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Diet and the Risk of Head and Neck Cancer: A Pooled Analysis in the INHANCE Consortium

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Conflict of interest statement

None declare.

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Abstract

We investigated the association between diet and head and neck cancer (HNC) risk using data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. The INHANCE pooled data included 22 case-control studies with 14,520 cases and 22,737 controls. Center-specific quartiles among the controls were used for food groups and frequencies per week were used for single food items. A dietary pattern score combining high fruit and vegetable intake and low red meat intake, was created. Odds ratios (OR) and 95% confidence intervals (CI) for the dietary items on the risk of HNC were estimated with a two-stage random effects logistic regression model. An inverse association was observed for higher frequency intake of fruit (4th vs. 1st quartile OR=0.52, 95% CI=0.43–0.62, p_{trend}<0.01) and vegetables (OR=0.66, 95% CI=0.49–0.90, p_{trend}=0.01). Intake of red meat (OR=1.40, 95% CI=1.13–1.74, p_{trend}=0.13) and processed meat (OR=1.37, 95% CI=1.14–1.65, p_{trend}<0.01) were positively associated with HNC risk. Higher dietary pattern scores, reflecting high fruit/vegetable and low red meat intake, were associated with reduced HNC risk (per score increment OR=0.90, 95% CI=0.84–0.97).

Keywords

Diet; head and neck cancer; fruit and vegetable; red meat; processed meat

Introduction

Head and neck cancer (HNC), defined as cancers of the oral cavity, oropharynx, hypopharynx, and larynx, is the sixth most common cancer in the world, accounting for about 900,000 cases and 300,000 deaths in 2008 [1]. Tobacco smoking and alcohol drinking are the two most important risk factors for HNC [2], contributing to over 70% of HNC cases [3]. Other important risk factors include passive smoking [4,5], human papillomavirus (HPV) infection [6], low body mass index (BMI) [7], and family history of cancer [8].

The inverse association of fruits and vegetables against HNC have been reported in many epidemiologic studies [9–16]. The recent World Cancer Research Fund (WCRF) report into diet and cancer summarized that the evidence was strong enough to support a probable causal relationship for a decreased HNC risk with non-starchy vegetables, fruits, and food containing carotenoids [17]. However, the evidence of the role of other food groups and the risk of HNC is inconsistent. Meat consumption was suggested to be a risk factor for several cancers [10,17–19], including HNC [9,15,20–22], but the association was not consistent [11,23]. Dairy products were positively associated with HNC in an American study [23], but the association was not observed in an Eastern European [11] or international study [24]. Even for vegetables, the evidence for cruciferous vegetables was not sufficient to make a conclusion in relation to HNC risks [11,12,17,23–31]. Moreover, residual confounding from smoking is still a major concern for the observed associations.

The International Head and Neck Cancer Epidemiology (INHANCE) Consortium is a collaboration of research groups leading large molecular epidemiology case-control studies of HNC (http://inhance.iarc.fr/). The consortium covers populations from Europe, North America, Latin America, India, Japan, and Australia. The large sample size enables us to explore the association between diet and HNC risk within never smokers to avoid the residual confounding from smoking. The geographic coverage helps us to explore the dietary effects on different background fruit and vegetable consumption levels. We took advantage of the data from the consortium to explore the associations between food groups and the risk of HNC.

Methods

The current analysis included 22 of the 26 studies in the consortium pooled data version 1.3. Compared with a previous publication [3], the current dataset included a US multicenter study [32], the MSKCC study [33], the Seattle-LEO study [34], the Western Europe study [9], the Saarland study [35], the Heidelberg study [36], and the Japan study [37]. Appendix 1 lists the recruitment periods, study designs (hospital- or population-based study), and participating rates for each study. There were 14,852 head and neck cancer cases and 22,987 controls.

Cases and controls with missing data on age, sex, or race/ethnicity, and cases with missing information on the site of origin of their cancer were excluded (332 cases and 250 controls). In total, 14,520 cases and 22,737 controls were included in the analysis. Among the cases, 3,859 were oral cancer, 4,755 were pharyngeal cancer, 1,513 were cancer of the oral cavity or pharynx not otherwise specified, 4,073 were laryngeal cancer and 320 overlapping (Table 1). Written informed consent was obtained from all study subjects and the studies were approved by relevant ethics committees at each of the institutes involved. Questionnaires were collected from all the individual studies, to assess the comparability of the collected data and of the wording of interview questions among the studies. Data from individual studies were received with personal identifiers removed. Each data item was checked for illogical or missing values and inconsistencies were resolved as necessary. Details on harmonizing questionnaire data have been published previously [2]. Briefly, the definitions for ever-smoking and drinking are different across studies. We reclassified ever tobacco smokers as those who have smoked at least 100 cigarettes or 100 cigars or 100 pipes in their lifetime. In our previous analyses, drinking (>3 drinks/day) was associated with an increased HNC risk [2] among never smokers, thus we classified heavy drinker as those who have consumed alcohol three or more drinks/day.

