Published in final edited form as:

Head Neck. 2008 September ; 30(9): 1193–1205. doi:10.1002/hed.20846.

Dairy Products, Leanness and Head and Neck Squamous Cell Carcinoma

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Abstract

As part of a population-based case-control study, we investigated the association of food groups and micronutrients estimated from a validated food frequency questionnaire (FFQ) with the risk of development of head and neck squamous cell carcinoma (HNSCC). Incident cases were accrued through Boston area hospitals from 1999 to 2003 and neighborhood controls were selected, matched by location, age and gender. There were 504 cases and 717 controls enrolled who completed the FFQ.

We observed a positive association between the consumption of dairy products and HNSCC. The odds of HNSCC in highest quintile of dairy intake was 1.64 (95% CI: 1.09-2.46), compared to subjects in the lowest quintile. There was a significant association between leanness with HNSCC. The odds of cancer among the leanest subjects was 5.8 (95% CI: 3.2-10.6) compared to a healthy BMI. Finally, intake of animal fat was positively associated with an elevation in cancer risk. The odds of HNSCC for high animal fat intake were 1.50 (0.99-2.27). Our data suggest that consumption of fruits and vegetables is not universally protective for HNSCC and that other food groups and nutrients may influence the risk for developing this disease.

Keywords

Head and Neck Neoplasm; Diet; Case-Control Studies; Obesity; Epidemiology

Introduction

HNSCC is the eighth most common cancer observed worldwide, the sixth most common cancer in developing nations and the tenth most common cancer in the United States (1,2). Throughout the world, reports suggest that the use of tobacco and alcohol accounts for approximately 75% of all HNSCCs (3-6), and perhaps most striking in the etiology of HNSCC is the interaction of tobacco with alcohol (3,7,8). Although the combination of tobacco and alcohol account for over 75% of the population attributable risk, other factors have been recognized as contributing

to the etiology of oral cancer. These include gastroesophageal reflux, occupation, infectious agents such as human papillomavirus, and diet (9).

Diet has been demonstrated repeatedly to be associated with the risk of developing many types of cancer (10-12). Several epidemiologic studies have reported that oral squamous cell cancer (OSCC) patients have lower consumption of fresh fruit than healthy controls (13-26). In a recent meta-analysis, a combined estimate based on 16 studies showed that each serving of fruit consumed per day reduced the risk of oral cancer by approximately 50% (27). Not included in the meta-analysis were the results from two recently published cohort studies that found divergent results. The European Investigation into Cancer and Nutrition (EPIC), found that, compared to the lowest quintile, the highest category of fruit intake showed significantly lower relative risk estimates for oral cancer (relative risk=0.6, 95% CI: 0.4-1.0) (26). Maserejian *et al.* (28) studied a cohort of health professionals and showed that total fruit consumption was not statistically significantly associated with either oral premalignant lesions or oral cancer after adjustment for other risk factors.

The evidence surrounding the association of vegetable intake with HNSCC risk is less certain. While some studies found no association, others suggest consumption of vegetables may reduce the risk of oral and pharyngeal cancers in subpopulations. Winn *et al.* (14) and McLaughlin *et al.* (13) found intake of vegetables was not related consistently to either an increased or decreased risk for oral cancer. Several others have reported a similar lack of association of oral cancer with vegetable consumption (29-33) (34-39). However, other studies reported an inverse association for vegetable consumption and oral cancer (18,19,21,24). Pavia *et al.* reported that vegetable intake was inversely associated with oral cancer and that regular intake reduced the risk of this disease by approximately 50% (32). By contrast, in the EPIC cohort study, vegetable consumption was not related to risk for upper aerodigestive cancer (26). Likewise, no inverse association was observed between vegetable intake and the risk of oral premalignancy or cancer from the Health Professionals Cohort study. In fact, in this work, green vegetable intake was marginally associated with an elevated risk (28).

The antioxidant vitamins A, B, C, E and beta-carotene may reduce the risk of HNSCC. In a population-based study, Gridley *et al.* (34) reported that vitamin supplements of any kind were associated with a reduced risk for oral cancer. Examination of individual supplement use found an inverse association with cancer risk (OR: 0.3, 95% CI: 0.1-0.8) only for vitamin E. Furthermore, the investigators reported that intake of vitamin A supplements was associated with a significantly reduced risk of OSCC after restricting inclusion of patients to those who did not take vitamin E. Several clinical trials have demonstrated that retinoids can reverse oral premalignancy and prevent the development of second primaries among patients with a primary oral cancer (35-39). However, recently, total intakes of vitamin C, vitamin A or carotenoids were reported not to be significantly associated with oral premalignancy or oral cancer in the Health Professionals Cohort Study (40).

As the role of diet on the incidence of HNSCC remains uncertain, we sought to examine the effect of diet on the risk of HNSCC utilizing the resources of our, population-based study of incident HNSCC arising in the greater Boston metropolitan area. In this well-defined population, we utilized a validated food frequency questionnaire to ascertain dietary patterns amongst cases and controls, as well as additional questionnaire based assessment of exposures, lifestyle, and demographics, to allow us to control for confounding factors in our analysis.

Materials and Methods

Study Population

From December 1999 until December 2003, all incident cases of head and neck cancers diagnosed at nine medical facilities in Boston were ascertained for inclusion in this study. These nine facilities, comprised of multi-specialty head and neck clinics and otolaryngology and radiation oncology departments within hospitals, diagnose and treat over three-quarters of all new HNSCC cases in the Greater Boston Metropolitan area and serve a population of approximately 3.5 million people. The Institutional Review Boards at all participating medical facilities approved the study and all participants provided written informed consent.

