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Natural vitamin C intake and the risk of head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium[a,,b]

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Abstract

Evidence of associations between single nutrients and head and neck cancer (HNC) is still more limited and less consistent than that for fruit and vegetables. However, clarification of the protective mechanisms of fruit and vegetables is important to our understanding of HNC etiology.

We investigated the association between vitamin C intake from natural sources and cancer of the oral cavity/pharynx and larynx using individual-level pooled data from ten case-control studies (5959 cases and 12248 controls) participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. After harmonization of study-specific exposure information via the residual method, adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using unconditional multiple logistic regression models on quintile categories of 'non-alcohol energy-adjusted' vitamin C intake. In the presence of heterogeneity of the estimated ORs among studies, we derived those estimates from generalized linear mixed models.

Higher intakes of vitamin C were inversely related to oral and pharyngeal (OR=0.54, 95% CI: 0.45–0.65, for the fifth quintile category versus the first one, p for trend<0.001) and laryngeal cancers (OR=0.52, 95% CI: 0.40–0.68, p for trend=0.006), although in the presence of heterogeneity among studies for both sites. Inverse associations were consistently observed for the anatomical subsites of oral and pharyngeal cancer, and across strata of age, sex, education, body mass index, tobacco, and alcohol, for both cancer sites.

The inverse association of vitamin C intake from foods with HNC may reflect a protective effect on these cancers; however, we cannot rule out other explanations.

Keywords

head and neck cancer; INHANCE; laryngeal cancer; oral and pharyngeal cancer; vitamin C

Introduction

Tobacco smoking and alcohol drinking are the major etiologic factors for cancers of the oral cavity, pharynx and larynx (head and neck cancer (HNC)) [1, 2]. Diet has been associated with HNC risk on the basis of international variation, time trends, and epidemiological research [3, 4, 5, 6], with a well-recognized protective role of fruit and vegetables. To various degrees, higher intakes of non-starchy vegetables, foods containing carotenoids, and fruit in general have been reported to be inversely related to HNC risk [7, 8, 5], especially among heavy smokers and/or drinkers. However, the strength of the evidence concerning fruit and vegetables has recently been downgraded to 'probable' in the 2007 World Cancer

Research Fund report for these cancers and in some important cohort studies for most cancers and for overall cancer risk [9, 10, 11]. This indicated the need for further research.

Fruit and vegetables are rich sources of compounds that have anti-carcinogenic properties, including vitamins, minerals, fiber, and phytochemicals in general. Several of these nutrients and bioactive compounds have antioxidant and antiproliferative activities, modulate steroid hormone concentrations and metabolism, and stimulate the immune system and synthesis and methylation of DNA [12, 13]. Among them, vitamin C from natural sources has been investigated since the early 1980's in epidemiological studies on upper aerodigestive tract cancer (UADTC) and its subsites, with the vast majority of studies finding inverse associations. However, data are still limited for laryngeal cancer [4, 14, 3].

The International Head and Neck Cancer Epidemiology (INHANCE) consortium [15] was established in 2004 to contribute elucidating the etiology of HNC by providing opportunities for pooled analyses of individual-level data on HNC on a large scale. Dietary habits have been previously investigated within the consortium, with results pointing to a possible protective effect of fruit and vegetables overall (total fruit intake, total vegetable intake excluding potatoes), of selected plant food items (green salad, lettuce, fresh tomatoes, citrus fruits, apples and pears, green vegetables and allium vegetables), as well as of 'a priori' and 'a posteriori' dietary patterns rich in fruit and vegetables [16, 17]. The specific goals of this analysis were: 1. to describe and account for central tendency and variation in the intakes of vitamin C for the populations under examination; 2. to investigate the association between vitamin C intake and the risks of two HNC outcomes - oral and pharyngeal cancer and laryngeal cancer; 3. to explore whether effect estimates differ by cancer subsites or across subgroups of subjects, with particular attention to nonsmokers/nondrinkers; 4. to explore the potential interaction effect between the intakes of vitamin C and of other selected factors - putatively associated to HNC and to our main exposure (other selected nutrients, total fruit and vegetables, supplemental use of vitamin C) - on the two HNC outcomes of interest.

