Dietary glycemic index, glycemic load, and head and neck cancer risk: a pooled analysis in an international consortium

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Abstract (max 150 words, unstructured)

High dietary glycemic index (GI) and glycemic load (GL) may increase cancer risk. However, limited information was available on GI and/or GL and head and neck cancer (HNC) risk. We conducted a pooled analysis on 8 case-control studies (4,081 HNC cases; 7,407 controls) from the International Head and Neck Cancer Epidemiology (INHANCE) consortium. We estimated the odds ratios (ORs) and 95% confidence intervals (CIs) of HNC, and its subsites, from fixed- or mixed-effects logistic models including center-specific quartiles of GI or GL. GI, but not GL, had a weak positive association with HNC ($OR_{Q4\ vs.\ Q1}$=1.16; 95% CI= 1.02-1.31). In sub-sites, we found a positive association between GI and laryngeal cancer ($OR_{Q4\ vs.\ Q1}$=1.60; 95% CI= 1.30-1.96) and an inverse association between GL and oropharyngeal cancer ($OR_{Q4\ vs.\ Q1}$=0.78; 95% CI= 0.63-0.97). This pooled analysis indicates a modest positive association between GI and HNC, mainly driven by laryngeal cancer.

BACKGROUND

Most head and neck cancers (HNCs) are attributed to tobacco smoking and/or alcohol drinking.[1] Diet has been suggested to play a role in HNC etiology, with non-starchy vegetables and selected healthy dietary patterns being inversely related with HNC risk. [2]

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Average daily glycemic index (GI) ranks carbohydrate foods based on the postprandial blood glucose response; average glycemic load (GL) estimates the impact of carbohydrate consumption using the GI, while taking into account the amount of carbohydrates that are consumed.[3] Higher GI and GL are moderately associated with risk of several cancers[4], likely because of stimulation of insulin release and bioactivity of insulin-like growth factor-1, which has proliferative, angiogenic, anti-apoptotic, and estrogen stimulating properties.[5]

Only two studies[6,7] have investigated the effect of GI and GL on HNC risk, with inconsistent findings; one of these studies[6] reported results by sub-site, based, however, on a limited number of cases.

The objective of this paper is to assess the association of GI or GL with HNC and its subsites (i.e., oral cavity, oropharynx, hypopharynx, and larynx) using pooled dietary data from eight case-control studies participating in the International Head and Neck Cancer

Epidemiology (INHANCE) consortium.[8]

METHODS

Within data version 1.5 of the INHANCE dataset, information on GI and GL was available from 3 case-control studies. In addition, we calculated GI and/or GL intakes from study-specific food items and food composition databases for another 5 studies, giving a total of 8 studies included in the analysis. Details on individual studies and data pooling methods have been previously described[8] and are summarized in **Supplementary Table S1**. Informed consents and institutional review board approvals were obtained within the framework of the original studies.

Selection of subjects

Cases were included if their cancer had been originally classified as invasive cancer of the oral cavity, pharynx, larynx, or unspecified oral cavity/pharynx. Corresponding controls from the original studies were included in the analysis. We excluded subjects with missing information on the site of origin of cancer, or GI or GL value, and those with missing or implausible (<500 or >5,500 kcal/day) non-alcohol energy intake. Thus, our analysis included 11,488 subjects, with 4,081 HNC cases and 7,407 controls (4,264 hospital-based and 3,143 population-based controls). There were 810 oral cavity, 1,172 oropharynx, 343 hypopharynx, 1,338 larynx, and 418 unspecified oral cavity/pharynx cancer cases.

Specification of variables

Study-specific food-frequency questionnaires (FFQs) and food composition tables allowed us to calculate individual values of GI and GL for the 4 studies lacking information on both the exposures [Los Angeles, Boston, Seattle (1985-1995) and Memorial Sloan Kettering Cancer Center (MSKCC) studies]. In detail, as described previously[9], the GI of a food was expressed as a percentage of the glycemic response elicited by white bread as a standard food with a GI of 100. The average daily GI for each subject was computed by summing the products of the GI value of each food times the amount of available carbohydrates in that food consumed per day, divided by the total amount of available carbohydrates (g) consumed per day. The average daily GL (g) was calculated by summing the products of the GI value of each food times the amount of available carbohydrates in that food consumed per day, divided by 100. Each GL unit represents the equivalent of 1 g of carbohydrate from white bread. Therefore, we preliminary converted frequencies of consumption into servings/day and servings/day into grams/day; then, we assigned the corresponding GI to each food item and applied the previous formulas to derived individual GI and GL values. For the North Carolina (2002-2006) study, information on individual values of GL was originally provided to the INHANCE Consortium Coordinating Center. We estimated GI as 100 multiplied with GL and divided by total available grams of carbohydrate intake (**Supplementary Material – text and Table S2** for GI/GL calculation and study-specific GI values).