Eligible cases had histologically confirmed HNSCC with international classification of disease (ICD9-0) codes of 141, 143-146, 148, 149 and 161. Any patients with carcinoma *in situ*, or cancers of the lip, salivary gland or nasopharyngeal tissues were excluded. Any patients with recurrent cancer of the head or neck were also excluded.

Population-based controls were frequency-matched (1:1) to cases by age group (+/- three years), gender and town/neighborhood of residence. Controls were selected randomly from the Resident Lists maintained by the State of Massachusetts for the 249 cities and towns within the study area. Details of the case-control ascertainment process have been detailed previously (8).

Participating cases and controls completed a self-administered questionnaire covering their medical history, demographic background and lifetime consumption habits of alcohol and tobacco. Case subjects received the questionnaire at their initial clinic visit to be collected at a later visit while control subjects received the questionnaire by mail and then returned them in-person. Both cases and controls reviewed the information provided in the questionnaire with a research assistant to answer any questions and clarify any responses.

Body mass index (BMI) was calculated using the study subjects' self-reported height and weight five years prior to date of enrollment. Subjects provided decade-specific information on cigarette smoking and alcohol consumption. Total pack-years of tobacco use were determined from the number of packs of cigarettes smoked per day summed over all the years for each decade of life the subject smoked. For alcohol consumption, the decade-specific questionnaire asked how many drinks per week of beer (1 glass, bottle or can), wine (4-ounce glass), and/or liquor (1 drink or shot, and whether a light or dark liquid) were consumed for every decade. This information was used to generate the "average drinks per week" across all types of alcoholic beverages.

Dietary Assessment

Information about dietary intake was collected using a self-administered 138 food item FFQ developed by the Nutrition Department of the Harvard School of Public Health. This instrument was validated in a group of female nurses and male health professionals living in Boston (41, 42). For each food in the FFQ participants were asked how often on average they consumed that a specified amount of that food during the year. Subjects were asked to report on their dietary habits five years prior to the interview date (43) in order to minimize the likelihood that the disease process impacted reported dietary intake. Subjects indicated their frequency of food item intake from nine multiple choice categories ranging from never to four or more times a day. Responses regarding individual food items were converted to daily intake of each item. This was then used to compute total servings of food groups (e.g. fruit, dairy or vegetables) per day. Food groupings were derived from the published literature.(32,44,45) (46). Details about the food groupings may be found in Appendix 1.

Nutrient intakes were calculated by multiplying the frequency of the food item consumption by the nutrient content of the specified serving size using food composition values from the Harvard School of Public Health's nutrient database derived from the US Department of Agriculture. Participants also provided information on vitamin supplements taken. This information was used to estimate nutrient values for both total dietary nutrients and supplements.

Statistical Analysis

Subjects who returned the FFQ were included in the analysis. Participants whose daily non-alcohol caloric intake was outside the plausible range of 500 to 3500 kcal/day for women and 800 to 4200 kcal/day for men were excluded. Subjects who left more than half the food item questions blank were not included in this analysis(47).

Unconditional logistic regression was performed using SAS (Version 9.1; SAS Institute, Cary, NC) to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between food groups or nutrient of interest and case status (48). The cut points for the food groups were obtained by dividing each into five even categories (quintiles) based on the distribution in controls and then rounding to the nearest whole or half serving for each cutoff. The nutrients were divided into quintiles, as determined by the distribution in controls. Models included age (continuous), gender, race (white vs. other) education (less than high school vs. at least high school), and BMI (using the standard weight status categories). Models were also adjusted for the primary risk factors, alcohol (as average drinks per week) and pack-years smoked. Furthermore, methods were used to account for confounding by total caloric intake and to minimize extraneous variation. In the food group analyses, total energy was controlled by including the total non-alcohol daily calories in the model. Nutrient intake was adjusted for non-alcohol total energy intake using the nutrient residual method (49). Tests for trend were calculated by assigning the median values of intake for each of the quintiles and including this variable in a logistic regression model, resulting in a one degree of freedom test. Frequency-matching allowed the use of unconditional regression with inclusion of the matching variables in the model (50).

Results

Eight hundred and twenty-three eligible cases were invited to participate; of these 57 refused to participate. Among the 766 subjects that consented, 44 did not complete the risk factor questionnaire. Of the remaining 722 cases, complete FFQ data were available on 529 participants, representing a final participation rate of 64%. A total of 1623 subjects were identified and eligible for participation as controls. Of these, 828 refused to participate and 795 subjects consented with 771 finally enrolled in the study. Six of the controls were excluded since they were matched to a case that subsequently became ineligible, such that 765 (47%) controls were enrolled and completed the study. Complete FFQ and risk factor questionnaire data were available on 742 controls. Of the 529 enrolled cases, we excluded 25 individuals who either were missing more than 50% of the food responses or were outside of the plausible range. Likewise, 24 controls were excluded, thus the final analysis included 504 cases and 718 controls.

Table 1 shows the distribution of cases and controls according age, gender and other characteristics. As expected from the study design, there were no substantial differences between cases and controls with respect to age and gender. Among controls, 93% reported their race to be Caucasian compared to 90% of the cases. Cases consumed substantially greater amounts of tobacco and alcohol; the mean weekly alcohol consumption among the cases was 23 drinks per week, and that of controls was 12 alcoholic drinks per week. The mean pack-years of smoking among cases was 37 pack-years, compared to 20 pack-years among controls.