Food questionnaires were designed by each individual study. For our analysis, we considered questionnaire wordings to group the food items (Appendix 2). In brief, four major food categories were grouped into: vegetables, fruits, animal products, and others (cereals and grains). Several food items and sub-food categories were identified within each major food categories. Two units were used in the analyses: center-specific quartiles among the controls for food groups and frequency per week (arbitrary chosen cutoffs: <once per week, 1–3 times per week, 3–7 times per week, and ≥7 times per week) for single food items. A score which indicated high consumption of fruit and vegetable intake (0 for the lowest quartile and 3 for the highest quartile) and low red meat (0 for the highest quartile and 3 for lowest quartile) was created for each subject by summing up the scores in each

food group. The association between dietary pattern scores and HNC risk was only considered for studies which contributed to all of the three food groups (fruit, vegetable, and red meat; Aviano, Italy Multicenter, Switzerland, Seattle, Tampa, Los Angeles, Puerto Rico, Latin America, Boston, US Multicenter, MSKCC, Seattle-LEO, Western Europe, and Japan).

The associations between food groups/items and HNC risk were assessed by estimating odds ratios (OR) and 95% confidence intervals (CI) with unconditional logistic regression models for each study. Pooled ORs were estimated with a random-effects logistic regression model [38]. To adjust for the potential confounders, the models included age (5-year categories), sex, race/ethnicity (categories), center, education level (categories), packyears of cigarette smoking (continuous), duration of cigar smoking (continuous), duration of pipe smoking (continuous), intensity of alcohol drinking (continuous), and weight (kg, continuous). Information on ethnicity was not collected in the Central Europe, Saarland, and Heidelberg studies. In these studies, all subjects were classified as non-Hispanic white, since the large majority of these populations are expected to be white. Information on education was not collected in the France, Rome, and Japan studies. Weight was not available in the Seattle and Heidelberg studies. Multiple imputations with the PROC MI procedure in the SAS package was applied to impute the missing values of education, considering case-control status, age, sex, race, and study regions. For the Japan study, education was imputed by case-control status, age, and sex, according to the Asian population in the North American studies, because the socioeconomic status in Japan is expected to be similar to that in the North American countries. Stratified analyses were conducted by cancer site (oral cavity, pharynx, oropharynx, and larynx), age (<45 years and ≥45 years), sex, race (White, Black, Hispanic, Asian, and Brazilian), geographic region (Europe, North America, Latin America, and Asia and others), study type (hospital-based and population-based), tobacco smoking status (never, former, and current), and intensity of alcohol drinking (≤3 drinks per day and >3 drinks per day). Heterogeneity across stratum was assessed by I^2 statistics and Q test [39]. Subset analyses were conducted according to the completeness of dietary questionnaire (all, at least 30% completed, at least 50% completed, and at least 80% completed) and in the studies which aimed at getting dietary habits at least one year before disease diagnosis/ interview.

Analyses were performed using SAS 9.1. Heterogeneity tests were performed by STATA SE11. All tests were two sided and statistical significance was assessed at the level of 0.05.

Results

Table 1 summarizes the characteristics of cases and controls from all studies. Overall, controls included more individuals who were women, were younger, had higher education, and had a heavier average weight than the cases.

Heterogeneity across studies was detected for almost all food groups/items. Pooled results from random-effects model were reported. Table 2 presents the OR and 95% CI for vegetables and the HNC risks. Overall vegetable intake (excluding potatoes) showed an inverse association with HNC (4^{th} vs. 1^{st} quartile: OR=0.66, 95% CI=0.49–0.90, p_{trend}=0.01). Similar associations were observed for non-starchy vegetables, especially green vegetables and allium vegetables, but not for cruciferous vegetables. Consumption of green salad, lettuce, and fresh tomatoes more than 7 times per week were associated with lower HNC risks compared to consumption less than once per week. Potato intake was associated with an increased risk of HNC (OR=1.24, 95% CI=1.05–1.46), especially for fried potatoes (OR=2.97, 95% CI=1.40–6.32).

