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Dietary fiber intake and head and neck cancer risk: A pooled analysis in the International Head and Neck Cancer Epidemiology consortium

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Abbreviations: BMI: body mass index; CI: confidence interval; DMV: department of motor vehicles; FFQ: food-frequency questionnaire; HNC: head and neck cancer; INHANCE: International Head and Neck Cancer Epidemiology consortium; L: large; M: medium; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; NA: not available; NE: Not estimable; NIH: National Institutes of Health; OR: odds ratio; S: small.

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

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The possible role of dietary fiber in the etiology of head neck cancers (HNCs) is unclear. We used individual-level pooled data from ten case-control studies (5959 cases and 12,248 controls) participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium, to examine the association between fiber intake and cancer of the oral cavity/pharynx and larynx. Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were estimated using unconditional multiple logistic regression applied to quintile categories of non-alcohol energy-adjusted fiber intake and adjusted for tobacco and alcohol use and other known or putative confounders. Fiber intake was inversely associated with oral and pharyngeal cancer combined (OR for 5th *vs*. 1st quintile category = 0.49, 95% CI: 0.40–0.59; *p* for trend <0.001) and with laryngeal cancer (OR = 0.66, 95% CI: 0.54–0.82, *p* for trend <0.001). There was, however, appreciable heterogeneity of the estimated effect across studies for oral and pharyngeal cancer combined. Nonetheless, inverse associations were consistently observed for the subsites of oral and pharyngeal cancers and within most strata of the considered covariates, for both cancer sites. Our findings from a multicenter large-scale pooled analysis suggest that, although in the presence of between-study heterogeneity, a greater intake of fiber may lower HNC risk.

What's new?
Higher intake of fruit and vegetables is thought to lower the risk of HNCs. These foods are rich in phytochemicals and vitamins, but could dietary fiber also play a role in this protective effect? In this analysis, the authors pooled data from 10 separate studies to examine the association between fiber intake and cancer of the oral cavity/pharynx and larynx. Their results suggest that a greater intake of fiber may indeed lower HNC risk.

There are >500,000 new cases of head and neck cancers (HNCs) diagnosed worldwide every year.[1] Approximately 60% of patients are diagnosed with advanced disease, for which prognosis is poor even with a multimodal treatment approach.[2,3] This situation emphasizes the importance of primary prevention of HNCs.

Although the combination of tobacco smoking and alcohol drinking accounts for approximately 80% of HNC risk,[4,5] a role of dietary factors in HNCs has been reported.[6–8] Higher intakes of non-starchy vegetables, foods containing carotenoids, and fruit in general are thought to probably protect against HNC.[8]

Fruit and vegetables are rich sources of compounds that have anti-carcinogenic properties, including vitamins, minerals, fiber, and phytochemicals.[9–12] Among them, dietary fiber could protect against cancer.[13–17] However, the association of dietary fiber with HNC has been sparingly assessed and, to date, the evidence is still limited,[18–28] although most,[18–23,25–28] but not all studies[24] indicated an inverse association with HNC risk.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium was established in 2004 to elucidate the aetiology of HNCs through pooled analyses of individual-level data on HNCs on a large scale.[29,30] To date, it includes 35 case-control studies, for a total of 25,478 cases and 37,111 controls.[31] Selected aspects of diet have been investigated within the consortium. Among relevant foods and food groups, an inverse association with HNC risk was found for higher intakes of fruit and vegetables, while no association was observed for some cereal and grain products.[32] In addition, higher intakes of selected micronutrients and food components from natural sources, like vitamin E, vitamin C, folate and carotenoids, have been previously found to reduce HNCs risk.[33–36]

The objective of this article is to assess the association between fiber intake and the risk of two HNC outcomes—oral and pharyngeal cancer combined and laryngeal cancer—adjusting for several confounders, including tobacco and alcohol use. Moreover, we evaluate whether the effect estimates differ by tumor subsite or in strata of selected factors, and explore the potential interaction of fiber intake with smoking and alcohol on the two HNC outcomes of interest.

Material and Methods

Design and subjects

Within version 1.5 of the INHANCE consortium pooled data set, 10 case-control studies collected information on total dietary fiber at the individual level.[6,37–46] Details on the

individual studies, harmonization of data and data pooling methods have been previously described for the consortium[30] and are summarized in Supporting Information Table 1 (Online Resource). Informed consent was obtained from study subjects. The investigations were approved by the relevant institutional review boards, according to the rules adopted in each country at the time of data collection.

Selection of subjects

Cases were included if their cancer had been originally classified as an invasive cancer of oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or HNC unspecified. Cases with cancers of the salivary glands or of the nasal cavity/ear/paranasal sinuses were excluded. The International Classification of Diseases coding used for the classification into subsites was previously specified.[29]

We removed from our analysis: (*i*) cases with missing information on the site of origin of their cancer; (*ii*) subjects with missing information on dietary fiber intake; and (*iii*) subjects with implausible (<500 or >5,500 kcal) or missing values on daily non-alcohol energy intake. Thus, the present analysis was based on a total of 18,207 subjects, with 5,959 HNC cases and 12,248 controls. There was a total of 1,385 oral cavity cancer cases, 1,653 oropharyngeal and 571 hypopharyngeal cancer cases (2,224 pharyngeal cancer cases), 805 unspecified oral cavity/pharynx cases (giving a total of 4,414 oral and pharyngeal cancer cases combined) and 1,545 laryngeal cancer cases.

Definition of the exposure variable

Intakes of total energy, several nutrients and food components, including fiber, were derived by combining information from study-specific food-frequency questionnaires (FFQs)—assessing subject's usual diet during a reference period preceding cancer diagnosis for cases or interview for controls—with that from country-specific food composition databases.[47–50] In detail, the current analysis considered total dietary fiber, which is fiber from foods only, and expressed its intake in grams/day. Comparability of total dietary fiber intakes was also improved by selecting intakes of fiber obtained with the enzymatic gravimetric methods [AOAC (Association of Official Analytical Chemist) 1980 or equivalents], rather than with the Englyst or Southgate ones,[51] when more estimates of total fiber intakes were simultaneously available in the single studies.