There was a small, albeit, non-significant association between failing to graduate from high school and risk of HNSCC after adjusting for age, gender, race, tobacco and alcohol (OR: 1.42, 95% CI: 0.92-2.18). The mean BMI among cases was 26.4 compared to 27.5 among controls. Having a BMI considered underweight by the National Institutes of Health (<18.5) was significantly associated with cancer risk after adjustment for age, race, gender, tobacco, and alcohol consumption (OR: 5.81, CI: 3.20-10.56) compared to those with what is considered a healthy BMI of between 18.5 and 25. Furthermore, an elevated BMI was inversely associated with cancer risk: participants with a BMI ≥ 30 had a significant 35% lower risk of cancer compared to individuals with a BMI between 18.5 and 25, (OR: 0.65, 95% CI: 0.46-0.92) after adjustment for age race, gender, tobacco and alcohol. It should be noted that this BMI, which is associated with cancer risk, was based upon the patient's weight 5 years prior to diagnosis (the period during which dietary intake was ascertained) and thus does not reflect changes in weight associated with disease onset. While the highest intake of total calories was marginally associated with the risk for HNSCC (OR: 1.35, 95% CI: 0.90-2.02), total non-alcohol calories were not associated with cancer risk in either the crude or adjusted models.

The frequency distribution, crude and adjusted odds ratios for food groups are shown in Table 2. Increased consumption of dairy foods was associated with an elevated risk of HNSCC. Consuming five or more servings per day of dairy products increased the risk of HNSCC by over 60% (OR: 1.64, 95% CI: 1.09 -2.46). The test for linear trend, as measured by the median values of the quintiles, suggested a significant dose response ($p < 0.01$). Of the foods included within the dairy group, butter, cottage cheese and ice cream were directly associated with a statistically significant increased risk for developing cancer (data not shown).

Comparing the highest quintile of fruit intake (three or more servings per day) to the lowest quintile (less than one serving per day), the odds of HNSCC, adjusted for age, race and gender, was estimated to be 0.66 (95% CI 0.47-0.94). However, the association became null in the multivariate model that also included BMI, education, tobacco, alcohol, and caloric intake (OR=1.01 (95% CI 0.67, 1.54)). Vegetable intake alone was not associated with decreased risk in either the crude or adjusted models. Total fruit and vegetable intake of six or more servings per day was associated with an odds ratio of 0.65 (95% CI: 0.46 – 0.91) in the model adjusted for age, race and gender, although the association disappeared in the fully adjusted model. Finally, a high consumption of cereals and starchy roots was associated with a reduced HNSCC risk after adjustment for age, gender, race, BMI, education, tobacco and non-alcohol calories (OR: 0.60, 95% CI: 0.37-0.98).

Table 3 shows the frequencies and the estimated magnitude of the associations of intake of macronutrients and micronutrients and the risk of HNSCC. Among individuals in the highest quintile of animal fat consumption, there was a 50% greater HNSCC risk compared to those in the lowest quintile controlling for age, race, gender, BMI, education, and tobacco and alcohol use. Among those whose daily fat intake exceeded 51.7 grams per day relative to a daily intake of less than 24.1 grams, the odds of developing cancer were 1.50 (95%: 0.99-2.27). After adjustment, the estimated total vitamin B12 consumption (from dietary and supplemental sources) in the highest two quintiles derived from the combination of dietary sources and supplementation was associated with a 60% increase in HNSCC risk (OR: 1.61, 95% CI: 1.05, 2.47). This elevated risk persisted when vitamin B12 intake was based upon dietary intake alone (OR: 1.55, 95% CI: 1.02-2.34) (data not shown). Carotene intake, estimated from diet alone and a combination of diet and supplements, was associated with an increased risk of HNSCC. Those individuals in the highest quintile of total carotene intake (12,737 IU or greater) had a 46% elevation in cancer risk adjusting for age, race, gender, BMI, education, tobacco and alcohol intake (OR: 1.46, 95% CI: 0.96-2.22). Trend tests were statistically significant for vitamin B12 ($p < 0.05$) and for carotene ($p = 0.05$). Estimated intake of folate, calcium, vitamins C, D, E, B1, B2, and B6 were not associated with increased HNSCC risk (Table 3).

Discussion

While the largest proportion of HNSCC cases may be explained by tobacco use and alcohol consumption, diet also may play a vital role in the etiology of this disease. In this Boston-based case-control study of oral, pharyngeal and laryngeal cancers, after controlling for smoking, alcohol and other risk factors, high consumption of fruits and/or vegetables did not afford any significant cancer protection. However, leanness (a low BMI) was observed to be a significant risk factor for developing HNSCC; the odds of being very lean among cases were almost six-times greater than the odds of being very lean among the controls. We also observed an elevated cancer risk associated with high intake of dairy products, vitamin B12, carotenes and animal fats.

Prior to controlling for tobacco and alcohol intake, high intake of fruits and/or vegetables was inversely associated with cancer risk; subjects in the highest quintile of fruit consumption (a median of 3.7 servings/day) had about one third of the risk of those in the lowest quintile (median of 0.5 servings/day). However, upon adjustment for tobacco and alcohol intake, fruit and vegetable intake was not associated with cancer risk. While this finding is at odds with some of the literature, dietary assessment methods used in previous studies may not have been sufficiently comprehensive to estimate total fruit and vegetable intake. Dietary assessment methods vary in the United States and Europe and this could account for some of the apparent discrepancies in results among studies. This result may also indicate a high degree of correlation between these risk factors and dietary patterns, such that once the residual confounding of lifestyle was controlled for in multivariate models, the effect of fruits and/or vegetable intake alone is no longer significant. In fact, we observed that fruit intake was negatively associated with both tobacco and alcohol consumption; Pearson's correlation coefficients of $r = -.14$ ($p < 0.001$) and $r = -0.15$ ($p < 0.001$), respectively were observed. Likewise, the coefficients for the correlation between vegetable intake and alcohol and tobacco use were, $r = -0.11$ ($P < 0.001$) and $r = -0.15$ ($P < 0.001$), respectively. Thus, individuals with "healthy" lifestyles (i.e. well-balanced diets high in fruits and vegetables, moderate alcohol consumption, and non-smoking) are generally at reduced risk, but being able to determine which of these factors individually contributes to the reduced risk is not possible. Furthermore, while Willet *et al.* (49,51) strongly encourage adjustment of total energy for validly estimating associations between nutrients and disease, not all prior oral cancer studies controlled for BMI or energy as we did in the final analysis. Therefore, some previous studies' findings may be partially the result of differences between cases and controls with respect to body size, physical activity, and metabolic efficiency.