Lower head and neck cancer risks were also observed for higher fruit intake (Table 3). Individuals who had the highest overall fruit intake had lower HNC risk (4^{th} vs. 1^{st} quartile OR =0.52, 95% CI=0.43–0.62, p_{trend}<0.01), especially with the highest intake of citrus fruits and apples and pears. On the other hand, higher intake of several meat products showed an increased risk for HNC (Table 4), notably for red meat (beef + pork: OR=1.40, 95% CI=1.13–1.74, p_{trend}=0.13) and processed meats (OR=1.37, 95% CI=1.14–1.65, p_{trend}<0.01), while white meat (poultry + fish) seemed to be inversely associated (OR=0.68, 95% CI=0.55–0.84, p_{trend}<0.01). Higher egg consumption was also associated with higher HNC risk (OR=1.44, 95% CI=1.12–1.86). No associations between cereals and grains and HNC risk were observed in these analyses (Table 5). Appendix 3 and Appendix Figure 1–6 show the results from the stratified analyses for the major findings. Ethnicity and study region seemed to be the major source of heterogeneity (I^2=73% for race and 83% for region for the association between red meat intake and HNC risk, and 59% for race, and 53% for region for the association with vegetable intake). A higher dietary pattern score, which indicated higher consumption of fruit and vegetable and lower consumption of red meat, was associated with lower HNC risk (Table 6, OR for each score increment=0.90, 95% CI=0.84–0.97, p_{trend}=0.01).

Table 7 presents the association between major food groups and HNC risks among subjects who were never smokers and light drinkers. Fruit intake was inversely associated with HNC risk (4^{th} vs. 1^{st} quartile: OR=0.66, 95% CI=0.48–0.92, p_{trend}=0.27), red meat intake was positively associated with HNC risk (OR=1.55, 95% CI=1.15–2.10, p_{trend}=0.19), and a high score was associated with lower HNC risk (7–9 vs. 0–2, OR=0.48, 95% CI=0.32–0.74, p_{trend}=0.04).

Discussion

Results from our data support the conclusions from earlier studies that a higher frequency of fruit and vegetable intake were inversely associated with HNC risk [9–15,19,22,24,26–28,30,40–47] and red meat and processed meat were positively associated with increased risks of HNC [9,15,16,20–22,28,31,40]. The associations were consistent among subjects who were never smokers and light drinkers. A dietary pattern high in fruit and vegetable and low in red meat intake was associated with decreased HNC risk. Ethnicity and study region could be the major sources of heterogeneity.

The associations between vegetable and HNC were observed mostly in smokers or heavy drinkers but not in never-smokers and light drinkers; this could be explained by residual confounding from smoking or drinking because smokers tend to consume more energy from alcohol and less energy from vegetables [48] and the measurement error might be correlated between diet and smoking behavior. In the present study, we adjusted for packyears of cigarette smoking as well as for duration of cigar and pipe use and drinking intensity for alcohol consumption, thus the residual confounding effect should have been minimized, although it might not be completely eliminated. Removing smoking and drinking variables from the regression model, the OR was 0.56 (95% CI=0.41–0.76) comparing the 4^{th} to the 1^{st} quartile; the ORs were 0.64 (95% CI=0.47–0.88) if adjusted for smoking variables and 0.59 (95% CI=0.44–0.79) if adjusted for drinking variable. All of these estimates were stronger than the full model estimate, OR=0.66, 95% CI=0.49–0.90 (Table 2). Reductions of the HNC risk in never smokers and light drinkers were observed with non-starchy vegetables and carrots (data not shown). An explanation for the limited association in never smokers could be that nutrients in vegetables, such as vitamin C, vitamin E, folate, fibre, and flavonoids, could modulate the carcinogenic effects of smoking by reducing the smoke-induced oxidative damage or inflammatory responses [49–52], thus the effects can only be observed in smokers. An alternative explanation is that the etiology of HNC in never smokers might be different from that in smokers [53–55], such as HPV, an established risk factor for oropharyngeal cancers [56]. A study has reported that HPV infection may modify the association between fruit intake and HNC risk [57].

We observed heterogeneity in the Asian (I^2=58.8%, p=0.033; Appendix figure 1). The p for heterogeneity was 0.74 if removing the Asians from the meta-analysis. Nevertheless, higher vegetable intake was associated with lower HNC risk in the Asian population.

Fruit intake was inversely associated with HNC in the current analyses, as previously reported [9,10,12,15,19,22,24,26–28,30,40–47,58], especially for citrus fruits, and apples and pears. Smoking status did not seem to influence the associations between fruit and HNC risk in the current analyses, as reported by other studies [10,27,28,30,41,42,58]. The inverse associations from fruit intake were consistent across subsites of HNC, strata of age and sex, and study type, i.e. population controls and hospital controls (Appendix Figure 2).

In terms of other food groups, we observed increased risks for a high frequency of red meat consumption (including beef and pork) and processed meat. Red meat and processed meat are convincing causes of colorectal cancer and suggestive causes of esophageal and lung cancers [17,21,59,60]. The mechanisms behind red meat and processed meat and cancer risks include iron over-storage or the oxidative stress resulting from free radicals [17] and the carcinogens generated or added during meat preparation [61] or preservation [17]. This increased risk was observed not only by comparing the relative high to the relative low consumption but also by comparing individuals who ate beef or pork greater than seven times per week to those who ate less than once per week.