Material and methods

Design and participants

Within the version 1.5 of the INHANCE consortium pooled data set, ten case-control studies provided information on vitamin C intake derived from natural sources at the individual level [18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. Details on the individual studies, harmonization of questionnaire data and data pooling methods for the consortium have been previously described [16, 17] and are reported in the Online Supplemental Material (Supplemental Table 1). Briefly, three of the selected studies were from Europe [18, 19, 27], six were from the United States [20, 21, 28, 22, 23, 25, 26], and one from Asia [24]. Six were hospital-based and four were population-based investigations. Study-specific questionnaires included a food-frequency questionnaire (FFQ) section to assess each subject's usual diet during a reference period preceding cancer diagnosis for cases, or interview for controls. The three studies from Europe (Italy Multicenter, Switzerland, Milan (2006–2009)) used the same FFQ. Previously published studies found that the two FFQs from Italy Multicenter-Switzerland-Milan (2006–2009) and Boston studies were reproducible and valid, the two

FFQs from US Multicenter and Memorial Sloan Kettering Cancer Center (MSKCC) studies were valid, and the two FFQs from Los Angeles and North Carolina studies were slightly modified from a previously validated FFQ [29, 30, 28, 31, 32]. The brief FFQs administered in the Buffalo and Japan studies were validated for the intakes of selected nutrients, including vitamin C [33, 34, 35]. Overall, the number and wording of FFQ questions were sufficiently detailed to allow for the calculation of intakes of total energy and several other nutrients [36, 37, 38], through study-specific food composition databases [39, 40, 41, 42, 43, 44].

Written informed consent was obtained from study subjects, and the investigations were approved by the relevant institutional review boards.

Selection of subjects

Cases were included if their tumor had been classified as an invasive tumor of oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or HNC unspecified. Subjects with cancers of the salivary glands [International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) codes C07–C08] or of the nasal cavity/ear/paranasal sinuses (ICD-O-2 codes C30–C31) were excluded. The ICD coding used for the classification into subsites was specified in detail previously [45].

Subjects with missing information on natural vitamin C intake (1075 subjects from 6 studies, who showed missing values on all the nutrient variables, probably due to missing information on the entire dietary section of the questionnaire) were removed from the original data. Subjects having an implausible (< 500 or > 5500 kcal) daily non-alcohol energy intake (defined as: total energy intake (kcal) - 100 * number of drinks per day, as 1 drink per day = 100 kcal) (343 subjects) or those having missing values (544 subjects) on non-alcohol energy intake were excluded from the analysis. Cases with missing information on the site of origin of their cancer (22 subjects, of which 21 belonging to the MSKCC study) were also removed.

Thus, the present analyses included a total of 18207 subjects, with 5959 HNC cases and 12248 controls. There was a total of 1385 oral cavity cancer cases, 1653 oropharyngeal and 571 hypopharyngeal cancer cases (2224 pharyngeal cancer cases), 805 unspecified oral cavity/pharynx cases (giving a total of 4414 oral and pharyngeal cancer cases), and 1545 laryngeal cancer cases.

Definition of the exposure variable

We carried out preliminary checks on vitamin C definitions, reference periods of intake and measurement units across studies. We extracted information on vitamin C intake from natural sources, and we consistently expressed these intakes on a daily basis. Results on vitamin C supplementation have already been published [46].

To assess the comparability of daily intakes across studies, we inspected the kernel density estimation plot [47] representing the study-specific empirical distributions of vitamin C intakes. We also compared study-specific summary statistics across studies. As preliminary

checks revealed strong differences across studies, we decided to compute 'non-alcohol energy-adjusted' vitamin C intakes within each study, referring to the residual method [48].

Statistical analysis

Participants were grouped into five categories according to quintiles of 'non-alcohol energy-adjusted' (adjusted hereafter) vitamin C intakes calculated among both cases and controls.