Two of the earliest case-control studies of oral cancer reported no difference in fruit consumption between cases and controls (52,53). Winn *et al.* (14) conducted an early hospital based case-control study in the rural southeast US and reported that a diet high in fruits and vegetables was significantly protective for oral and pharyngeal cancer, with a relative risk of 0.52 for high compared to infrequent consumption controlling for demographics, tobacco and alcohol. However, the authors of this study ascertained 60% of their dietary intake information for cases from the next-of-kin. Furthermore, half of the next-of-kin interviews were conducted among the cases' children (14), an ascertainment method which may introduce serious reporting biases and significant misclassification.

Unlike some of the previous investigations, our study of HNSCC was population-based and avoided the use of hospitalized controls whose diet and nutritional status might have contributed to hospitalization. Likewise, we did not rely on next-of-kin or any other proxies for collection of the dietary information from either cases or controls. Furthermore, we made a rigorous effort to ensure dietary and BMI measurements represented a period of time (five years) prior to the onset of disease, ensuring that recent changes in diet due to mouth or throat

problems would not influence the findings. This large, population-based study also employed detailed assessment of tobacco and alcohol use as well as dietary assessment across a very broad variety of food groups using a validated FFQ.

A large population-based case-control study conducted in four regions of the US through SEER cancer registries did not observe a protective association of vegetables on oral and pharyngeal cancer risk, although high fruit consumption was observed to be statistically associated with a diminished cancer risk (13), but again a large proportion of participants' (22%) dietary information was obtained through proxy. Most recently, a case control study conducted in North Carolina that employed a Block FFQ found no significant association between either fruit or vegetable intake and the risk for HNSCC (33).

In the current study, the cases were leaner yet had higher total energy intake than control participants. Increased body mass was associated with a lower cancer risk among those in the highest quintile of BMI. This observation is consistent with much of the literature (25,54,55). It also is consistent with the observation that other smoking-related cancers, including lung cancer, are inversely associated with BMI (56). Interestingly, this result stands in contrast to cancers at many other anatomic sites where obesity is a major risk factor. Breast, kidney and colorectal cancer have been reported to be positively associated with obesity (57). While our result is consistent with the majority of the literature, the mechanism responsible for this rather striking observation remains unclear. It is possible that body mass alters the effective carcinogen dose or the metabolic response to toxins, however there is little data to address this and considerable additional research is needed to understand this consistent finding.

Any protection from HNSCC afforded by increased consumption of fruits and vegetables might be mediated through micronutrients, such as carotenes and vitamins. Consequently, we examined this issue separately and, consistent with our results for fruits and vegetables, there was no association between consumption of most of the nutrients considered and cancer risk. In fact, we observed strong positive associations for consumption of carotenes, vitamin B12 and animal fat and cancer risk. McLaughlin *et al.* (13) in the largest US study conducted to date, did not find associations of carotene, folate or retinol with cancer risk (although they reported total fat was positively associated with oral cancer risk). Marshall *et al.* (15) observed no association for between either fat or carotene intake and oral cancer. These findings are in contrast to several other studies that found that intake of key nutrients were inversely associated with oral cancer risk (16). Negri *et al* (58) reported significant inverse associations for carotene, vitamins E, C, B6, thiamin, folic acid, niacin, potassium and iron. Although Petridou *et al.* (32) from a case-control study in Greece reported no associations between specific micronutrients and oral cancer.

The finding of an elevated risk for HNSCC associated with dairy consumption was unexpected and warrants further examination. Franceschi *et al.* (59) reported a similar significant elevation in oral and pharyngeal cancer risk for the highest quintile of meats, milk and butter consumption. In addition, the finding of an increased risk for animal fat is of considerable interest and is supported by other studies as well (13,15,59).

Recall bias, a limitation among many case-control studies, could have been responsible for a portion of the associations observed in other studies reported to date. This would most likely transpire if healthy controls overestimated their fruit and vegetable intake and patients underreported their intake. Differential recall of past diet likely is not responsible for the apparent lack of association observed for fruits and vegetables in our investigation.

Another consideration for case-control studies is the influence of selection bias. Traditionally, subject participation is high for cases but lower for control subjects; those who participate are more likely to be health conscious and thus to consume more fruits and vegetables than non-

participants. Approximately 31% of the cases and 9% of the controls were excluded because they either failed to complete the FFQ or had non plausible values for total energy. Both the included cases and controls reported lower levels of alcohol consumption than their excluded counterparts: 24 vs. 30 drinks per week for cases and 12 vs. 19 drinks per week for controls. However, among the included cases, tobacco use was slightly elevated compared to the excluded cases, 37 pack-years vs. 36 pack-years, respectively. In contrast to the cases, included controls reported lower tobacco use compared to those that were not included, 20 pack-years vs. 25 pack-years, respectively. Furthermore, the included cases and controls reported both higher income and education than the excluded cases and controls. Therefore, included participants in our study were slightly healthier than their excluded counterparts. With the exception of tobacco use, risk factors did not differ between case patients and healthy controls. While selection for healthier subjects may have transpired in the subset providing diet data, it likely did not dramatically differ with respect to case status, and hence any selection bias likely to be minimal.