On the other hand, we observed an inverse association between red meat and HNC risk from studies in Asia. This could be because that the Japanese population (the only study contributed to this sub-analyses) generally consumes less red meat [62] and more vegetables [17,63] than populations from the North America or Western Europe.

In contrast, we observed an inverse association between white meat (a combination of poultry, fish, and shellfish) and HNC. The epidemiological evidence for the association between white meat and HNC has been inconsistent. A prospective investigation in the US (the NIH-AARP cohort, [64]) found an inverse association between poultry and fish intake and digestive and respiratory cancers, including a strong inverse association between poultry intake and laryngeal cancer among women. The authors attributed the inverse association to the red meat substitution effects. Relative to red meat, poultry and fish are lower in saturated fat and heme iron and may result in less exposure to free radicals or carcinogens generated during the processing of red meat or processed meat [64]. Alternatively, poultry is high in zinc, which might protect against oxygen radicals and lipid peroxidation that can promote carcinogenesis [65]. Fish contains omega-3 fatty acids, which is associated with better immune function [66]. However, poultry and fish intake could be an indicator of general nutritional status. Nevertheless, the heterogeneity was not evident in any subgroups (Appendix Figure 4) and a decreasing trend (though not statistical significant) was observed among never smoker and light drinkers (Table 7). Mutual adjustment for red and white meat did not change the associations between HNC and white and red meat substantially.

We also observed an increased risk for consuming more than three eggs per week compare to less than one egg per week. The association has been observed previously, but results have been inconsistent [15,16,25,27–29,31,40,44–47,67–69]. We performed principal component analysis on food items for each study in our consortium. Egg consumption showed an association with meat intake in most of the studies: Milan, Aviano, Italy Multicenter, Switzerland, Central Europe, Seattle, North Carolina, Tampa, Los Angeles, Latin America, Boston, US Multicenter, MSKCC, Seattle-LEO, and Japan. On the other hand, there were associations between egg intake and fruit and vegetable intakes for other studies: France, Puerto Rico, IARC Multicenter, and Saarland. Egg consumption might be a marker of special diet requirements. However, stratification by fruit, vegetable, red meat, or processed meat intake did not alter the observed positive associations.

Because high intake of some dietary items might be correlated with lower intake of other items, we addressed this pattern with a score, which reflects high intake of fruit and vegetable and low intake of red meat. We observed that a higher score was associated with a reduced HNC risk. The association was consistent across subsites of HNC, sex, race, region, type of controls, dietary information at least one year before diagnosis or interview, and completeness of FFQ (Appendix Figure 6) and was retained in the never smoker and light drinker population (Table 7). This observation further strengthens the fact that healthier dietary habit, i.e. high fruit and vegetable and low red meat intake, plays a role in HNC.

Although our study included a large numbers of subjects from studies from different geographic areas with different dietary patterns, these properties may be also a limitation of the study. Though we assessed that heterogeneity may have partly been due to study design or characteristics of the study populations, there were other potential source of heterogeneity that we were not able to control. First, questionnaires were not standardized but each study had its own questionnaire aiming at their specific population and testing for different hypotheses. To overcome this limitation, we have tried to group the detailed food items into broad food groups and analyzed the food groups and food items in both relative (quartiles) and absolute frequencies (times/week), using a random-effect model. Second, the quantity of food consumed was not available for most of the studies. All of the above may contribute to the observed heterogeneity across studies. Other limitations include: total energy intake, an important confounder for dietary intake analysis, was not available for all studies. We adjusted for weight to address this limitation because weight would reflect the energy intake in middle-aged adults [70]. A subset analysis restricted to studies that provided total energy intake showed that the point estimates did not substantially change after adjustment for total energy intake or weight. Multiple comparisons were made; some of the observed association might be due to chance. Although there were some limitations from difficulties in standardizing questionnaires, our study provided unique opportunities to explore differences in subgroups and potential sources of heterogeneity. Unlike meta-analysis, we had individual level data in our database. All data were evaluated and standardized across all studies [2], thus we were able to adjust the potential confounders consistently.

Generally speaking, previous case-control studies on diet and HNC risks reported stronger associations than did cohort studies [10, 12, 22]. While recall bias could result in relatively strong associations in case-control studies, behavior change after recruitment in cohort studies could also dilute the associations. In addition, the inclusion criteria for the control group might alter the true distribution of exposures in the base population (selection bias). Hospital-based studies excluding controls with diseases that share risk factors with HNC might increase the selection probability of unexposed controls, if the exposure is associated with the risk factors, and bias the estimates away from null. Nevertheless, no heterogeneity was observed between population- and hospital-based studies, and case-control studies and cohort studies yield similar messages on diet and HNC risks, i.e. lower HNC risks with higher fruit and vegetable consumption and lower meat consumption, especially red meat. Our study further provides evidence of these associations among never smokers and light drinkers.