Finally, to adjust for the (study-specific) effect of daily energy intake excluding alcohol, we computed "non-alcohol energy-adjusted" fiber intake within each study, on both cases and controls, based on the residual method.[52]

Statistical analysis

We estimated the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of oral and pharyngeal cancer combined (including oral cavity, oropharyngeal, hypopharyngeal, unspecified oral cavity/pharyngeal cancer) and laryngeal cancer for quintile categories of "non-alcohol energy-adjusted" fiber intake (calculated on both cases and controls from all studies combined) using unconditional multiple logistic regression models.[53] Models included adjustment for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking (see Table 1 for a complete list of the covariate categories used). Tests for linear trend were computed referring to the median values of "non-alcohol energy-adjusted" fiber intake within the selected quintile categories.

For oral and pharyngeal cancer combined, separate analyses were conducted by anatomical subsite (oral cavity, oro/hypopharynx and oral cavity or pharynx not otherwise specified). For both cancer sites, we carried out stratified analyses by age, sex, education, geographic region, body mass index (BMI), tobacco (cigarettes, cigars, pipes, snuff or chewing products) smoking status, alcohol consumption (see Tables 3 and 4 for categories used) and heterogeneity between/among strata (possible effect modification) was tested using likelihood ratio tests.[53]

In addition, we investigated potential confounding by other dietary factors, including some nutrients [total carotenoids, vitamin C, vitamin E and iron (for the last nutrient, information was not available in the Buffalo study)], total fruit, and total vegetables.

We also carried out a sensitivity analysis, excluding each study one at a time to ensure that the magnitude of the overall estimates were not dependent on any specific study.[54]

In all the analyses described, when the p values for heterogeneity between studies was <0.1, we estimated the corresponding ORs and CIs specifying a random intercept-random slope generalized linear mixed model with a logit link function and binomial family.[55] We also adopted a complete-case approach to the analysis, where subjects with no missing information on the final database (including information on cancer sites, exposure and confounding variables) were considered for the analysis. However, as the Japan study did not provide information on education (3,495 subjects), we defined an extra category of education with all missing values, to avoid the exclusion of the study from the analysis.

All statistical tests were two-sided. Calculations were carried out using the open-source statistical computing environment R,[56] with its libraries "lme4"[57] and "nnet."[58]

Results

Table 1 shows selected characteristics of HNC cases (separately for oral and pharyngeal cancer combined and for laryngeal cancer) and controls under investigation. Over 70% of the included subjects were white. The US Multicenter study provided cases of oral and pharyngeal cancer only.

Table 1. Distribution of cases of oral and pharyngeal cancer combined, laryngeal cancer and controls according to selected variables. International Head and Neck Cancer Epidemiology (INHANCE) consortium

	Oral and pharyngeal cases	(%)	Laryngeal cases	(%)	Controls	(%)
			Age (years)			
<40	208	4.7	26	1.7	681	5.6
40–44	194	4.4	45	2.9	563	4.6
45–49	446	10.1	123	8.0	949	7.7
50–54	645	14.6	188	12.2	1,731	14.1
55–59	816	18.5	271	17.5	2,079	17.0
60–64	713	16.2	290	18.8	2,029	16.6
65–69	658	14.9	279	18.1	1,931	15.8
70–74	474	10.7	227	14.7	1,540	12.6
>=75	260	5.9	96	6.2	743	6.1
Missing	0	0.0	0	0.0	2	0.0
			Sex			
Female	1,187	26.9	244	15.8	3,541	28.9
Male	3,223	73.0	1,300	84.1	8,702	71.0
Missing	4	0.1	1	0.1	5	0.0
			Race			
Black	387	8.8	116	7.5	535	4.4
Others (with Asians)	463	10.5	101	6.5	3,089	25.2
White (with Hispanics)	3,555	80.5	1,324	85.7	8,596	70.2
Missing	9	0.2	4	0.3	28	0.2
			Study center			
Boston	313	7.1	71	4.6	611	5.0
Buffalo	396	9.0	168	10.9	1,190	9.7
Italy Multicenter						
Milan	169	3.8	24	1.6	621	5.1
Pordenone	471	10.7	409	26.5	1,528	12.5
Latina	95	2.2	0	0.0	425	3.5
Japan (2001–2005)	407	9.2	86	5.6	3,002	24.5
Los Angeles	246	5.6	60	3.9	828	6.8
Milan (2006–2009)	131	3.0	200	12.9	691	5.6
MSKCC	74	1.7	32	2.1	123	1.0
North Carolina (2002–2006)	687	15.6	374	24.2	1,120	9.1
Switzerland	367	8.3	121	7.8	877	7.2
US Multicenter						
Atlanta	129	2.9	0	0.0	134	1.1
New Jersey	467	10.6	0	0.0	459	3.7
Los Angeles	398	9.0	0	0.0	501	4.1
San Francisco	64	1.4	0	0.0	138	1.1
			Education			
<= Junior high school	863	19.6	603	39.0	2,723	22.2
Some high school	885	20.0	258	16.7	1,240	10.1
High school graduate	588	13.3	237	15.3	1,267	10.3
Technical school, some college	1,174	26.6	214	13.9	2,305	18.8

Table 1. Distribution of cases of oral and pharyngeal cancer combined, laryngeal cancer and controls according to selected variables. International Head and Neck Cancer Epidemiology (INHANCE) consortium (Continued)