Statistical analysis

Multiple logistic regression models were used to estimate the odds ratios (ORs) of HNC and the corresponding 95% confidence intervals (CIs) according to center-specific quartiles of GI or GL among controls (**Supplementary Tables S3** for descriptive statistics of GI and GL distributions). In the presence of heterogeneity of GI or GL intakes across centers, we used a random-slope logistic regression model, whereas a fixed-effects model was used otherwise.[10] The models included the following potential confounders: age, sex, race/ethnicity, study center, education, cigarette smoking intensity, cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity, and the product term of cigarette smoking and alcohol drinking intensities. For GI, models were further adjusted for energy intake without alcohol; for GL, models were further adjusted for energy intake without alcohol and carbohydrates. For both GI and GL models, we used center-specific control-based quartiles of energy intake. Separate analyses were carried out by HNC sub-sites and in strata of selected covariates. In sensitivity analyses, we further adjusted for history of diabetes or excluded subjects with diabetes (information available for 6 studies). Analyses were performed using the SAS software (version 9.4, SAS Institute, Cary, NC).

RESULTS

Characteristics of our sample were presented in **Supplementary Table S4**. The highest GI quartile category (Q4) was associated with a higher HNC risk ($OR_{Q4\ vs.\ Q1}$=1.16; 95% CI= 1.02-1.31, p_{trend}=0.037**, Table 1**). Across HNC sub-sites, GI was associated with an increased laryngeal cancer risk ($OR_{Q4\ vs.\ Q1}$=1.60; 95% CI= 1.30-1.96, p_{trend}<0.001), but excluding laryngeal cancer cases, the $OR_{Q4\ vs.\ Q1}$ was 1.01 (95% CI= 0.88-1.16, p_{trend}=0.90) (data not shown). Little associations between GL and cancers of the oral cavity, hypopharynx, and larynx were observed. An inverse association was found between oropharyngeal cancer risk and GL ($OR_{Q4\ vs.\ Q1}$=0.78; 95% CI= 0.63-0.97, p_{trend}=0.009). Results did not materially change when excluding subjects with diabetes or when additionally adjusting models by diabetes history. No heterogeneity was observed in strata of covariates (**Supplementary Table S5**).

DISCUSSION

In this large dataset, we observed a positive association between GI and HNC risk, essentially driven by laryngeal cancer. GL was not associated with the risk of overall HNC or its sub-sites, except for a possible inverse association with oropharyngeal cancer.

Inconsistent associations of GI and GL with HNC risk may be partly due to differences in the underlying dietary patterns. Indeed, higher dietary GL is strongly associated with higher carbohydrate intakes, while a higher GI is also associated with lower intakes of dairy products, legumes, fruit and vegetables.[11] In line with this hypothesis, an overlapping INHANCE-based analysis including 7 of the 8 current studies showed a positive association of laryngeal cancer with an "*Animal products and cereals*" dietary pattern, which was simultaneously based on high-GI (e.g. cereals) and low-GL (e.g. meat) foods.[10]

Only two previous studies[6,7] have examined the association between GI or GL and HNC risk, with one of them partially overlapping with the current dataset.[6] An analysis[6] of three Italian case-control studies on upper aero-digestive tract cancers reported a positive association with higher GI ($OR_{Q5\ vs.\ Q1}$=1.5; 95% CI=1.1-2.0) and GL ($OR_{Q5\ vs.\ Q1}$=1.8; 95% CI=1.1-2.9) in quintiles. Although in the same direction, the association was weaker with oral and pharyngeal cancers combined or laryngeal cancer.[6] Findings from the National Institutes of Health–AARP Diet and Health Study (1,239 HNC cases; 446,177 participants) reported a null association with GI and a possible inverse association with GL in women ($OR_{Q5\ vs.\ Q1}$=0.63; 95% CI=0.34-1.19), in the absence of a clear dose-response relationship.[7]

Limitations of the current analyses included possible recall bias and non-differential misclassification of GI/GL quartiles. In addition, food items contributing to GI differed in part across regions (Supplementary Table S2**)**. However, all our FFQs were either reproducible and valid or were modifications of existing FFQs, already tested for reproducibility and validity. We were able to adjust for major potential confounders and our large sample size provided the necessary statistical power to examine the association in HNC sub-sites and strata.[8]

In conclusion, findings from this large-scale pooled analysis support a positive effect of average daily GI on the risk of HNC, and in particular of laryngeal cancer.

ADDITIONAL INFORMATION

Ethical approval and consent to participate: The Informed consent and institutional review board approval were obtained within the framework of the original studies, according to the rules existing at the time of data collection. In addition, a central Institutional Review Board approval was obtained from the University of Utah, #42912.

Consent to publish: Not applicable.

Data availability: The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Conflicts of interest: The authors declare no competing interests.

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Genomics of the UCLA Jonsson Comprehensive Cancer Center; 4. **Swiss study**: Swiss League against Cancer and the Swiss Research against Cancer/Oncosuisse [KFS-700, OCS-1633]; 5. **Milan (2006-2009) study**: AIRC and Italian Ministry of Education [PRIN 2009 X8YCBN]; 6. **Boston study**: NIH [R01CA078609 and R01CA100679]; 7. **Seattle (1985-1995) study**: NIH [R01CA048996 and R01DE012609]; 8. **MSKCC study**: NIH [R01CA051845].

Authors' contributions: C. Chang contributed to write, review, and/or revision of the manuscript; Y.A.L. contributed to the acquisition of the pooled data; C. Chang contributed to the analysis, and V.E. performed statistical support; C.L.V., V.E., F.T., and Z.Z. contributed substantially to the interpretation of data and were involved in drafting and revising the manuscript; D.S., A.F.O., J.P.Z., Z.Z., H.M., C.L.V., F.L., W.G., K.K., M.M., C.Chen, S.M.S., S.S. and G.Y. conducted research and provided single-study databases; L.S.A.A. and M.P. provided advice on nutritional issues; P.B., Y.A.L., and M.H. are the INHANCE study coordinators; all authors approved the final version of the manuscript.