Supplementary Material

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Table 1

Characteristics of the study population

	Cases		Controls	
	N	**%**	**N**	**%**
Total	14520		22737	
Age				
<40	527	3.6	1361	6.0
40–45	726	5.0	1380	6.1
45–50	1420	9.8	2188	9.6
50–55	2140	14.7	3347	`4.7
55–60	2680	18.5	3869	17.0
60–65	2560	17.6	3728	16.4
65–70	2138	14.7	3195	14.1
70–75	1516	10.4	2409	10.6
>=75	813	5.6	1260	5.5
Sex				
Men	11443	78.8	16457	72.4
Women	3077	21.2	6280	27.6
Race				
White	10341	71.2	16069	70.7
Black	543	3.7	653	2.9
Hispanic	155	1.1	361	1.6
Asia	1146	7.9	3764	16.6
Other	144	1.0	184	0.8
Brazilian	2191	15.1	1706	7.5
Education				
None	497	3.4	344	1.5
Junior High School	5440	37.5	7307	32.1
Some High School	2538	17.5	3054	13.4
High School	1366	9.4	1865	8.2
Some College	2009	13.8	3598	15.8
Some Graduate	1027	7.1	2558	11.3
Missing	1643	11.3	4011	17.6
Subtype				
Oral cavity	3859	26.6		
Pharynx	4755	32.7		
Oral/pharynx NOS	1513	10.4		
Larynx	4073	28.1		
Head and neck NOS	320	2.2		

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for vegetable intake and head and neck cancer risk

Quartiles Vegetables	1st quartile	2nd quartile			3rd quartile			4th quartile			P for trend	No. of studies	P for heterogeneity[1]
	Ca/co	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI			
Overall (excluding potato)	4558/5039	3195/5123	0.77	(0.68–0.87)	2750/4952	0.77	(0.66–0.90)	2465/5659	0.66	(0.49–0.90)	0.01	22	<0.01
Non-starchy vegetables	4508/5052	2920/4564	0.78	(0.70–0.86)	2678/5063	0.74	(0.64–0.84)	2209/4708	0.68	(0.51–0.90)	0.03	20	<0.01
Green vegetables	4439/4574	2819/4636	0.77	(0.69–0.87)	2790/5107	0.73	(0.64–0.84)	2043/4285	0.65	(0.53–0.81)	<0.01	18	<0.01
Cruciferous vegetables	3071/3896	2859/4510	0.92	(0.80–1.05)	2455/4328	0.87	(0.78–0.97)	1792/3617	0.85	(0.66–1.08)	0.66	17	<0.01
Allium vegetables	1263/2073	1053/1442	0.98	(0.76–1.26)	1056/1572	0.86	(0.71–1.05)	576/1026	0.66	(0.54–0.81)	0.02	8	0.02
Spinach	1458/2061	1184/1910	0.92	(0.74–1.16)	1134/2017	0.87	(0.76–1.01)	914/1694	0.92	(0.74–1.14)	0.38	11	<0.01
Carrots	4567/4998	3143/5089	0.79	(0.73–0.86)	2526/4446	0.76	(0.68–0.86)	1771/3912	0.64	(0.57–0.72)	<0.01	18	<0.01
Tomatoes	3142/3154	2938/3695	0.83	(0.73–0.94)	2690/3947	0.83	(0.70–0.99)	2442/3373	0.80	(0.63–1.00)	0.06	16	<0.01
Beans or Peas	2358/3659	3190/4530	1.03	(0.87–1.23)	3121/4632	0.92	(0.76–1.12)	2123/3197	0.97	(0.77–1.22)	0.21	16	<0.01
Potatoes	1707/2450	2174/3094	1.06	(0.91–1.24)	2376/3163	1.09	(0.97–1.23)	2330/2649	1.24	(1.05–1.46)	0.09	12	<0.01
Frequency per week	**<1 time/week**	**1–3 times/week**			**3–7 times/week**			**>=7 times/week**					
Raw spinach	648/978	22/37	1.06	(0.22–5.22)	22/32	1.83	(0.64–5.23)	4/0	-	-	0.18	4	1.00
Cooked spinach	640/954	68/84	1.34	(0.28–6.34)	31/41	1.22	(0.49–3.05)	3/0	-	-	0.36	4	0.57
Green salad	2010/1521	1907/2248	0.75	(0.67–0.85)	2441/4352	0.66	(0.55–0.79)	1897/3080	0.60	(0.45–0.79)	0.13	12	<0.01
Lettuce	650/533	673/718	0.86	(0.64–1.17)	715/1054	0.68	(0.50–0.93)	277/528	0.52	(0.36–0.76)	0.02	4	0.13
Cabbage	2430/3454	1268/2575	0.92	(0.80–1.07)	423/1480	0.82	(0.71–0.95)	67/255	0.95	(0.43–2.13)	0.55	10	<0.01
Broccoli	2684/4317	872/2235	0.80	(0.70–0.92)	294/897	0.78	(0.61–0.99)	22/97	0.73	(0.37–1.41)	0.97	10	0.21
Mustard greens	1414/2251	132/135	1.46	(0.91–2.35)	40/42	1.39	(0.67–2.85)	16/12	3.19	(0.40–25.7)	0.60	6	0.17
Raw carrots	2018/3289	247/840	0.65	(0.44–0.98)	81/252	0.77	(0.32–1.86)	20/80	0.62	(0.16–2.36)	0.20	4	<0.01
Cooked carrots	1891/3338	369/929	0.80	(0.30–2.18)	98/170	1.21	(0.73–2.02)	5/26	0.86	(0.02–31.9)	0.44	4	<0.01
Fresh tomatoes	1842/1734	2361/2377	0.89	(0.74–1.07)	2379/2660	0.81	(0.71–0.93)	1401/1722	0.77	(0.64–0.92)	0.05	9	<0.01
Tomato sauce	1503/2080	823/1136	1.09	(0.88–1.34)	569/621	1.04	(0.79–1.37)	111/185	1.06	(0.69–1.64)	0.18	6	0.09
Tomato juice	1959/3159	458/400	1.50	(1.13–2.00)	208/179	1.34	(0.95–1.89)	110/92	1.55	(0.96–2.50)	0.12	5	0.58
Pumpkin	3037/3723	346/570	0.89	(0.66–1.19)	124/223	0.76	(0.49–1.17)	45/62	0.92	(0.46–1.87)	0.07	7	<0.01
Tofu	916/2502	208/1177	1.05	(0.66–1.67)	117/674	0.96	(0.64–1.46)	30/164	0.86	(0.32–2.27)	0.33	4	0.23
Boiled potatoes	809/1861	1495/2762	1.23	(0.97–1.56)	398/697	1.07	(0.62–1.86)	128/237	0.98	(0.34–2.78)	0.36	7	<0.01
Fried potatoes	1147/2816	1046/1854	1.37	(0.87–2.16)	238/283	2.23	(0.70–7.11)	42/36	2.97	(1.40–6.32)	0.09	6	<0.01
Yam	2614/3715	361/466	1.10	(0.88–1.39)	60/65	1.41	(0.81–2.45)	12/18	0.90	(0.22–3.64)	0.61	8	0.04