	Oral and pharyngeal cases	(%)	Laryngeal cases	(%)	Controls	(%)
>= College graduate	491	11.1	145	9.4	1,703	13.9
Missing	413	9.4	88	5.7	3,010	24.6
Cigarette smoking status						
Never	806	18.3	91	5.8	4,868	39.7
Former	1,387	31.4	707	45.8	4,330	35.4
Current	2,210	50.1	735	47.6	2,986	24.4
Missing	11	0.2	12	0.8	64	0.5
Cigarette smoking intensity (number of cigarettes/day)						
Never smoker	806	18.3	91	5.9	4,868	39.7
0–10	471	10.7	149	9.6	1,949	15.9
11–20	1,466	33.2	628	40.6	3,169	25.9
>20	1,633	37.0	661	42.8	2,137	17.4
Missing	38	0.9	16	1.0	125	1.0
Cigarette smoking duration (years)						
Never smoker	806	18.3	91	5.9	4,868	39.7
0–20	443	10.0	102	6.6	2,166	17.7
>20	3,132	71.0	1,343	86.9	5,123	41.8
Missing	33	0.7	9	0.6	91	0.7
Cigar smoking status						
Never cigar user	3,583	81.2	1,323	85.6	8,545	69.8
Ever smoked >=100 cigars in a lifetime	394	8.9	118	7.6	636	5.2
Missing	437	9.9	104	6.7	3,067	25.0
Pipe smoking status						
Never pipe user	3,579	81.1	1,325	85.8	8,327	68.0
Ever smoked >= 100 pipes in a lifetime	399	9.0	115	7.4	864	7.1
Missing	436	9.9	105	6.8	3,057	25.0
Alcohol drinking intensity (number of drinks/day)						
Never drinker	548	12.4	187	12.1	3,156	25.8
<1	1,030	23.3	250	16.2	4,022	32.8
>=1–<3	973	22.0	344	22.3	2,934	24.0
>=3–<5	647	14.7	250	16.2	1,215	9.9
>=5	1,216	27.5	514	33.3	921	7.5

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

Cases were less educated, more often smokers and alcohol drinkers than controls.

Supporting Information Table 2 describes the distribution of raw values of fiber intake across studies and in all the studies combined. Study-specific distributions were skewed to the right. The reported summary statistics showed different values across studies, with the Buffalo, Italy Multicenter and Milan studies showing the highest values and the Los Angeles study the lowest values of fiber intake.

Table 2 provides the ORs, and the corresponding 95% CIs, for oral and pharyngeal cancer combined and for laryngeal cancer by quintile categories of fiber intake. For oral and pharyngeal cancer combined, we reported mixed-effects estimates with appreciable heterogeneity of the effect estimates across studies (p values for heterogeneity <0.001); for laryngeal cancer, however, there was less heterogeneity across studies (p values $= 0.633$), so fixed effects are reported. Fiber intake was inversely associated with oral and pharyngeal

Table 2. Odds ratios (ORs)[1] of oral and pharyngeal cancer combined, and laryngeal cancer and corresponding 95% confidence intervals (CIs) on fiber intake quintile categories. International Head and Neck Cancer Epidemiology (INHANCE) consortium

	Oral and pharyngeal cases	Controls	OR (95% CI)[2]	$p_{studies}$[3]	Laryngeal cases	Controls	OR (95% CI)[2]	$p_{studies}$[3]
I Quintile[4]	1,062	1,430	1 (reference)	<0.001	373	1,430	1 (reference)	0.633
II Quintile[4]	793	1,751	0.71 (0.61–0.82)		262	1,751	0.74 (0.60–0.90)	
III Quintile[4]	721	1,889	0.65 (0.57–0.75)		252	1,889	0.72 (0.58–0.88)	
IV Quintile[4]	677	1,986	0.55 (0.46–0.66)		251	1,986	0.71 (0.57–0.87)	
V Quintile[4]	641	1,940	0.49 (0.40–0.59)		265	1,940	0.66 (0.54–0.82)	
$p_{for\ linear\ trend}$			<0.001				<0.001	

[1]Estimated from multiple logistic regression models adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking.
[2]For the oral and pharyngeal cancer, heterogeneity between studies was appreciable and we reported the mixed-effects estimates derived from the corresponding generalized linear mixed model; for laryngeal cancer, there was less heterogeneity between studies and we reported the fixed-effects estimates.
[3]p for heterogeneity between studies.
[4]The cut-offs for the quintile categories of fiber intake were: −0.786, −0.322, 0.129, and 0.729, respectively.

cancer risk: the OR for the highest quintile category of fiber intake compared to the lowest one was 0.49 (95% CI: 0.40–0.59; p values for linear trend <0.001). For laryngeal cancer, the OR for the highest versus lowest quintile category was 0.66 (95% CI: 0.54–0.82; p values for linear trend <0.001). In the influence analyses, the point estimates of the ORs of oral and pharyngeal cancer combined did not materially change after the exclusion of any study; the detected heterogeneity between studies was similar to that of the main analysis when excluding any study at a time from the analysis. However, after excluding the Italy Multicenter study from the main analysis, the OR of laryngeal cancer was closer to unity (OR = 0.96, 95% CI: 0.74–1.24 for the last quintile category) and the corresponding heterogeneity between studies was reduced.

Decreasing ORs with higher fiber intakes were also observed across oral cavity and pharyngeal cancer subsites: the OR for the highest versus lowest quintile category was 0.39 (95% CI: 0.29–0.52) for oral cavity, 0.54 (95% CI: 0.45–0.64) for oropharynx and hypopharynx combined, and 0.46 (95% CI: 0.33–0.65) for oral cavity or pharynx not otherwise specified (Supporting Information Table 3—Online Resource). In addition, the ORs for the oropharynx were similar to those of the hypopharynx site (*e.g.*, for the highest vs lowest quintile category, OR = 0.58, 95% CI: 0.48–0.70 and OR = 0.55, 95% CI: 0.41–0.74, respectively; data not shown) but, given the limited number of hypopharyngeal cancer cases, we combined the results of these subsites.

Tables 3 and 4 show the ORs of oral and pharyngeal cancer combined and laryngeal cancer by strata of selected variables. An inverse association between fiber intake and risk of either cancer site was present in most of the strata, in accordance with the main findings from Table 2. However, there was appreciable heterogeneity in risk for laryngeal cancer across strata of geographic region, with only the three European studies showing a moderate inverse association (OR for the 5th *vs.* 1st quintile category = 0.45; 95% CI: 0.34–0.60; p for heterogeneity = 0.015). An appreciable heterogeneity between studies was present for several strata when considering oral and pharyngeal cancer combined, but not for most strata when laryngeal cancer was considered.