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Supplementary information: Supplementary information is available at the British

Journal of Cancer’s website.

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Table 1. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) of glycemic index and glycemic load on cancers of head and neck, oral cavity, oropharynx, hypopharynx, and larynx. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Head and neck cancer (No. cases=3,967, No. controls=7,250[b])	Oral cavity cancer (No. cases =780, No. controls=7,250[b])	Oropharyngeal cancer (No. cases=1,151, No. controls=7,250[b])	Hypopharyngeal cancer (No. cases =328, No. controls=6,866[b])	Laryngeal cancer (No. cases =11,299, No. controls=6,443[b])
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Glycemic Index					
I Quartile	Reference	Reference	Reference	Reference	Reference
II Quartile	1.04 (0.91, 1.18)	0.92 (0.70, 1.20)	0.93 (0.77, 1.13)	0.87 (0.61, 1.23)	1.33 (1.08, 1.65)
III Quartile	1.02 (0.90, 1.17)	1.08 (0.66, 1.75)	0.90 (0.74, 1.09)	0.95 (0.68, 1.35)	1.28 (1.04, 1.59)
IV Quartile	1.16 (1.02, 1.31)	1.21 (0.81, 1.81)	0.93 (0.76, 1.12)	0.84 (0.59, 1.20)	1.60 (1.30, 1.96)
$P_{for\ linear\ trend}$	0.037	0.63	0.40	0.46	<0.001
$P_{heterogeneity}$[c,d]	0.35	0.03	0.41	0.22	0.66
Glycemic Load					
I Quartile	Reference	Reference	Reference	Reference	Reference
II Quartile	0.94 (0.82, 1.07)	0.88 (0.70, 1.12)	0.91 (0.75, 1.11)	0.78 (0.54, 1.13)	0.95 (0.76, 1.18)
III Quartile	0.89 (0.78, 1.02)	0.86 (0.68, 1.10)	0.75 (0.61, 0.92)	0.74 (0.51, 1.09)	1.03 (0.83, 1.28)
IV Quartile	0.91 (0.79, 1.05)	0.89 (0.69, 1.15)	0.78 (0.63, 0.97)	0.84 (0.57, 1.22)	1.03 (0.82, 1.28)
$P_{for\ linear\ trend}$	0.15	0.37	0.009	0.41	0.63
$P_{heterogeneity}$[c,d]	0.52	0.30	0.97	0.24	0.68

a. Models adjusted for age, sex, race/ethnicity, study center, education level, center-specific control-based quartiles of energy intake (without alcohol for glycemic index; without alcohol and carbohydrate for glycemic load), 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 smoking intensity and alcohol drinking intensity. b. The number of controls differed across sub-sites because a few studies considered cancers of the oral cavity, oropharynx, and hypopharynx only; therefore, they contributed to the analysis with fewer controls than those studies with all cancer sub-sites included (see Supplementary Table 4). c. P-value for heterogeneity between study centers. d. Based on the likelihood ratio test of heterogeneity between study centers, we reported the fixed-effects estimates when $P_{heterogeneity} > 0.1$ and the mixed-effects estimates when $P_{studies} < 0.1$.

Supplementary Material

Manuscript: “Dietary glycemic index, glycemic load, and head and neck cancer risk: a pooled analysis in an international consortium”

METHODS (extended)

Glycemic index and glycemic load checking

Information on individual values of glycemic index (GI) and glycemic load (GL) was originally provided to the International Head and Neck Cancer Epidemiology (INHANCE) Consortium Coordinating Center by the Principal Investigators of the Italy Multicenter, Switzerland, and Milan (2006-2009) studies. Calculation of GI and GL was based on the same (reproducible and valid) food-frequency questionnaire (FFQ) and food-composition tables[1] across the three studies. An extended description was provided in full elsewhere.[2] For those studies, we checked missing or inconsistent values and solved inconsistencies, when possible.

Glycemic index and glycemic load estimation

GI and GL were estimated for Los Angeles, Boston, Seattle (1985-1995) and Memorial Sloan Kettering Cancer Center (MSKCC) studies from their FFQs by the following steps:

1. Converting the consumption frequency to servings per day

For Boston and Seattle (1985-1995) studies, a daily serving for each food item was obtained by DIETSYS Nutrient Analysis System. For the Los Angeles study, daily serving was calculated by using consumption frequency times the weight of none, daily, weekly, monthly and yearly consumption frequency (0, 1, 1/7, 1/30.42 and 1/365, respectively). For the MSCKK study, the raw data from INHANCE consortium only contained the information of frequency per month instead of daily, weekly, monthly and yearly consumption frequency. Hence, a daily serving was calculated by:

(monthly frequency/30.42) * the serving size. The weights for small, medium and large serving size were 0.5, 1 and 1.25, respectively.