The ORs were adjusted for age, sex, race, center, education level, packyears of cigarette smoking, duration of cigar smoking, duration of pipe smoking, intensity of alcohol drinking, and weight.

[1] An overall p for heterogeneity across studies

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for fruit intake and head and neck cancer risk

Quartiles Fruits	1st quartile	2nd quartile			3rd quartile			4th quartile			P for trend	No. of studies	P for heterogeneity[1]
	Ca/co	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI			
Overall	4962/4889	3040/5040	0.69	(0.61–0.77)	2640/5473	0.63	(0.55–0.73)	2108/5119	0.52	(0.43–0.62)	<0.01	22	<0.01
Citrus	4098/4365	2884/4360	0.75	(0.69–0.82)	2355/4163	0.74	(0.62–0.89)	1790/3729	0.66	(0.56–0.77)	<0.01	16	<0.01
Apples and pears	4224/3563	2673/3502	0.74	(0.62–0.88)	2033/3407	0.61	(0.52–0.71)	1629/3166	0.61	(0.52–0.73)	<0.01	15	<0.01
Banana	3393/3939	2621/3197	0.91	(0.81–1.02)	2042/2694	0.83	(0.71–0.98)	1832/2555	0.76	(0.59–0.97)	0.02	14	<0.01
Peaches	2336/2323	1592/2543	0.80	(0.67–0.94)	1246/2003	0.73	(0.56–0.93)	1376/2461	0.76	(0.58–1.00)	0.02	12	<0.01
Cantaloupe	1277/1418	851/1323	0.76	(0.64–0.90)	679/1193	0.75	(0.63–0.89)	576/948	0.85	(0.62–1.17)	<0.01	9	0.05
Frequency per week	**<1 time/week**	**1–3 times/week**			**3–7 times/week**			**>=7 times/week**					
Citrus	3349/3512	1944/3170	0.65	(0.49–0.85)	1944/3179	0.59	(0.51–0.69)	1310/2520	0.51	(0.41–0.64)	<0.01	9	<0.01
Apples and pears	4081/3560	1885/2394	0.72	(0.54–0.97)	1427/2215	0.61	(0.52–0.73)	1679/3482	0.61	(0.44–0.86)	<0.01	12	<0.01
Banana	4804/5719	2391/2944	0.87	(0.74–1.03)	1666/2194	0.81	(0.64–1.02)	1194/1712	0.72	(0.51–1.01)	0.22	14	<0.01
Peaches	1679/1867	956/1782	0.74	(0.58–0.95)	634/1309	0.75	(0.60–0.93)	464/933	0.64	(0.37–1.10)	0.02	5	0.03
Cantaloupe	2704/3596	510/959	0.86	(0.67–1.12)	166/295	1.06	(0.66–1.72)	74/157	0.77	(0.50–1.19)	0.54	8	0.03