Head and neck cancers are strongly associated with both alcohol and tobacco intake, both of which were measured in great detail. The consumption of fruits and vegetables has been inversely associated with these two risk factors (60). Studies of diet and HNSCC that fail to control for confounding variables such as tobacco and alcohol may distort any association between fruit and vegetable consumption with HNSCC. In our work, by adjusting for tobacco and alcohol intake, the crude inverse associations between fruits and vegetables with cancer risk disappeared. We did not find any other possible confounders that appreciably altered the effect estimates. While residual confounding, as always, remains possible its effect is likely minimal.

In conclusion, while diet may modify the risk of HNSCC, it is clear that the strongest risk factors remain alcohol and tobacco use. While consumption of fruits and vegetables may decrease overall risk, much of this protection may be confounded by high levels of tobacco and alcohol intake. In addition, dramatic differences across continents and ethnic groups, with resultant variations in diet, may be a key limitation in generalizing findings from the various studies reported to date.

Acknowledgements

We thank the study participants, the collaborating clinicians and the research staff involved throughout the study.

Supported by NIH grants CA78609, CA100679, T32 ES07155 and The Flight Attendants Medical Research Institute.

Appendix 1

The total vegetable group consisted of the following food items: tomatoes, tomato juice, tomato sauce, salsa, tofu/soy beans, string beans, broccoli, cabbage/coleslaw, cauliflower, Brussels sprouts, raw carrots, cooked carrots/carrot juice, corn, peas/lima beans, mixed vegetables, beans/lentils, dark orange squash, eggplant/zucchini/summer squash, yams/sweet potatoes, cooked spinach, raw spinach, kale/mustard greens/chard, iceberg lettuce, romaine/leaf lettuce, and celery. Total cruciferous vegetable consumption was calculated from five food items: broccoli, cabbage/coleslaw, cauliflower, Brussels sprouts, kale/mustard/chard greens. The total fruit group consisted of: raisins, prunes, bananas, cantaloupe, fresh apples/pears, apple juice, oranges, orange juice, grapefruit, grapefruit juice, other fruit juices, strawberries, blueberries, and peaches/apricots/plums. The total meat group was made up of: eggs, egg beaters, bacon, chicken/turkey sandwich, other chicken/turkey with skin, other chicken/turkey without skin, beef/pork hot dogs, chicken/turkey hot dogs, salami/bologna/other sandwich meat, sausage/kielbasa/other processed meat, lean hamburger, regular hamburger, beef/pork/lamb sandwich or mixed dish, pork, beef/lamb, beef/calf/pork liver, chicken/turkey liver. The

total fish group consisted of: canned tuna, fish cakes/sticks, shrimp/lobster/scallops/clams, dark meat fish, light meat fish. The cereals group consisted of 22 food items: cold breakfast cereal, cooked oatmeal, other cooked breakfast cereal, white bread, dark bread, bagel/English muffin/roll, muffin/biscuit, brown rice, white rice, pasta, tortillas, other grains, pancake/waffle, French fries, baked/boiled/mashed potatoes, potato/corn chips, crackers, pizza, pretzels, oat bran, other bran, wheat germ. Total nuts and beans consumption was calculated from five food items: tofu, beans, peanuts, other nuts, peanut butter. The total dairy intake was calculated from the following: skim milk, 1%/2% milk, whole milk, cream/sour cream, frozen yogurt/sherbet/non-fat ice cream, ice cream, flavored yogurt, plain yogurt, cottage/ricotta cheese, cream cheese, other cheese, butter.

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Table 1
Distribution of cases and controls and corresponding odds ratios and confidence intervals for selected variables

Factor	Cases				Controls				OR [*]	95% CI [*]	OR ^{**}	95% CI ^{**}
	Level	N	%	N	%							
Age	<50	90	17.9	104	14.5			ref ²		ref		
	>=50 to <60	153	30.4	224	31.2			1.55	(1.12, 2.14)	1.39	(1.00, 1.94)	
	>=60 to <70	150	29.8	214	29.9			2.37	(1.66, 3.38)	1.91	(1.32, 2.76)	
	>=70	111	22.0	175	24.4			5.18	(3.67, 7.32)	3.83	(2.67, 5.49)	
Race	White	452	89.7	663	92.5			ref		ref		
	Non_White	52	10.3	54	7.5			1.72	(1.20, 2.46)	1.48	(1.02, 2.14)	
Gender	Male	350	69.4	514	71.7			3.56	(2.54, 4.98)	2.53	(1.77, 3.60)	
	Female	154	30.6	203	28.3			6.50	(4.31, 9.80)	4.37	(2.84, 6.71)	
Site	Oral	248	49.2					2.26	(1.53, 3.35)	1.42	(0.92, 2.18)	
	Larynx	97	19.2					ref		ref		
	Pharynx	151	30.0									
	missing	8	1.6									
Pack Years	<1	103	20.4	269	37.5							
	>=1 to <25	116	23.0	208	29.0			1.55	(1.12, 2.14)	1.39	(1.00, 1.94)	
	>=25 to <45	101	20.0	126	17.6			2.37	(1.66, 3.38)	1.91	(1.32, 2.76)	
	>=45	184	36.5	114	15.9			5.18	(3.67, 7.32)	3.83	(2.67, 5.49)	
	<10	220	43.7	490	68.3			ref		ref		
Drinks/Week	>=10 to <20	67	13.3	101	14.1			1.72	(1.20, 2.46)	1.48	(1.02, 2.14)	
	>=20 to <40	115	22.8	84	11.7			3.56	(2.54, 4.98)	2.53	(1.77, 3.60)	
	>=40	102	20.2	42	5.9			6.50	(4.31, 9.80)	4.37	(2.84, 6.71)	
	No HSD [†]	72	14.3	50	7.0			2.26	(1.53, 3.35)	1.42	(0.92, 2.18)	
Education	HSD	428	84.9	662	92.3			ref		ref		
	missing	4	0.8	5	0.7							
BMI	<18.5	65	12.9	17	2.4			4.96	(2.80, 8.79)	5.81	(3.20, 10.56)	
	>=18.5 to <25	172	34.1	222	31.0			ref		ref		
	>=25 to <30	181	35.9	294	41.0			0.82	(0.62, 1.08)	0.89	(0.66, 1.20)	