2. Converting daily serving to daily intake in gram

Grams per portion size for each food item were obtained from the U.S. Department of Agriculture (USDA).[3] USDA Nutrient Database Standard Reference, version 16 (SR16)[4] provides the grams per portion size as well as the nutritional composition for each food item. Daily intake (gram) was calculated by multiplying the daily serving of specific food item by its grams per portion size. Available carbohydrate per 100 grams for each food item was also obtained from the same source. We defined available carbohydrate to be the USDA-based value for grams of carbohydrate per 100 grams minus the USDA value for grams of dietary fiber per 100 grams. Daily available carbohydrate intake (g/day) was calculated by summing the products of available carbohydrate (g/100g) of the specific food item by daily intakes (g) and dividing by 100.

3. Assigned glycemic index value to each food item

We linked GI values (using a scale assuming bread=100) to each food item using the published GI estimates. We searched for the most similar food item within the international GI tables[5,6], considering only studies in healthy subjects and conducted in the United States or Canada. Whenever more than one GI value was provided for the same type of food in the international table, the average GI value was assigned to that food item. When the food item could not be found in the tables, we then searched the GI values compiled by Flood et al..[7] The process of linkage was carried out by manual reviewing the GI tables to identify the best matches for each food item in the questionnaire.

4. Daily glycemic index and glycemic load calculation

Average dietary GI and GL were calculated by the following formula[3,8,9]:

$$Average\ dietary\ GI = \frac{\sum(GI\ \ of\ each\ food\ item * available\ grams\ of\ carbohydrate\ intake\ of\ each\ food\ item)}{total\ available\ grams\ of\ carbohydrate\ intake}$$

$$Daily\ GL = \frac{\sum(GI\ \ of\ each\ food\ item * available\ grams\ of\ carbohydrate\ intake\ of\ each\ food\ item)}{100}$$

where the sum was carried out across all foods consumed by each subject. Each GL unit represents the effect of consuming one gram of carbohydrate from bread.

For the North Carolina (2002-2006) study, information on individual values of daily GL was originally provided to the INHANCE Consortium Coordinating Center by the Principal Investigators. We estimated dietary GI as 100 multiplied with GL divided by total available grams of carbohydrate intake.

Supplementary Tables

Supplementary Table 1. Characteristics of individual studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium used in the current analysis.

Study Reference paper	Recruitment period	Source (cases/ controls)	Participation rate, % (cases/controls)	Age eligibility (years)	Number of subjects (cases/ controls)	Questionnaire, administration, reference period for the recall, reproducibility and validity	Frequency	Serving size[a]	# Food items (including non-alcoholic beverages)
Italy Multicenter Bosetti et al., 2003[b]	1990-1999	Hospital/Hospital-unhealthy	>95/>95	18-80	1261/2716	FFQ, interviewer-administered, 2 year before disease, reproducible and valid	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
Switzerland Levi et al., 1998[b]	1991-1997	Hospital/Hospital-unhealthy	>95/>95	<80	516/883	FFQ, interviewer-administered, 2 year before disease, reproducible and valid	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
Los Angeles, CA, USA Cui et al., 2006	1999-2004	Cancer registry/ Neighborhood	49/68	18-65	417/1005	FFQ, interviewer-administered, during the past year, modification of an existing FFQ, tested for reproducibility and validity	Raw data	M	78 (including 11 non-alcoholic beverages)
Boston, MA, USA Peters et al., 2005	1999-2004	Hospital/ Residential records	88.7/48.7	≥18	584/659	FFQ, self-administered, during the past year, reproducible and valid	Categories	M	138 (including 12 non-alcoholic beverages)
New York, MSKCC, USA Schantz et al., 1997	1992-1994	Hospital/Blood donors	NA	NA	134/169	FFQ–diet history, self-administered, during the past year, modification of an existing FFQ, tested for reproducibility and validity [c]	Raw data	S/M/L	88 (including 5 non-alcoholic beverages)
Milan (2006-2009), Italy Bravi et al., 2013 [b]	2006-2009	Hospital/Hospital-unhealthy	>95/>95	18-80	367/750	FFQ, interviewer-administered, 2 years before disease, reproducible and valid	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
North Carolina (2002-2006), USA Divaris et al., 2010[c]	2002-2006	Cancer registry/ DMV files	82/61	20-80	1368/1396	FFQ, interviewer-administered, during the past year, modification of an existing FFQ, tested for reproducibility and validity	Categories	M	72 (including 5 non-alcoholic beverages) questions
Seattle (1985-1995), WA, USA Rosenblatt et al, 2004 [d]	1985-1995	Cancer registry/ Random digit dialing	54.4/63.3; 63.0/60.9	18-65	407/607	FFQ, interviewer-administered, 5 years ago, reproducible and valid	Raw data	S/M/L	106 (including 7 non-alcoholic beverages)

ABBREVIATIONS: DMV: Department of Motor Vehicles; FFQ: food-frequency questionnaire; S: small; M: medium; MSKCC: Memorial Sloan Kettering Cancer Center; L: large; NA: not available.

a. A quantification of the medium serving size was provided in all the studies. b. Italy Multicenter, Milan (2006-2009) and Switzerland studies were based on the same food-frequency questionnaire. c. The food-frequency questionnaire from the North Carolina study provided combined questions concerning consumption of specific food items and corresponding condiment habits or fat content of the food item of interest (i.e. while asking for cooked or raw vegetable consumption, the food frequency questionnaire asked for extra information on fat, sauce, or dressing added after cooking or at the table). d. Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