Figure 1 shows the combined effect of fiber intake and alcohol or tobacco consumption on oral and pharyngeal cancer combined and laryngeal cancer. No deviation from multiplicative interaction was found for either cancer site (p values for interaction—Panel A: 0.123; Panel B: 0.084; Panel C: 0.612; Panel D: 0.430). In addition, when comparing never/light drinkers with a higher than median consumption of fiber, the ORs for subjects with a lower than median consumption and ≥5 drinks/day of alcohol were 11.45 (95% CI 9.61–13.65) for oral and pharyngeal cancer combined (Panel A), and 5.36 (95% CI 3.30–8.71) for laryngeal cancer (Panel B). Compared to never smokers with a higher than median consumption of fiber, the ORs for subjects consuming a lower than median amount of fiber and being smokers of >20 cigarettes/day were 6.33 (95% CI 5.30–7.55) for oral and pharyngeal cancer combined (Panel C), and 26.34 (95% CI 18.28–37.95) for laryngeal cancer (Panel D).

In the sensitivity analyses considering additional adjustment for one extra nutrient at a time, the point estimates for quintiles of fiber intake were generally in line with the ones from the main analysis, although the ORs were higher for both cancer sites. The only exception was the adjustment by iron intake, which modified the OR of laryngeal cancer for the highest quintile category of fiber intake to 0.52 (95% CI: 0.44–0.62). With the additional adjustment by total fruit or total vegetable intake, the inverse association between dietary fiber intake and either tumor site was consistent, although the associations were less strong than in the main analysis for oral cavity and pharyngeal cancer combined.

Table 3. Odds ratios (ORs)[1,2] of oral and pharyngeal cancer combined and corresponding 95% confidence intervals (CIs) on fiber intake quintile categories, in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium

	OR (95% CI)				
	II Quintile	III Quintile	IV Quintile	V Quintile	$p_{studies}$[3]
Age (years)					
<55	0.66 (0.50–0.87)	0.57 (0.45–0.72)	0.57 (0.44–0.76)	0.60 (0.48–0.77)	<0.001
≥ 55	0.72 (0.61–0.85)	0.70 (0.59–0.82)	0.54 (0.45–0.66)	0.46 (0.35–0.59)	0.007
p_{strata}[4]		0.073			
Sex					
Female	0.88 (0.68–1.14)	0.80 (0.60–1.06)	0.67 (0.52–0.87)	0.57 (0.43–0.75)	0.617
Male	0.67 (0.56–0.80)	0.63 (0.54–0.73)	0.53 (0.43–0.66)	0.48 (0.39–0.59)	<0.001
p_{strata}[4]		0.635			
Education					
≤high school graduate	0.64 (0.54–0.76)	0.66 (0.54–0.79)	0.55 (0.45–0.68)	0.49 (0.39–0.61)	0.009
≥some college	0.80 (0.65–0.97)	0.66 (0.54–0.81)	0.59 (0.47–0.73)	0.54 (0.43–0.69)	0.174
p_{strata}[4]		0.640			
Geographic region[5]					
Europe	0.56 (0.44–0.71)	0.59 (0.47–0.74)	0.48 (0.38–0.61)	0.45 (0.34–0.61)	0.017
America	0.79 (0.67–0.93)	0.69 (0.57–0.83)	0.60 (0.47–0.77)	0.50 (0.39–0.66)	<0.001
Asia	0.94 (0.69–1.27)	0.62 (0.44–0.86)	0.42 (0.29–0.61)	0.38 (0.26–0.56)	NE
p_{strata}[4]		0.178			
Body mass index					
<25 kg/m^2	0.75 (0.62–0.92)	0.63 (0.52–0.76)	0.55 (0.45–0.67)	0.45 (0.35–0.57)	0.264
≥25 kg/m^2	0.69 (0.54–0.88)	0.69 (0.57–0.83)	0.58 (0.46–0.73)	0.58 (0.46–0.71)	<0.001
p_{strata}[4]		0.117			
Tobacco smoking status					
Never user	0.75 (0.55–1.03)	0.87 (0.65–1.16)	0.67 (0.48–0.93)	0.63 (0.44–0.89)	0.095
Former user	0.90 (0.69–1.17)	0.65 (0.48–0.88)	0.69 (0.49–0.98)	0.65 (0.49–0.86)	0.012
Current user	0.66 (0.54–0.82)	0.57 (0.46–0.70)	0.53 (0.42–0.65)	0.51 (0.40–0.66)	0.169
p_{strata}[4]		0.188			
Alcohol drinking intensity[6]					
Never/light drinker	0.86 (0.71–1.05)	0.83 (0.68–1.01)	0.71 (0.56–0.88)	0.59 (0.44–0.78)	0.003
Moderate drinker	0.67 (0.52–0.87)	0.56 (0.44–0.72)	0.49 (0.39–0.62)	0.42 (0.34–0.54)	0.007
Heavy drinker	0.49 (0.33–0.72)	0.46 (0.33–0.66)	0.45 (0.32–0.63)	0.43 (0.31–0.60)	0.009
p_{strata}[4]		0.085			

ABBREVIATIONS: NE: not estimable.
[1]Estimated from multiple logistic regression models adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking, when appropriate.
[2]The first quintile category was considered as the reference one.
[3]p for heterogeneity between studies. When the p value was <0.1 within strata, we reported mixed-effects estimates derived from the corresponding generalized linear mixed model.
[4]p for heterogeneity across strata. When fixed- and mixed-effects models were estimated for different categories of the same stratification variable, likelihood ratio tests for heterogeneity across strata had to be based on comparable mixed-effects models, and therefore we re-fitted one or more mixed-effects models to replace the original fixed-effects ones. We consistently reported the corresponding stratum-specific mixed-effects models instead of the fixed-effects ones.
[5]Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, Memorial Sloan Kettering Cancer Center, North Carolina (2002–2006), and US Multicenter studies. Asia included Japan study only. As Asia included Japan study only, there was no possibility to assess heterogeneity between studies in the Asia stratum.
[6]The never/light drinker category included never drinkers and subjects who drink <1 drink per day; the moderate drinker category included subjects drinking between 1 (included) and 5 drinks per day; the heavy drinker category included subjects drinking 5 drinks per day or more.