Factor	Level	Cases			Controls				
		N	%	N	%				
Total Calories	>=30	86	17.1	184	25.7	0.62	(0.45, 0.86)	0.65	(0.46, 0.92)
	<1500	98	19.4	147	20.1	0.98	(0.73, 1.33)	1.01	(0.73, 1.39)
	1500 to <2500	256	50.8	397	55.4	ref		ref	
	2500 to <3000	81	16.1	103	14.4	1.23	(0.88, 1.71)	1.20	(0.84, 1.70)
Total Non-Alcohol Calories	3000+	69	13.7	70	9.8	1.54	(1.06, 2.24)	1.35	(0.90, 2.02)
	<1500	130	25.8	176	24.6	1.09	(0.83, 1.44)	1.07	(0.79, 1.43)
	1500 to <2500	255	50.6	389	54.3	ref		ref	
	2500 to <3000	68	13.5	95	13.3	1.10	(0.77, 1.56)	1.10	(0.76, 1.59)
	3000+	51	10.1	57	8.0	1.36	(0.90, 2.06)	1.27	(0.81, 1.99)

¹ High School Degree

² Reference group

* Logistic regression model adjusted for age, race and gender

** Logistic regression model adjusted for age, race, gender, tobacco and/or alcohol

Table 2
Odds Ratios and Confidence Intervals for Selected Food Groups

Food Group	Quintiles					Test for Trend
	1	2	3	4	5	
Fruits	Servings/Day	<1.0	>=1.0 to <1.5	>=1.5 to <2.0	>=2.0 to <3.0	>=3.0
	Median	0.50	1.27	1.72	2.39	3.70
	# Cases	154	90	69	95	96
	# Controls	158	116	116	178	149
	OR [*]	referent	0.80	0.62	0.55	0.66
Vegetables	95% CI [*]		(0.56, 1.14)	(0.42, 0.89)	(0.40, 0.77)	(0.47, 0.94)
	OR ^{**}	referent	0.92	0.77	0.72	1.01
	95% CI ^{**}		(0.61, 1.37)	(0.50, 1.17)	(0.49, 1.07)	(0.67, 1.54)
	Servings/Day	<1.5	>=1.5 to <2.0	>=2.0 to <2.5	>=2.5 to <3.5	>=3.5
	Median	1.04	1.76	2.25	2.93	4.57
Fruits and Vegetables	# Cases	163	74	65	101	101
	# Controls	191	121	119	140	146
	OR [*]	referent	0.73	0.64	0.85	0.80
	95% CI [*]		(0.51, 1.04)	(0.44, 0.93)	(0.61, 1.19)	(0.57, 1.12)
	OR ^{**}	referent	0.70	0.71	1.14	1.07
Cruciferous Vegetables	95% CI ^{**}		(0.47, 1.06)	(0.46, 1.09)	(0.78, 1.68)	(0.71, 1.61)
	Servings/Day	<2.5	>=2.5 to <3.5	>=3.5 to <4.5	>=4.5 to <6.0	>=6.0
	Median	1.87	3.00	4.01	5.15	7.55
	# Cases	142	80	89	89	104
	# Controls	145	119	140	149	164
Cruciferous Vegetables	OR [*]	referent	0.70	0.66	0.62	0.65
	95% CI [*]		(0.48, 1.01)	(0.46, 0.94)	(0.43, 0.88)	(0.46, 0.91)
	OR ^{**}	referent	0.74	0.89	0.80	0.99
	95% CI ^{**}		(0.49, 1.12)	(0.59, 1.33)	(0.53, 1.22)	(0.65, 1.52)
	Servings/Week	<0.5	>=0.5 to <1.5	>=1.5 to <2.0	>=2.0 to <3.0	>=3.0
Cruciferous Vegetables	Median	0.14	0.98	1.68	2.38	4.13
	# Cases	88	178	61	62	115