Supplementary Table 2. Glycemic index values for selected food items in the food frequency questionnaires included in the current analysis. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Boston and North Carolina (2002-2006)[a]			Los Angeles			MSKCC and Seattle[a]			Italy Multicenter, Switzerland, and Milan (2006 - 2009)[a]		
Food item	**GI**	**GI x CHO[b]**	**Food item**	**GI**	**GI x CHO[b]**	**Food item**	**GI**	**GI x CHO[b]**	**Food item**	**GI**	**GI x CHO[b]**
Potatoes-bake/boil/mash	158	3865	Other white potatoes (boiled, baked, potato salad, mashed)	159	3762	Other potatoes, yams	158	1932	Maize (polenta)	106	4325
Pretzels	119	2564	Other cold cereals such as Corn Flakes, Rice Krispies	114	2847	Other cold cereals	114	2840	Bread	101	3232
Cold breakfast cereal	114	2136	Corn bread, corn muffins, corn tortillas	108	2920	Watermelon (in season)	109	592	Biscuits	95	4057
Pancakes/waffles[c]	110	5578	White bread (including sandwiches), bagels, etc.	104	6075	Other soups	108	1721	Fruit or jam pies	93	6092
Chowder/cream soup	108	1721	Watermelon (in season)	103	1118	Corn bread, corn muffins, corn tortillas	108	2924	Sugar	89	262
Regular muffins/biscuits	107	3327	Rice	103	3985	White bread, rolls, crackers (include sandwiches)	105	4198	Pizza	86	6321
Doughnuts	107	2682	Cantaloupe (in season)	93	1079	Rice	103	3389	Risotto	86	6125
White bread, including pita	105	2099	French fries, fried potatoes, hash browns	91	2764	Other fruit juices, fortified fruit drinks	97	2324	Ice cream	83	1718
Jam/jelly/syrup/honey	104	1404	Regular soft drinks (not diet)	90	6298	Hamburgers, cheeseburgers, meat loaf	94	3000	Lasagne, tortellini with meat filling	64	3611
White rice	103	4519	Beef stew or pot pie with vegetables	89	1093	Cantaloupe (in season)	93	299	Pasta/rice with tomato sauce	62	4371

ABBREVIATIONS: GI: glycemic index; CHO: available carbohydrate; MSKCC: Memorial Sloan Kettering Cancer Center.
a. For Italy Multicenter, Switzerland, and Milan (2006 - 2009) studies, the same questionnaire was used. For Boston, North Carolina, MSKCC, and Seattle studies, different questionnaires with similar high glycemic index food items were used. We, therefore, combined their information in this table.
b. GI x CHO: product of the (available) carbohydrates content per food serving times its GI value in the food-frequency questionnaire.
c. Pancakes/waffles item was present in the Boston study only.

Supplementary Table 3. Descriptive statistics on glycemic index and glycemic load across study centers and in all the studies combined. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Study Center	Q1 (25th)	Median	Q3 (75th)
Glycemic Index			
Overall	71.53	76.25	81.07
Boston	79.69	82.74	85.5
Italy Multicenter			
Pordenone	70.61	74.77	78.7
Milan	70.88	74.56	78.06
Latina	72.29	76.19	79.31
Los Angeles	72.37	77.33	82.52
MSKCC	76	80.16	83.97
Milan (2006-2009)	74.64	78.44	81.55
North Carolina (2002-2006)	69.55	72.97	76.39
Seattle (1985-1995)	76.96	80.02	83.64
Switzerland	67.9	75.01	82.94
Glycemic Load			
Overall	141.69	191.73	253.07
Boston	169.39	221.98	284.74
Italy Multicenter			
Pordenone	171.7	213.63	267.14
Milan	146.54	191.72	240.18
Latina	165.07	213.3	260.19
Los Angeles	113.74	161.49	238.64
MSKCC	90.42	138.24	182.26
Milan (2006-2009)	167.86	203.88	250.75
North Carolina (2002-2006)	119.86	163.59	217.67
Seattle (1985-1995)	119.75	166.65	207.98
Switzerland	112.37	169.94	245.69

