4)	94 (28.0)	173 (27.5)		—	—	—	—	
NOS	30 (25.9)	35 (18.7)	62 (18.5)	103 (16.4)		—	—	—	—	
Total Lifetime Alcohol										
Q1	16 (14.7)	22 (12.4)	36 (11.1)	60 (10.2)	<0.001	73 (21.3)	94 (27.3)	87 (25.4)	73 (21.3)	<0.001
Q2	18 (16.5)	29 (16.3)	33 (10.2)	58 (9.8)		100 (29.2)	84 (24.4)	70 (20.4)	78 (22.7)	
Q3	40 (36.7)	42 (23.6)	69 (21.3)	84 (14.2)		107 (31.3)	84 (24.4)	75 (21.9)	68 (19.8)	
Q4	35 (32.1)	85 (47.8)	186 (57.4)	389 (65.8)		55 (16.1)	71 (20.6)	101 (29.4)	108 (31.5)	
Missing	7	9	12	38		7	11	10	16	

*Test between E-DII quartiles

NOS: Not Otherwise Specified

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Table 2

Odds ratios for quartiles of energy-adjusted dietary inflammatory index for all cases compared with controls, Carolina Head and Neck Cancer (CHANCE) Study, 2001 to 2007.

	All Cases (N = 1268)			Larynx (N = 445)			Oral Cavity (N = 165)			Oropharynx (N = 343)		
	OR* (95% CI)	p-value	P for trend	OR* (95% CI)	p-value	P for trend	OR* (95% CI)	p-value	P for trend	OR* (95% CI)	p-value	P for trend
E-DII												
Q1	1.00		<0.001	1.00		<0.001	1.00		0.007	1.00		<0.001
Q2	1.37 (1.00, 1.89)	0.050		1.77 (1.06, 3.02)	0.030		1.53 (0.8, 3.01)	0.21		1.03 (0.61, 1.76)	0.900	
Q3	1.93 (1.43, 2.62)	<0.001		2.05 (1.26, 3.42)	0.004		1.70 (0.92, 3.28)	0.10		1.96 (1.24, 3.16)	0.005	
Q4	2.91 (2.16, 3.95)	<0.001		3.49 (2.17, 5.77)	<0.001		2.47 (1.34, 4.75)	0.01		2.92 (1.86, 4.70)	<0.001	

E-DII: Energy-adjusted dietary inflammatory index **OR:** Odds Ratio; **CI:** Confidence Interval

*Multivariable model adjusted for education, income, smoking, total lifetime alcohol intake, age, race, and sex

Table 3

Interaction odds ratios for smoking and E-DII dichotomized at the median, Carolina Head and Neck Cancer (CHANCE) Study, 2001 to 2007.

	< E-DII Median		≥ E-DII median		
	N, Cases/Controls	**OR (95% CI)**	**N, Cases/Controls**	**OR (95% CI)**	**E-DII OR (95% CI) within smoking strata**
<10 pack-years	83/409	1.00	187/229	2.23 (1.62, 3.09)	2.23 (1.62, 3.09)
≥10 pack-years	169/301	3.17 (2.30, 4.39)	723/334	6.25 (4.64, 8.4)	1.97 (1.53, 2.55)
					RERI: 2.83 (1.36, 4.30)

Table 4

Interaction odds ratios for alcohol and E-DII dichotomized at the median, Carolina Head and Neck Cancer (CHANCE) Study, 2001 to 2007.

	< DII Median		≥ DII median		
	N Cases/Controls	**OR (95% CI)**	**N Cases/Controls**	**OR (95% CI)**	**DII OR (95% CI) within alcohol strata**
< Median alcohol consumption	80/330	1	190/308	1.90 (1.37, 2.65)	1.90 (1.37, 2.65)
≥ Median alcohol consumption	180/301	2.29 (1.64, 3.22)	712/344	4.95 (3.58, 6.84)	1.49 (1.17, 1.91)
					RERI: 1.75 (0.77, 2.75)