[1] An overall p for heterogeneity across studies

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) for meat and eggs and head and neck cancer risk

Quartiles Animal Products	1st quartile Ca/co	2nd quartile Ca/co	OR	95% CI	3rd quartile Ca/co	OR	95% CI	4th quartile Ca/co	OR	95% CI	P for trend	No. of studies	P for heterogeneity[4]
Overall meats	3084/4883	3003/5224	0.96	(0.87–1.05)	3095/5311	0.99	(0.85–1.15)	3385/4890	1.05	(0.87–1.27)	0.36	21	<0.01
Red meat[1]	1926/3852	2283/4456	1.12	(0.98–1.29)	2382/3894	1.16	(1.00–1.34)	2858/3081	1.40	(1.13–1.74)	0.13	15	<0.01
Beef	1750/2733	2028/2776	1.13	(0.97–1.32)	1990/2863	1.14	(0.99–1.32)	2951/3106	1.37	(1.16–1.61)	<0.01	12	<0.01
Pork	1795/3185	2343/3204	1.14	(0.94–1.39)	2065/2403	1.42	(1.13–1.78)	2003/1789	1.48	(1.19–1.83)	0.03	11	<0.01
White meat[2]	4442/5158	3896/5364	0.81	(0.70–0.95)	2816/4809	0.75	(0.64–0.86)	1909/4843	0.68	(0.55–0.84)	<0.01	20	<0.01
Poultry	2647/3941	3471/5423	0.94	(0.82–1.07)	2277/3868	0.91	(0.76–1.09)	1669/2836	0.82	(0.64–1.05)	0.03	16	<0.01
Seafood[3]	3054/4135	3720/5768	0.84	(0.76–0.94)	2936/4598	0.86	(0.77–0.97)	2294/3883	0.83	(0.74–0.94)	0.02	19	<0.01
Processed meat	2758/5038	2910/4856	1.21	(1.05–1.38)	2999/5185	1.13	(0.97–1.30)	3763/5057	1.37	(1.14–1.65)	<0.01	21	<0.01
Egg	2145/4172	2869/5093	1.04	(0.89–1.21)	2750/5360	1.11	(0.99–1.25)	3172/4068	1.44	(1.12–1.86)	0.11	20	<0.01
Milk and dairy products	3148/4540	2692/4584	0.97	(0.83–1.13)	2378/4733	0.96	(0.79–1.18)	2618/4454	1.01	(0.77–1.34)	0.96	19	<0.01
Frequency per week	**<1 time/week**	**1–3 times/week**			**3–7 times/week**			**>=7 times/week**					
Beef	860/870	1803/1861	1.15	(0.92–1.45)	1514/1622	1.19	(0.91–1.56)	960/658	1.55	(1.07–2.23)	0.34	4	0.91
Pork	4970/7611	2645/2542	1.28	(0.99–1.65)	485/369	1.37	(1.13–1.66)	106/59	1.81	(1.15–2.84)	0.16	11	<0.01
Boiled chicken	1491/2910	639/1413	1.00	(0.71–1.42)	145/438	0.93	(0.65–1.34)	19/67	0.78	(0.29–2.09)	0.77	5	0.03
Fried chicken	1184/2413	1229/2351	1.14	(0.83–1.57)	176/411	1.00	(0.50–2.03)	17/39	0.82	(0.16–4.21)	0.29	6	<0.01
Liver	4640/10968	866/1509	1.35	(1.02–1.79)	73/95	1.15	(0.73–1.81)	14/15	1.99	(0.59–6.74)	<0.01	12	<0.01
Egg	2443/4534	3707/7303	1.07	(0.93–1.23)	3482/5278	1.41	(1.12–1.77)	1304/1578	1.48	(1.20–1.82)	0.03	20	<0.01

[1] Included beef and pork

[2] Included poultry, fish, and shellfish

[3] Included fish and shellfish

[4] An overall p for heterogeneity across studies

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Table 5

Odds ratios (OR) and 95% confidence intervals (CI) for cereal and grain products and head and neck cancer risk