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

Supplementary Table 4. Distribution of selected characteristics among controls and cancer cases of head and neck, oral cavity, oropharynx, hypopharynx, and larynx. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Controls (7407), n(%)	Head and neck cases (4081), n(%)	Oral cavity cases (810), n(%)	Oropharynx cases (1172), n(%)	Hypopharynx cases (343), n(%)	Larynx cases (1338), n(%)
Age (years)						
17 to 40	461 (6.2)	152 (3.7)	41 (5.1)	46 (3.9)	2 (0.6)	22 (1.6)
40 to 44	434 (5.9)	195 (4.8)	41 (5.1)	63 (5.4)	13 (3.8)	46 (3.4)
45 to 49	720 (9.7)	475 (11.6)	93 (11.5)	177 (15.1)	36 (10.5)	111 (8.3)
50 to 54	1206 (16.3)	668 (16.4)	130 (16.0)	234 (20.0)	67 (19.5)	170 (12.7)
55 to 59	1338 (18.1)	823 (20.2)	161 (19.9)	258 (22.0)	75 (21.9)	257 (19.2)
60 to 64	1084 (14.6)	638 (15.6)	123 (15.2)	159 (13.6)	60 (17.5)	242 (18.1)
65 to 69	1021 (13.8)	569 (13.9)	105 (13.0)	139 (11.9)	52 (15.2)	231 (17.3)
70 to 74	847 (11.4)	391 (9.6)	74 (9.1)	76 (6.5)	28 (8.2)	186 (13.9)
75 to 89	294 (4.0)	170 (4.2)	42 (5.2)	20 (1.7)	10 (2.9)	73 (5.5)
Missing	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex						
Female	2382 (32.2)	874 (21.4)	269 (33.2)	217 (18.5)	57 (16.6)	196 (14.6)
Male	5020 (67.8)	3202 (78.5)	538 (66.4)	954 (81.4)	286 (83.4)	1141 (85.3)
Missing	5 (0.1)	5 (0.1)	3 (0.4)	1 (0.1)	0 (0.0)	1 (0.1)
Race						
Black	340 (4.6)	335 (8.2)	62 (7.7)	81 (6.9)	23 (6.7)	118 (8.8)
Others (with Asians)	107 (1.4)	76 (1.9)	9 (1.1)	29 (2.5)	3 (0.9)	15 (1.1)
White (with Hispanics)	6917 (93.4)	3653 (89.5)	733 (90.5)	1060 (90.4)	315 (91.8)	1200 (89.7)
Missing	43 (0.6)	17 (0.4)	6 (0.7)	2 (0.2)	2 (0.6)	5 (0.4)
Study center						
Boston	611 (8.2)	358 (8.8)	76 (9.4)	160 (13.7)	33 (9.6)	64 (4.8)
Italy Multicenter						
Milan	621 (8.4)	193 (4.7)	57 (7.0)	57 (4.9)	24 (7.0)	24 (1.8)
Pordenone	1527 (20.6)	880 (21.6)	79 (9.8)	220 (18.8)	105 (30.6)	436 (32.6)
Latina	425 (5.7)	95 (2.3)	40 (4.9)	34 (2.9)	7 (2.0)	0 (0.0)
Los Angeles	1018 (13.7)	400 (9.8)	49 (6.0)	144 (12.3)	16 (4.7)	83 (6.2)
MSKCC	123 (1.7)	106 (2.6)	52 (6.4)	11 (0.9)	10 (2.9)	32 (2.4)
Milan (2006-2009)	691 (9.3)	331 (8.1)	79 (9.8)	36 (3.1)	14 (4.1)	203 (15.2)
North Carolina (2002-2006)	1120 (15.1)	1057 (25.9)	152 (18.8)	298 (25.4)	47 (13.7)	373 (27.9)
Seattle (1985-1995)	394 (5.3)	175 (4.3)	93 (11.5)	74 (6.3)	0 (0.0)	0 (0.0)
Switzerland	877 (11.8)	486 (11.9)	133 (16.4)	138 (11.8)	87 (25.4)	123 (9.2)
Education						
No education	20 (0.3)	14 (0.3)	3 (0.4)	4 (0.3)	1 (0.3)	5 (0.4)
Less than junior high school	2603 (35.1)	1386 (34.0)	221 (27.3)	332 (28.3)	143 (41.7)	592 (44.2)
Some high school	803 (10.8)	678 (16.6)	162 (20.0)	185 (15.8)	62 (18.1)	215 (16.1)
High school graduate	917 (12.4)	660 (16.2)	133 (16.4)	185 (15.8)	58 (16.9)	197 (14.7)
Technical school, some college	1510 (20.4)	748 (18.3)	176 (21.7)	239 (20.4)	44 (12.8)	204 (15.2)
More than college graduate	1550 (20.9)	588 (14.4)	114 (14.1)	224 (19.1)	35 (10.2)	123 (9.2)
Missing	4 (0.1)	7 (0.2)	1 (0.1)	3 (0.3)	0 (0.0)	2 (0.1)