Food Group	Quintiles					Test for Trend
	1	2	3	4	5	
Dairy	# Controls	104	239	119	86	169
	OR *	referent	0.87	0.60	0.82	0.78
	95% CI *		(0.62, 1.23)	(0.39, 0.91)	(0.53, 1.27)	(0.54, 1.14)
	OR **	referent	1.00	0.80	1.18	0.97
	95% CI **		(0.68, 1.49)	(0.50, 1.29)	(0.72, 1.94)	(0.63, 1.50)
	Servings/Day	<1.5	>=1.5 to <2.0	>=2.0 to <2.5	>=2.5 to <4.0	>=4.0
Meat	Median	1.02	1.76	2.24	3.19	5.13
	# Cases	120	70	51	139	124
	# Controls	202	118	86	182	129
	OR *	referent	1.01	1.03	1.32	1.66
	95% CI *		(0.70, 1.47)	(0.68, 1.56)	(0.96, 1.82)	(1.18, 2.32)
	OR **	referent	1.05	1.13	1.41	1.64
Fish	95% CI **		(0.69, 1.60)	(0.71, 1.80)	(0.98, 2.03)	(1.09, 2.46)
	Servings/Day	<1.0	>=1.0 to <1.5	>=1.5 to <2.0	>=2.0 to <2.5	>=2.5
	Median	0.72	1.25	1.72	2.19	3.04
	# Cases	111	112	127	73	81
	# Controls	168	179	153	92	125
	OR *	referent	0.99	1.30	1.25	1.02
Fish	95% CI *		(0.71, 1.39)	(0.93, 1.82)	(0.84, 1.85)	(0.70, 1.49)
	OR **	referent	0.99	1.39	1.06	0.77
	95% CI **		(0.67, 1.46)	(0.94, 2.05)	(0.66, 1.71)	(0.46, 1.29)
	Servings/Week	<1.0	>=1.0 to <1.5	>=1.5 to <2.0	>=2.0 to <3.0	>=3.0
	Median	0.63	1.26	1.82	2.38	4.41
	# Cases	123	76	96	103	106
Fish	# Controls	134	117	134	156	176
	OR *	referent	0.72	0.80	0.73	0.66
	95% CI *		(0.49, 1.04)	(0.56, 1.14)	(0.51, 1.04)	(0.47, 0.93)
	OR **	referent	0.86	0.96	1.03	0.88
	95% CI **		(0.56, 1.31)	(0.63, 1.45)	(0.62, 1.53)	(0.58, 1.33)

Food Group	Quintiles					Test for Trend
	1	2	3	4	5	
Cereals and Starchy Roots	Servings/Day	<2.5	>=2.5 to <3.5	>=3.5 to <4.5	>=4.5 to <5.5	>=5.5
	Median	1.92	3.02	4.02	4.98	6.56
	# Cases	155	110	91	56	92
	# Controls	156	171	150	102	138
	OR [*]	referent	0.66 (0.47, 0.91)	0.61 (0.44, 0.87)	0.57 (0.38, 0.84)	0.68 (0.48, 0.96)
	95% CI ^{**}					
Legumes and Nuts	OR ^{**}	referent	0.64 (0.44, 0.93)	0.59 (0.39, 0.89)	0.61 (0.37, 0.99)	0.60 (0.37, 0.98)
	95% CI ^{**}					
	Servings/Week	<1.0	>=1.0 to <2.0	>=2.0 to <4.0	>=4.0 to <6.0	>=6.0
	Median	0.56	1.54	3.29	4.69	8.05
	# Cases	146	91	112	52	103
	# Controls	146	149	172	98	152
	OR [*]	referent	0.61 (0.43, 0.87)	0.66 (0.47, 0.92)	0.54 (0.36, 0.82)	0.69 (0.49, 0.97)
	95% CI [*]					
	OR ^{**}	referent	0.69 (0.47, 1.02)	0.68 (0.47, 0.99)	0.56 (0.35, 0.91)	0.72 (0.48, 1.08)
	95% CI ^{**}					

* Logistic regression model adjusted for age, race and gender

** Logistic regression model adjusted for age, race, gender, bmi, education, tobacco, alcohol and non_alcohol caloric intake

Table 3
Odds Ratios and Confidence Intervals by Quintile of Micronutrient Intake (Including Supplements)

Nutrient	Quintile					Test for Trend
	1 (lowest)	2	3	4	5 (highest)	
Vitamin B1 (including supplements)	Range (mg)	1.33-1.77	1.78-2.42	2.43-3.13	3.14+	
	Median (mg)	1.06	1.56	2.09	2.78	3.96
	# Cases	116	86	91	104	107
	# Controls	140	144	146	143	144
	OR*	ref	0.73	0.77	0.89	0.94
	95% CI*		(0.51, 1.10)	(0.62, 1.27)	(0.66, 1.34)	0.73
Vitamin B2 (including supplements)	OR**	ref	0.89	0.92	1.18	0.21
	95% CI**		(0.58, 1.36)	(0.60, 1.42)	(0.77, 1.81)	
	Range (mg)	<1.55	1.55-2.13	2.14-2.89	2.90-3.85	3.86+
	Median (mg)	1.22	1.87	2.47	3.31	4.76
	# Cases	91	103	88	114	108
	# Controls	139	144	144	144	146
Vitamin B6 (including supplements)	OR*	ref	1.13	0.97	1.25	0.27
	95% CI*		(0.78, 1.64)	(0.67, 1.42)	(0.87, 1.80)	
	OR**	ref	1.27	1.15	1.52	0.13
	95% CI**		(0.83, 1.94)	(0.73, 1.81)	(0.99, 2.33)	
	Range (mg)	<1.70	1.70-2.39	2.40-3.27	3.28-4.64	4.65+
	Median (mg)	1.37	2.02	2.73	3.94	5.95
Vitamin B12 (including supplements)	# Cases	85	103	111	107	98
	# Controls	142	144	143	141	147
	OR*	ref	1.24	1.34	1.32	0.61
	95% CI*		(0.85, 1.79)	(0.93, 1.94)	(0.91, 1.92)	
	OR**	ref	1.51	1.72	1.88	0.33
	95% CI**		(0.98, 2.32)	(1.10, 2.69)	(1.21, 2.91)	
Vitamin B12 (including supplements)	Range (mcg)	<4.86	4.86-7.09	7.10-10.15	10.16-15.54	15.55+
	Median (mcg)	3.69	5.94	8.41	12.35	23.26
	# Cases	83	98	80	121	122