Quartiles Cereals and grains	1st quartile	2nd quartile			3rd quartile			4th quartile			P for trend	No. of studies	P for heterogeneity[1]
	Ca/co	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI			
Overall	2837/5074	2212/3972	0.82	(0.70–0.96)	2244/3972	0.95	(0.78–1.16)	2244/4081	0.98	(0.80–1.22)	0.81	16	<0.01
Breakfast cereals	1000/1285	842/1355	1.00	(0.84–1.18)	738/1293	0.88	(0.67–1.15)	646/1251	0.93	(0.71–1.23)	0.25	9	<0.01
Bread	2525/4094	2261/3770	0.92	(0.81–1.05)	2284/3901	1.00	(0.81–1.22)	2221/3845	0.98	(0.69–1.41)	0.84	15	<0.01
Corn bread	2535/3833	1886/2339	1.12	(1.00–1.27)	1073/1467	1.06	(0.86–1.30)	1218/1305	1.27	(1.03–1.55)	0.50	9	<0.01
Pasta and rice	2079/3748	2074/3820	0.97	(0.78–1.21)	3267/5137	1.01	(0.82–1.25)	1976/3020	1.16	(0.95–1.42)	0.25	15	<0.01
Frequency per week	**<1 time/week**	**1–3 times/week**			**3–7 times/week**			**>=7 times/week**					
Corn bread	4763/6662	1336/1605	1.07	(0.88–1.30)	440/471	1.13	(0.93–1.38)	346/373	1.24	(0.97–1.58)	0.27	9	<0.01
Rice	948/1241	484/966	0.83	(0.67–1.03)	279/616	0.85	(0.64–1.11)	818/3336	1.10	(0.66–1.83)	0.31	8	0.05
Corn	1639/2128	788/990	0.95	(0.79–1.15)	277/337	0.99	(0.76–1.30)	36/31	1.59	(0.43–5.85)	0.01	7	0.03

[1] An overall p for heterogeneity across studies

Table 6

Odds ratios (OR) and 95% confidence intervals (CI) for dietary pattern scores[1] and head and neck cancer risks

Scores	Cases	Controls	OR[2]	95% CI
0	466	325	1.00	
1	858	754	0.94	(0.74–1.18)
2	1435	1506	0.87	(0.70–1.08)
3	1866	2423	0.72	(0.58–0.88)
4	1535	2557	0.63	(0.49–0.82)
5	1377	2570	0.60	(0.39–0.91)
6	1051	2332	0.54	(0.37–0.78)
7	482	1590	0.42	(0.26–0.67)
8	258	895	0.41	(0.27–0.63)
9	102	401	0.34	(0.24–0.49)
Every 1 score increment			0.90	(0.84–0.97)
p trend			0.01	

[1]Include Aviano, Italian Multicenter, Switzerland, Seattle, Los Angeles, Puerto Rico, South America, Boston, US Multicenter, MSKCC, Seattle-LEO studies, Western Europe, and Japan studies. The higher scores indicate higher fruit and vegetable and lower red meat consumption.

[2]The ORs were adjusted for age, sex, race, center, education level, packyears of cigarette smoking, duration of cigar smoking, duration of pipe smoking, intensity of alcohol drinking, and weight

Table 7

Odds ratios (OR) and 95% confidence intervals (CI) for selected food groups and head and neck cancer risks among never smokers and light drinkers (<=3 drinks/day)

	Case	Control	OR	95% CI
Overall Vegetable				
1st quartile	260	1425	1.00	
2nd quartile	246	1618	0.84	(0.67–1.06)
3rd quartile	233	1572	0.89	(0.71–1.12)
4thquartile	276	1832	0.85	(0.60–1.19)
p for trend			0.15	
Overall Fruits				
1st quartile	255	1180	1.00	
2nd quartile	243	1512	0.76	(0.59–0.95)
3rd quartile	247	1837	0.66	(0.47–0.94)
4thquartile	240	1776	0.66	(0.48–0.92)
p for trend			0.27	
Red meat				
1st quartile	181	1257	1.00	
2nd quartile	194	1466	0.94	(0.72–1.23)
3rd quartile	190	1187	1.26	(0.89–1.77)
4thquartile	164	794	1.55	(1.15–2.10)
p for trend			0.19	
White meat				
1st quartile	277	1398	1.00	
2nd quartile	290	1559	0.85	(0.59–1.24)
3rd quartile	237	1514	0.70	(0.54–0.90)
4thquartile	226	1705	0.62	(0.35–1.12)
p for trend			0.09	
Processed meat				
1st quartile	290	1848	1.00	
2nd quartile	264	1618	1.02	(0.79–1.31)
3rd quartile	220	1558	0.34	(0.04–2.91)
4thquartile	183	1286	1.12	(0.90–1.39)
p for trend			0.62	
Scores				
0–2	110	556	1.00	
3–4	206	1256	0.77	(0.56–1.06)
5–6	197	1486	0.64	(0.43–0.95)
7–9	115	1016	0.48	(0.32–0.74)
p for trend			0.04	