Table 4. Odds ratios (ORs)[1,2] of laryngeal cancer and corresponding 95% confidence intervals (CIs) on fiber intake quintile categories, in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium

	OR (95% CI)				
	II Quintile	III Quintile	IV Quintile	V Quintile	$p_{studies}$[3]
Age (years)					
<55	0.98 (0.64–1.50)	0.76 (0.46–1.23)	0.65 (0.40–1.04)	0.66 (0.44–1.01)	0.131
≥ 55	0.70 (0.52–0.93)	0.67 (0.53–0.86)	0.69 (0.50–0.93)	0.60 (0.48–0.76)	0.075
p_{strata}[4]		0.534			
Sex					
Female	0.79 (0.46–1.33)	0.81 (0.50–1.31)	0.63 (0.38–1.04)	0.68 (0.41–1.13)	0.243
Male	0.81 (0.59–1.11)	0.66 (0.51–0.87)	0.68 (0.48–0.96)	0.64 (0.48–0.86)	0.002
p_{strata}[4]		0.721			
Education					
≤high school graduate	0.63 (0.48–0.82)	0.67 (0.53–0.85)	0.61 (0.45–0.85)	0.65 (0.48–0.88)	0.050
≥some college	1.18 (0.79–1.77)	0.58 (0.32–1.04)	0.90 (0.60–1.34)	0.59 (0.39–0.89)	0.056
p_{strata}[4]		0.050			
Geographic region[5]					
Europe	0.55 (0.41–0.74)	0.54 (0.39–0.73)	0.52 (0.33–0.80)	0.45 (0.34–0.60)	0.002
America	1.19 (0.76–1.87)	0.92 (0.63–1.36)	1.08 (0.80–1.48)	1.00 (0.74–1.37)	0.238
Asia	1.33 (0.68–2.61)	1.50 (0.78–2.91)	0.33 (0.12–0.85)	0.85 (0.40–1.83)	NE
p_{strata}[4]		0.015			
Body mass index					
<25 kg/m^2	0.81 (0.59–1.12)	0.61 (0.44–0.84)	0.70 (0.45–1.07)	0.56 (0.37–0.85)	0.335
≥25 kg/m^2	0.78 (0.52–1.17)	0.70 (0.49–1.00)	0.67 (0.47–0.96)	0.66 (0.50–0.86)	0.004
p_{strata}[4]		0.560			
Tobacco smoking status					
Never user	0.57 (0.24–1.38)	0.65 (0.27–1.56)	0.73 (0.33–1.63)	0.87 (0.39–1.94)	0.399
Former user	0.83 (0.58–1.19)	0.73 (0.51–1.05)	0.64 (0.40–1.03)	0.81 (0.58–1.14)	0.375
Current user	0.81 (0.54–1.20)	0.68 (0.47–0.99)	0.57 (0.41–0.78)	0.60 (0.42–0.85)	<0.001
p_{strata}[4]		0.669			
Alcohol drinking intensity[6]					
Never/light drinker	0.99 (0.64–1.53)	0.69 (0.39–1.23)	0.99 (0.70–1.40)	0.87 (0.60–1.25)	0.030
Moderate drin	0.73 (0.53–1.00)	0.74 (0.54–1.02)	0.66 (0.43–1.01)	0.53 (0.38–0.74)	0.130
Heavy drinker	0.73 (0.37–1.41)	0.53 (0.35–0.81)	0.43 (0.28–0.66)	0.49 (0.33–0.73)	0.236
p_{strata}[4]		0.383			

ABBREVIATIONS: NE: not estimable.

[1]Estimated from multiple logistic regression models adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking, when appropriate.

[2]The first quintile category was considered as the reference one.

[3]p for heterogeneity between studies. When the p value was <0.1 within strata, we reported mixed-effects estimates derived from the corresponding generalized linear mixed model.

[4]p for heterogeneity across strata. When fixed- and mixed-effects models were estimated for different categories of the same stratification variable, likelihood ratio tests for heterogeneity across strata had to be based on comparable mixed-effects models, and therefore we re-fitted one or more mixed-effects models to replace the original fixed-effects ones. We consistently reported the corresponding stratum-specific mixed-effects models instead of the fixed-effects ones.

[5]Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, Memorial Sloan Kettering Cancer Center, North Carolina (2002–2006), and US Multicenter studies. Asia included Japan study only. As Asia included Japan study only, there was no possibility to assess heterogeneity between studies in the Asia stratum.

[6]The never/light drinker category included never drinkers and subjects who drink <1 drink per day; the moderate drinker category included subjects drinking between 1 (included) and 5 drinks per day; the heavy drinker category included subjects drinking five drinks per day or more.