Nutrient	Quintile					Test for Trend
	1 (lowest)	2	3	4	5 (highest)	
Carotenes (including supplements)	# Controls	143	143	144	143	144
	OR [*]	ref	1.22	0.99	1.54	1.57
	95% CI [*]		(0.84, 1.77)	(0.67, 1.45)	(1.07, 2.22)	(1.08, 2.27)
	OR ^{**}	ref	1.33	1.05	1.77	1.61
	95% CI ^{**}		(0.87, 2.03)	(0.67, 1.64)	(1.16, 2.69)	(1.05, 2.47)
	Range (IU)	<3685	3685-5299	5300-7677	7678-1212736	12737+
Vitamin E (including supplements)	Median (IU)	2556.54	4490.19	6280.77	9676.10	16870.62
	# Cases	106	90	108	100	100
	# Controls	143	143	144	143	144
	OR [*]	ref	0.86	1.02	0.95	0.94
	95% CI [*]		(0.59, 1.23)	(0.71, 1.45)	(0.66, 1.36)	(0.65, 1.35)
	OR ^{**}	ref	0.95	1.38	1.31	1.46
Folate (including supplements)	95% CI ^{**}		(0.63, 1.44)	(0.92, 2.08)	(0.86, 2.00)	(0.96, 2.22)
	Range (mg)	<6.40	6.40-9.29	9.30-17.30	17.31-29.97	29.98+
	Median (mg)	4.79	7.64	11.88	22.35	72.70
	# Cases	118	81	99	116	90
	# Controls	142	144	144	143	144
	OR [*]	ref	0.68	0.84	1.01	0.79
Folate (including supplements)	95% CI [*]		(0.47, 0.98)	(0.59, 1.19)	(0.71, 1.43)	(0.55, 1.13)
	OR ^{**}	ref	0.94	1.07	1.39	1.12
	95% CI ^{**}		(0.61, 1.45)	(0.68, 1.69)	(0.92, 2.11)	(0.72, 1.73)
	Range (mcg)	<327	327-437	438-617	618-799	800+
	Median (mcg)	251.16	381.58	524.65	702.92	961.60
	# Cases	120	78	103	103	100
Folate (including supplements)	# Controls	143	143	144	143	144
	OR [*]	ref	0.66	0.88	0.88	0.86
	95% CI [*]		(0.46, 0.96)	(0.62, 1.25)	(0.62, 1.26)	(0.61, 1.23)
	OR ^{**}	ref	0.79	1.15	1.22	1.20
	95% CI ^{**}		(0.52, 1.21)	(0.76, 1.73)	(0.81, 1.82)	(0.79, 1.80)

Nutrient	Quintile					Test for Trend
	1 (lowest)	2	3	4	5 (highest)	
Vitamin C (including supplements)	Range (mg)	93-146	147-206	207-569	570+	
	Median (mg)	63.05	176.68	263.09	765.41	
	# Cases	107	102	107	71	
	# Controls	143	144	143	144	
	OR [*]	ref	0.96	1.02	0.68	0.01
	95% CI [*]		(0.79, 1.59)	(0.71, 1.46)	(0.46, 0.99)	
Vitamin D (including supplements)	OR ^{**}	ref	1.47	1.54	1.23	0.99
	95% CI ^{**}		(0.90, 2.02)	(1.00, 2.38)	(0.79, 1.90)	
	Range (IU)	<139	224-414	415-610	611+	
	Median (IU)	97.80	293.52	536.45	785.08	
	# Cases	100	99	130	85	
	# Controls	143	144	143	144	
Calcium (including supplements)	OR [*]	ref	1.01	1.34	0.88	0.82
	95% CI [*]		(0.64, 1.34)	(0.94, 1.91)	(0.60, 1.27)	
	OR ^{**}	ref	1.19	1.72	1.16	0.09
	95% CI ^{**}		(0.65, 1.52)	(1.16, 2.55)	(0.75, 1.78)	
	Range (mg)	<570	570-738	934-1343	1344+	
	Median (mg)	461.17	663.74	1106.05	1586.25	
Animal Fat	# Cases	121	83	120	85	
	# Controls	143	144	143	144	
	OR [*]	ref	0.70	1.01	0.71	0.28
	95% CI [*]		(0.57, 1.16)	(0.71, 1.42)	(0.49, 1.03)	
	OR ^{**}	ref	0.84	1.39	0.89	0.96
	95% CI ^{**}		(0.68, 1.53)	(0.93, 2.07)	(0.59, 1.35)	
Animal Fat	Range (gm)	<24.1	24.1-32.5	41.2-51.6	51.7+	
	Median (gm)	18.79	28.70	45.92	63.13	
	# Cases	85	89	107	139	
	# Controls	143	144	143	144	
	OR [*]	ref	1.09	1.34	1.73	<0.01

Nutrient	Quintile					Test for Trend
	1 (lowest)	2	3	4	5 (highest)	
95% CI*		(0.70, 1.50)	(0.74, 1.59)	(0.92, 1.95)	(1.20, 2.48)	
OR**	ref	1.08	1.01	1.37	1.50	0.02
95% CI**		(0.71, 1.65)	(0.66, 1.55)	(0.90, 2.09)	(0.99, 2.27)	

* Logistic regression model adjusted for age, race and gender

** Logistic regression model adjusted for age, race, gender, bmi, education, tobacco, alcohol and non_alcohol caloric intake (residual method)