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

Supplementary Table 4. (continued) Distribution of selected characteristics among controls and cancer cases of head and neck, oral cavity, oropharynx, hypopharynx, and larynx. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Controls (7407), n(%)	Head and neck cases (4081), n(%)	Oral cavity cases (810), n(%)	Oropharynx cases (1172), n(%)	Hypopharynx cases (343), n(%)	Larynx cases (1338), n(%)
Cigarette smoking status						
Never	3111 (42.0)	578 (14.2)	137 (16.9)	216 (18.4)	24 (7.0)	80 (6.0)
Former	3060 (41.3)	1738 (42.6)	244 (30.1)	523 (44.6)	150 (43.7)	683 (51.0)
Current	1210 (16.3)	1749 (42.9)	424 (52.3)	430 (36.7)	169 (49.3)	566 (42.3)
Missing	26 (0.4)	16 (0.4)	5 (0.6)	3 (0.3)	0 (0.0)	9 (0.7)
Cigarette smoking intensity (number of cigarettes/day)						
Never smokers	3111 (42.0)	579 (14.2)	137 (16.9)	216 (18.4)	24 (7.0)	81 (6.1)
> 0 to 10	1367 (18.5)	460 (11.3)	85 (10.5)	150 (12.8)	29 (8.5)	138 (10.3)
> 10 to 20	1791 (24.2)	1493 (36.6)	285 (35.2)	403 (34.4)	124 (36.2)	563 (42.1)
> 20 to 30	530 (7.2)	719 (17.6)	137 (16.9)	198 (16.9)	71 (20.7)	250 (18.7)
>30 to 40	352 (4.8)	558 (13.7)	110 (13.6)	145 (12.4)	61 (17.8)	204 (15.2)
40+	184 (2.5)	227 (5.6)	45 (5.6)	53 (4.5)	24 (7.0)	88 (6.6)
Missing	72 (1.0)	45 (1.1)	11 (1.4)	7 (0.6)	10 (2.9)	14 (1.0)
Cigarette smoking duration (years)						
Never smokers	3111 (42.0)	579 (14.2)	137 (16.9)	216 (18.4)	24 (7.0)	81 (6.1)
> 0 to 10	560 (7.6)	143 (3.5)	25 (3.1)	62 (5.3)	6 (1.7)	20 (1.5)
> 10 to 20	858 (11.6)	263 (6.4)	62 (7.7)	83 (7.1)	20 (5.8)	67 (5.0)
> 20 to 30	1062 (14.3)	691 (16.9)	139 (17.2)	222 (18.9)	69 (20.1)	203 (15.2)
>30 to 40	978 (13.2)	1173 (28.7)	242 (29.9)	339 (28.9)	114 (33.2)	398 (29.7)
40+	820 (11.1)	1220 (29.9)	200 (24.7)	247 (21.1)	110 (32.1)	565 (42.2)
Missing	18 (0.2)	12 (0.3)	5 (0.6)	3 (0.3)		4 (0.3)
Cigar smoking status						
Never cigar user	6980 (94.2)	3729 (91.4)	747 (92.2)	1073 (91.6)	318 (92.7)	1219 (91.1)
Ever smoked more than 100	402 (5.4)	330 (8.1)	56 (6.9)	95 (8.1)	22 (6.4)	112 (8.4)
Missing	25 (0.3)	22 (0.5)	7 (0.9)	4 (0.3)	3 (0.9)	7 (0.5)
Pipe smoking status						
Never pipe user	6870 (92.8)	3747 (91.8)	742 (91.6)	1073 (91.6)	316 (92.1)	1235 (92.3)
Ever smoked more than 100	508 (6.9)	311 (7.6)	64 (7.9)	97 (8.3)	24 (7.0)	90 (6.7)
Missing	29 (0.4)	23 (0.6)	4 (0.5)	2 (0.2)	3 (0.9)	13 (1.0)
Alcohol drinking intensity (number of drinks/day)						
Never drinker	1741 (23.5)	395 (9.7)	91 (11.2)	107 (9.1)	16 (4.7)	114 (8.5)
<1	2260 (30.5)	674 (16.5)	154 (19.0)	225 (19.2)	18 (5.2)	172 (12.9)
1 to < 3	1898 (25.6)	797 (19.5)	158 (19.5)	233 (19.9)	57 (16.6)	279 (20.9)
3 to < 5	818 (11.0)	607 (14.9)	125 (15.4)	146 (12.5)	59 (17.2)	222 (16.6)
5+	689 (9.3)	1605 (39.3)	281 (34.7)	461 (39.3)	193 (56.3)	550 (41.1)
Missing	1 (0.0)	3 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