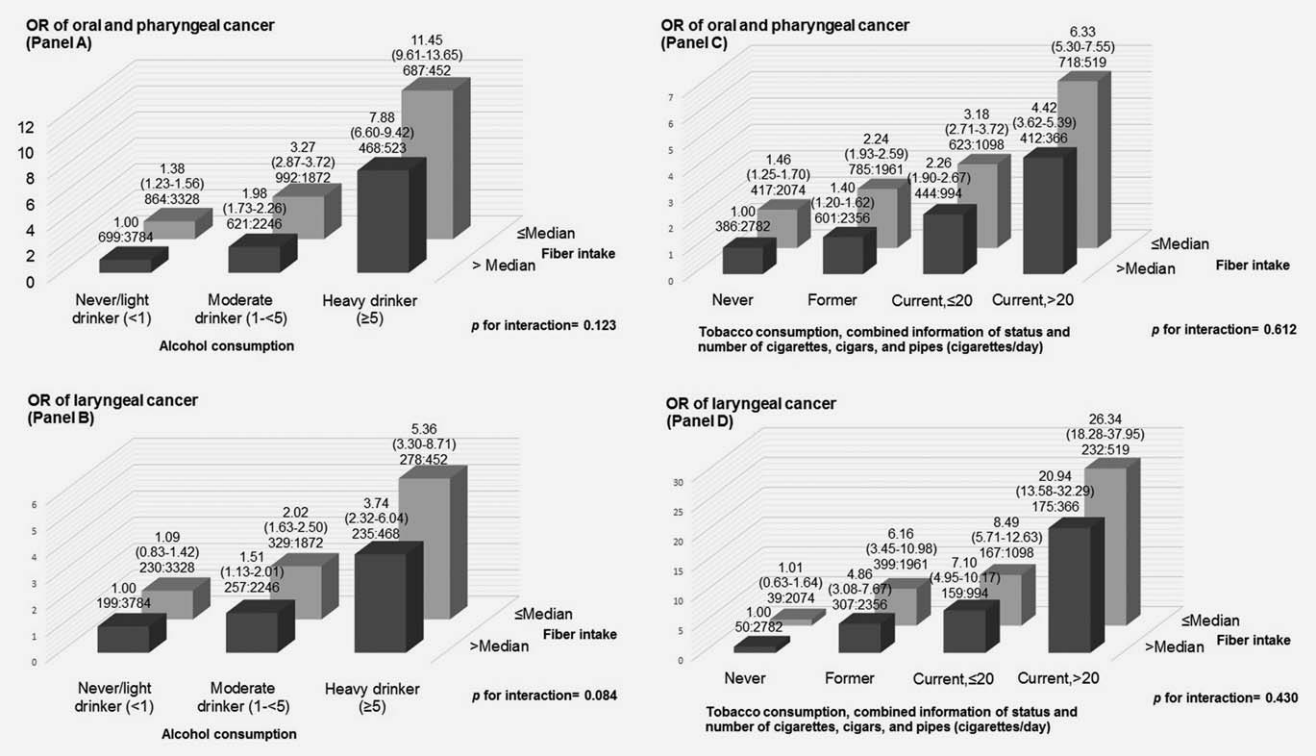

Figure 1. Odds ratios (ORs) of oral and pharyngeal, and laryngeal cancer, and corresponding 95% confidence intervals (CIs), according to alcohol or tobacco consumption and "non-alcohol energy-adjusted" fiber intake. International Head and Neck Cancer Epidemiology (INHANCE) consortium. (*a*) The odds ratios were derived from mixed-effects logistic regression models adjusted for age, sex, education, race/ethnicity, study center, combined smoking habits of cigarettes, cigars and pipes, and alcohol drinking, when appropriate. (*b*) The number of cases and controls within each category was indicated below the corresponding OR as: "number of cases: number of controls."

Discussion

In this pooled analysis of ten case–control studies providing information on dietary fiber within the INHANCE consortium—the largest dataset to date on the issue—we found inverse associations between dietary fiber intake and the risk of oral and pharyngeal cancer, as well as of laryngeal cancer. Similar results were observed across oral and pharyngeal cancer subsites and in most of the strata considered.

Several plausible mechanisms have been reported for such a favorable effect of dietary fiber.[13–16] First, dietary fiber may reduce glycemic load[59] and improve insulin sensitivity, favorably influencing insulin-like growth factor I (IGF-1), which is a promoter of the process of carcinogenesis.[60] Second, dietary fiber appears to have an anti-inflammatory role, via the production of short-chain fatty acids by gut bacteria with antiproliferative and pro-apoptosis properties.[14,16] Third, dietary fiber may also bind carcinogens and thereby limit their contact with upper digestive tract epithelia.[14,17] Finally, fiber-rich foods generally tend to have a higher content of antioxidants.[17] However, a higher fiber intake may simply be an indicator of a diet rich in fruit, vegetables and pulses, and whole gains, and, on this way, poorer in refined cereals, meat and animal fats, which have been positively associated with a higher HNC risk.[11,61,62] Still, adjustment by fruit and vegetables, as well as selected micronutrients, only marginally affected the main results on fiber intake. Similarly, dietary fiber may simply be an indicator of a better general life-style pattern.

Some of the studies contributing data to our pooled analysis have already published separate reports on dietary fiber and HNC cancer risk.[18,19,25,27] Besides them, at least two other cohorts[26,28] and five case-control studies,[20–24] most of which conducted before 2000, provided results on the issue. Among the most recent and largest studies, the National Institutes of Health (NIH)-AARP Diet and Health Study, a US cohort of ~500,000 elderly participants including 1867 HNC cases developed during ~11 years of follow-up, found an inverse association with fiber intake among women (OR 0.61, 95% CI: 0.42–0.89 for the upper quintile), consistent across subsites, and a weaker one among men (OR 0.88, 95% CI: 0.73–1.05).[28] Similarly, in a cohort of over 34,000 postmenopausal women and 169 incident cases from the Iowa Women's Health Study, an inverse association for fiber intake was observed for cancers of the upper aerodigestive tract combined (OR 0.57, 95% CI: 0.36–0.92 for the upper tertile). In detail, a higher fiber intake decreased oral and pharyngeal cancer (53 cases, OR 0.49), but not laryngeal cancer risk (21 cases, OR 1.82).[26] Among the earlier investigations, a Chinese case-control study including 404 matched cases of oral cancer showed a strong inverse association for total dietary fiber

(OR 0.38, 95% CI: 0.19–0.74 for the upper quartile), and for dietary fiber from vegetables and fruits, but no relation with fiber from other sources.[23] Reduced risks of oral and pharyngeal cancer for higher intakes of fibers were also observed in an Australian case-control study on 41 male cases (OR 0.14, 95% CI: 0.1–0.4 for the upper tertile),[22] and in a US case-control study on 290 matched cases (OR 0.6, 95% CI: 0.4–0.9 for 1-standard deviation increase in intake).[21] In addition, an inverse association with laryngeal cancer was found for energy-adjusted fiber intake in a US case-control study including 250 male cases.[20] The only study reporting little or no association with fiber intake was conducted in Uruguay, had a case-control design and included 133 cases of cancer of the upper aerodigestive tract, among which 33 were oral/pharyngeal cancers and 34 were laryngeal cancers.[24]

In interpreting our findings, there are some limitations. Concerning fiber intake, we were unable to assess the separate effect of different subtypes of fiber on HNC risk. Indeed, separate information on dietary fiber from vegetables, fruits or cereal grains was available in four studies and that on total soluble and insoluble fiber in five studies only. In addition, pooling dietary data is challenging[34] and the various populations included in the analysis differ in many respects, including exposure to alcohol and tobacco. For these and other reasons, some heterogeneity among studies is to be expected. In our analysis, we identified heterogeneity among studies for oral and pharyngeal cancer combined and in several strata of interest, including subsites of oral and pharyngeal cancer. Our inspection of study-specific distributions, stratified and influence analyses showed also heterogeneity between European and American studies in the case of laryngeal cancer. However, it is difficult to isolate the effect of control sources (hospital- *vs*. population-based) from that of geographic region (the three studies from Europe were all hospital-based and 4/6 American studies were population-based). The identified heterogeneity cannot, therefore, be attributed to selection bias and to different types of controls. In addition, our results may be biased by a non-differential misclassification of individual intakes (*i.e*., due to measurement error), and by differential misclassification derived from recall bias.

Our analysis also had several strengths. The large sample size provides the opportunity to consider cancer subsites and subgroups of interest with adequate statistical power. We could control for the potential confounding effect of tobacco smoking, alcohol drinking and their interaction, using information on status, duration and intensity for smoking and intensity for alcohol. Moreover, the inverse association with fiber intake was consistent across strata of tobacco smoking and alcohol drinking. We also assessed the presence of a potential bias related to the assumption of a single unknown education level in the Japan study, by comparing fiber effect estimates in the non-Japanese study population, adjusting versus not adjusting for education (but adjusting for other covariates). This sensitivity analysis provided reassuring results, with very similar ORs for both cancer sites (*e.g*., for the last quintile category, OR of oral cavity and pharyngeal cancer combined = 0.49, 95% CI: 0.40–0.59 and 0.49, 95% CI: 0.40–0.59, with and without the adjustment for education level, respectively; OR of laryngeal cancer = 0.57, 95% CI: 0.48–0.68 and 0.57, 95% CI: 0.48–0.69, with and without the adjustment for education level, respectively). In addition, we applied uniform criteria to define our exposure of interest. Finally, we found that effect estimates were similar in the different tumor subsites, suggesting that the action of dietary fiber represents a general mechanism for HNC risk, rather than a site-specific one.

In conclusion, findings from this large-scale pooled analysis indicated that fiber may play a protective role against HNC. Future studies that examine country-specific sources of dietary fiber—including fruits, vegetables, beans, nuts, brown rice, whole-grain breads, biscuits and pasta—are warranted to further elucidate which foods are the main determinants of the inverse association observed between fiber intake and the incidence of HNCs.

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References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
2. Seiwert TY, Cohen EE. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer* 2005;92:1341–8.
3. Garavello W, Bertuccio P, Levi F, et al. The oral cancer epidemic in central and eastern Europe. *Int J Cancer* 2010;127:160–71.
4. Zeka A, Gore R, Kriebel D. Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis. *Cancer Causes Control* 2003; 14:897–906.
5. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18:541–50.
6. Bravi F, Bosetti C, Filomeno M, et al. Foods, nutrients and the risk of oral and pharyngeal cancer. *Br J Cancer* 2013;109:2904–10.
7. Edefonti V, Bravi F, La Vecchia C, et al. Nutrient-based dietary patterns and the risk of oral and pharyngeal cancer. *Oral Oncol* 2010;46:343–8.
8. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. AICR: Washington, DC, ed. 2007.
9. Pavia M, Pileggi C, Nobile CG, et al. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr* 2006;83:1126–34.

10. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr.* 2003;78:559S–69S.
11. Lucenteforte E, Garavello W, Bosetti C, et al. Dietary factors and oral and pharyngeal cancer risk. *Oral Oncol* 2009;45:461–7.
12. Freedman ND, Park Y, Subar AF, et al. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer* 2008;122:2330–6.
13. Ferguson LR, Chavan RR, Harris PJ. Changing concepts of dietary fiber: implications for carcinogenesis. *Nutr Cancer* 2001;39:155–69.
14. Kaczmarczyk MM, Miller MJ, Freund GG. The health benefits of dietary fiber: beyond the usual suspects of type 2 diabetes mellitus, cardiovascular disease and colon cancer. *Metabol: clin Exp.* 2012;61:1058–66.
15. Latino-Martel P, Cottet V, Druesne-Pecollo N, et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. *Crit Rev Oncol Hematol* 2016;99:308–23.
16. Moore MA, Park CB, Tsuda H. Soluble and insoluble fiber influences on cancer development. *Crit Rev Oncol/Hematol* 1998;27:229–42.
17. Slavin J, Jacobs D, Marquart L. Whole-grain consumption and chronic disease: protective mechanisms. *Nutr Cancer* 1997;27:14–21.
18. McLaughlin JK, Gridley G, Block G, et al. Dietary factors in oral and pharyngeal cancer. *J Natl Cancer Inst* 1988;80:1237–43.
19. Gridley G, McLaughlin JK, Block G, et al. Diet and oral and pharyngeal cancer among Blacks. *Nutr Cancer* 1990;14:219–25.
20. Freudenheim JL, Graham S, Byers TE, et al. Diet, smoking, and alcohol in cancer of the larynx: a case-control study. *Nutr Cancer* 1992;17:33–45.
21. Marshall JR, Graham S, Haughey BP, et al. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. *Eur J Cancer B Oral Oncol* 1992;28B:9–15.
22. Kune GA, Kune S, Field B, et al. Oral and pharyngeal cancer, diet, smoking, alcohol, and serum vitamin A and beta-carotene levels: a case-control study in men. *Nutr Cancer* 1993;20:61–70.
23. Zheng T, Boyle P, Willett WC, et al. A case-control study of oral cancer in Beijing, People's Republic of China. Associations with nutrient intakes, foods and food groups. *Eur J Cancer B Oral Oncol* 1993;29B:45–55.
24. De Stefani E, Ronco A, Mendilaharsu M, et al. Diet and risk of cancer of the upper aerodigestive tract–II. Nutrients. *Oral Oncol* . 1999;35:22–6.
25. Soler M, Bosetti C, Franceschi S, et al. Fiber intake and the risk of oral, pharyngeal and esophageal cancer. *Int J Cancer* 2001;91:283–7.
26. Kasum CM, Jacobs DR, Jr., Nicodemus K, et al. Dietary risk factors for upper aerodigestive tract cancers. *Int J Cancer* 2002;99:267–72.
27. Pelucchi C, Talamini R, Levi F, et al. Fibre intake and laryngeal cancer risk. *Ann Oncol* 2003;14: 162–7.
28. Lam TK, Cross AJ, Freedman N, et al. Dietary fiber and grain consumption in relation to head and neck cancer in the NIH-AARP Diet and Health Study. *Cancer Causes Control* . 2011;22: 1405–14.
29. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 2007;99:777–89.
30. Conway DI, Hashibe M, Boffetta P, et al. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. *Oral Oncol* 2009;45:743–6.
31. Winn DM, Lee YC, Hashibe M, et al. The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer. *Oral Dis* 2015;21:685–93.
32. Chuang SC, Jenab M, Heck JE, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 2012;23:69–88.
33. Edefonti V, Hashibe M, Parpinel M, et al. Vitamin E intake from natural sources and head and neck cancer risk: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. *Br J Cancer* 2015;113:182–92.
34. Edefonti V, Hashibe M, Parpinel M, et al. Natural vitamin C intake and the risk of head and neck cancer: a pooled analysis in the international head and neck cancer epidemiology consortium. *Int J Cancer* 2015;137:448–62.
35. Galeone C, Edefonti V, Parpinel M, et al. Folate intake and the risk of oral cavity and pharyngeal cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology Consortium. *Int J Cancer* 2015;136:904–14.
36. Leoncini E, Edefonti V, Hashibe M, et al. Carotenoid intake and head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Eur J Epidemiol* 2016;31:369–83.
37. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48:3282–7.
38. Schantz SP, Zhang ZF, Spitz MS, et al. Genetic susceptibility to head and neck cancer: interaction between nutrition and mutagen sensitivity. *Laryngoscope* 1997;107:765–81.
39. Levi F, Pasche C, La Vecchia C, et al. Food groups and risk of oral and pharyngeal cancer. *Int J Cancer* 1998;77:705–9.
40. Bosetti C, Gallus S, Trichopoulou A, et al. Influence of the Mediterranean diet on the risk of cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 2003;12:1091–4.
41. Peters ES, McClean MD, Liu M, et al. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. *Cancer Epidemiol Biomarkers Prev* 2005;14:476–82.
42. Cui Y, Morgenstern H, Greenland S, et al. Polymorphism of Xeroderma Pigmentosum group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. *Int J Cancer* 2006;118:714–20.
43. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2006;15:1829–34.
44. Jayaprakash V, Rigual NR, Moysich KB, et al. Chemoprevention of head and neck cancer with aspirin: a case-control study. *Arch Otolaryngol Head Neck Surg* 2006;132:1231–6.
45. Suzuki T, Wakai K, Matsuo K, et al. Effect of dietary antioxidants and risk of oral, pharyngeal and laryngeal squamous cell carcinoma according to smoking and drinking habits. *Cancer Sci* 2006;97: 760–7.
46. Divaris K, Olshan AF, Smith J, et al. Oral health and risk for head and neck squamous cell carcinoma: the Carolina Head and Neck Cancer Study. *Cancer Causes Control* 2010;21:567–75.
47. Dresser CM. From nutrient data to a data base for a health and nutrition examination survey. Organization, coding and values-real or imputed. Proceeding of the 8th National Nutrient Data Base Conference Minneapolis, MN, 1983. 92–104.
48. US Department of Agriculture (USDA), Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 26 and previous versions. Nutrient Data Laboratory Home Page: Available at: http://www.ars.usda.gov/Services/docs.htm?docid=8964 Accessed on June 10, 2017.
49. Resource Council, Science and Technology Agency, the Government of Japan (2000) Standard Tables of Food Composition in Japan, 5th Revised Version (in Japanese with English translation). Ministry of Finance Printing Bureau: Tokyo, Japan, ed., 2000.
50. Gnagnarella P, Salvini S, Parpinel M. Food Composition Database for Epidemiological Studies in Italy. Version 1, 2015. Available at: http://www.bda-ieo.it/ Accessed on June 10, 2017.
51. Greenfield H, Southgate DAT. Food Composition Data. Production, Management and Use. 2nd Ed. Rome, Italy: FAO/WHO, 2003.
52. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124:17–27.
53. Hosmer DW, Lemeshow S. Applied Logistic Regression, 2nd ed. New York, NY: Wiley, 2000.
54. Deeks JJ HJ, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses, In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011.
55. Pinheiro JC, Bates DM Mixed-effects models in S and S-PLUS. New York, NY: Springer-Verlag, 2000.
56. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2016. Available at: http://www.R-project.org. (Accessed on July 27, 2016).
57. Bates D, Maechler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, 2015:1–48.
58. Venables WN, Ripley BD. Modern Applied Statistics with S. 4th edn. New York, NY: Springer, 2002.
59. Augustin LS, Kendall CW, Jenkins DJ, et al. Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis* 2015;25:795–815.
60. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 2000;92:1472–89.
61. Franceschi S, Favero A, Conti E, et al. Food groups, oils and butter, and cancer of the oral cavity and pharynx. *Br J Cancer* 1999;80:614–20.
62. Bosetti C, La Vecchia C, Talamini R, et al. Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. *Int J Cancer* 2002;100:355–60.