Supplementary Table 5. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) of glycemic index and glycemic load on head and neck cancer in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Glycemic Index				Glycemic Load			
	II Quartile	III Quartile	IV Quartile	$P_{studies}$[c]	II Quartile	III Quartile	IV Quartile	$P_{studies}$[c]
Age (years)								
17 to 54	1.20 (1.00, 1.45)	1.15 (0.97, 1.36)	1.34 (1.10, 1.64)	0.923	1.06 (0.82, 1.37)	1.03 (0.77, 1.37)	0.99 (0.76, 1.30)	0.805
55 to 89	0.93 (0.76, 1.14)	0.98 (0.71, 1.35)	1.06 (0.83, 1.36)	0.058	1.00 (0.77, 1.31)	0.89 (0.62, 1.28)	0.95 (0.74, 1.23)	0.023
P_{strata}[b]		0.676				0.690		
Sex								
Female	1.04 (0.81, 1.33)	1.08 (0.84, 1.40)	1.23 (0.96, 1.58)	0.051	0.92 (0.72, 1.18)	0.99 (0.76, 1.28)	1.02 (0.76, 1.37)	0.550
Male	1.04 (0.89, 1.21)	1.00 (0.86, 1.16)	1.11 (0.96, 1.29)	0.565	0.93 (0.79, 1.09)	0.85 (0.72, 1.00)	0.87 (0.74, 1.02)	0.598
P_{strata}[b]		0.277				0.677		
Education								
<= Junior high school	0.65 (0.37, 1.15)	0.77 (0.54, 1.11)	0.92 (0.53, 1.58)	0.061	0.90 (0.64, 1.26)	0.78 (0.53, 1.14)	0.64 (0.34, 1.17)	0.003
<= High school	1.10 (0.81, 1.51)	1.12 (0.77, 1.62)	1.53 (1.04, 2.26)	0.331	1.11 (0.67, 1.84)	0.95 (0.60, 1.51)	1.20 (0.73, 1.96)	0.272
>= Some college	1.02 (0.83, 1.25)	1.05 (0.89, 1.26)	1.07 (0.91, 1.27)	0.504	1.09 (0.92, 1.29)	0.95 (0.84, 1.08)	0.90 (0.77, 1.04)	0.970
P_{strata}[b]		0.991				0.516		
Tobacco smoking status								
Never	0.91 (0.70, 1.19)	1.02 (0.78, 1.32)	1.03 (0.79, 1.34)	0.572	1.06 (0.81, 1.38)	0.93 (0.70, 1.24)	0.89 (0.65, 1.22)	0.328
Former	1.11 (0.92, 1.34)	1.03 (0.85, 1.25)	1.24 (1.03, 1.49)	0.579	0.97 (0.80, 1.19)	0.92 (0.75, 1.12)	0.98 (0.80, 1.21)	0.708
Current	1.01 (0.77, 1.31)	0.99 (0.76, 1.28)	1.10 (0.86, 1.42)	0.356	0.82 (0.63, 1.07)	0.86 (0.66, 1.14)	0.82 (0.62, 1.08)	0.634
P_{strata}[b]		0.621				0.855		
Cigarette smoking intensity (number of cigarettes/day)								
Never	0.91 (0.70, 1.19)	1.02 (0.79, 1.33)	1.03 (0.79, 1.34)	0.573	1.07 (0.82, 1.39)	0.93 (0.70, 1.24)	0.89 (0.65, 1.22)	0.312
>0 to 20	1.10 (0.92, 1.33)	0.99 (0.82, 1.19)	1.25 (1.04, 1.50)	0.246	0.93 (0.77, 1.12)	0.85 (0.70, 1.03)	0.96 (0.79, 1.18)	0.700
>20	0.98 (0.75, 1.28)	1.08 (0.83, 1.40)	1.10 (0.85, 1.42)	0.526	0.90 (0.69, 1.19)	1.00 (0.76, 1.32)	0.81 (0.61, 1.08)	0.465
P_{strata}[b]		0.830				0.533		
Alcohol drinking intensity								
Never/light	1.08 (0.88, 1.34)	1.03 (0.83, 1.28)	1.16 (0.95, 1.43)	0.414	1.14 (0.93, 1.41)	1.00 (0.79, 1.25)	1.04 (0.82, 1.32)	0.779
Moderate	1.04 (0.84, 1.29)	1.07 (0.87, 1.32)	1.14 (0.92, 1.41)	0.272	0.89 (0.72, 1.10)	0.85 (0.68, 1.06)	0.90 (0.71, 1.14)	0.495
Heavy	1.03 (0.77, 1.38)	1.11 (0.83, 1.49)	1.27 (0.96, 1.69)	0.943	0.75 (0.54, 1.04)	0.86 (0.62, 1.18)	0.79 (0.57, 1.08)	0.988
P_{strata}[b]		0.623				0.063		
BMI (kg/m^2)								
Underweight	0.50 (0.18, 1.40)	1.12 (0.50, 2.51)	1.09 (0.25, 4.73)	0.310	0.50 (0.16, 1.54)	0.75 (0.23, 2.37)	0.62 (0.16, 2.36)	0.294
Normal	1.04 (0.84, 1.30)	1.13 (0.91, 1.41)	1.22 (1.00, 1.48)	0.630	0.90 (0.72, 1.12)	0.79 (0.63, 1.00)	0.81 (0.64, 1.02)	0.737
Overweight/Obese	1.07 (0.77, 1.50)	0.95 (0.56, 1.60)	1.02 (0.78, 1.32)	0.014	0.97 (0.81, 1.16)	0.94 (0.78, 1.13)	0.95 (0.78, 1.15)	0.153
P_{strata}[b]		0.471				0.472		
Study design								
Hospital-based controls	1.20 (1.00, 1.45)	1.13 (0.94, 1.36)	1.29 (1.07, 1.54)	0.238	0.96 (0.79, 1.16)	0.95 (0.78, 1.15)	1.00 (0.82, 1.22)	0.261
Population-based controls	0.90 (0.74, 1.08)	0.94 (0.79, 1.13)	1.08 (0.91, 1.30)	0.561	0.98 (0.81, 1.18)	0.89 (0.73, 1.09)	0.84 (0.68, 1.04)	0.911
P_{strata}[b]		0.983				0.672		
Region								
Europe	1.20 (1.00, 1.45)	1.10 (0.91, 1.32)	1.29 (1.07, 1.55)	0.384	0.93 (0.77, 1.13)	0.92 (0.76, 1.12)	0.98 (0.81, 1.20)	0.431
North America	0.90 (0.75, 1.09)	0.98 (0.82, 1.17)	1.09 (0.91, 1.30)	0.388	1.01 (0.84, 1.22)	0.93 (0.77, 1.13)	0.88 (0.71, 1.08)	0.554
P_{strata}[d]		0.770				0.432		

a. Adjusted for age, sex, race/ethnicity, study center, education levels, energy intake (without alcohol for glycemic index; without alcohol and carbohydrate for glycemic load), 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 smoking and alcohol drinking, when appropriate. b. P for heterogeneity across strata. c. P for heterogeneity between study centers. When $P_{studies} < 0.1$ in one of the strata, we consistently reported the stratum-specific mixed-effects estimates for every stratum.

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