We estimated the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of oral and pharyngeal cancer (including oral, oropharynx, hypopharynx, unspecified oral/pharynx cancer), and laryngeal cancer, separately, for each quintile category using unconditional multiple logistic regression models [49]. Tests for linear trend were computed for all models scoring the quintiles as numbers from 1 to 5. To adjust for potential confounders, the main analysis included the following set of variables in all the models: age, sex, education, race/ethnicity, study center, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity, and the interaction between cigarette intensity and alcohol drinking intensity (see tables for categories used).

We tested for the presence of heterogeneity among studies for the effect of quintile categories of adjusted vitamin C intake by calculating likelihood ratio tests comparing the deviance statistics from the models including versus excluding the interaction terms between quintile categories and study. As the p-value for heterogeneity among studies was less than 0.1, we used a mixed-effects modelling approach [50, 51] and replaced the fixed-effects ORs and CIs with the corresponding mixed-effects ones. We derived those estimates specifying a random intercept-random slope generalized linear mixed model (GLMM) with a logit link function and binomial family. The random-effects terms included were the random intercept and four random slope terms (one for each quintile category included, except for the reference one), all sharing study center as the common grouping factor. No correlations between random effects were allowed. We reported restricted maximum likelihood (REML) estimates, as they provided better estimates of variance components [50].

As a sensitivity analysis, we further investigated the potential role of other factors putatively associated with HNC and vitamin C intake, including several *a priori* selected micronutrients (monounsaturated fatty acids, polyunsaturated fatty acids, folate, lutein plus xeaxanthin, total carotenoids, betacarotene equivalents, cryptoxanthin, lycopene, vitamin E, fiber) (quintile categories of adjusted nutrient intake), total fruits and total vegetables (categories of intake based on study-specific quartiles among the controls), and supplement use of vitamin C (never/ever). For each factor, we fitted both the additive and the interaction models including the extra adjustment variable and the interaction terms between quintile categories of adjusted vitamin C intake and extra adjustment variable of interest. We tested for the significance of the adjustment variable or of the interaction effect calculating the corresponding likelihood ratio tests. When the interaction term was non significant at the 0.05 level, we reported results from the additive model. Similarly, non-alcohol energy intake was further adjusted for in the models, to check for a potential reduction in the random error

due to a strong association between non-alcohol energy intake and the outcomes of interest, independent of nutrient intake.

For oral and pharyngeal cancer, separate analyses were conducted by anatomical subsite [49]. As the p-value for heterogeneity among studies was less than 0.1, we fitted the GLMMs to derive the subsite estimates. For both cancers, stratified analyses were conducted by age, sex, education, geographic region, control source, study period, body mass index at time of interview, tobacco smoking, and alcohol drinking. Heterogeneity across strata was tested by calculating likelihood ratio tests comparing the deviance statistics from the models including versus excluding the interaction terms between quintile categories of vitamin C intake and stratification variable. When the p-value for heterogeneity among studies was less than 0.1 within strata, we reported mixed-effects estimates derived from the corresponding GLMMs. When, for a single stratification variable, fixed- and mixed-effects models were estimated within different strata, likelihood ratio tests for heterogeneity across strata were 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 examined whether the results from the fixed- and mixed-effects logistic regression models and those from the two-stage random-effects model [52] were comparable to each other in terms of the magnitude of the effect. In the two-stage random-effects model, we excluded the MSKCC study, containing fewer than 100 cases of either cancer site. We quantified inconsistencies across studies and their impact on the analysis by using Cochrane's Q and the I^2 statistics [53, 54]. We also conducted an influence analysis, in which each study was excluded one at a time to ensure that overall estimates were not dependent on any specific study.

All statistical tests were two-sided. Calculations were performed using the open-source statistical computing environment R [55], with its libraries "lme4" [56] and "nnet" [57], and Stata (Release 11).

Results

Table 1 shows some descriptive statistics on raw values of vitamin C intake across studies and in all the studies combined. Study-specific distributions were all skewed to the right, with median intakes being always smaller than the corresponding mean intakes.

Selected characteristics of cases and controls are shown in Table 2, separately for oral and pharyngeal, and for laryngeal cancer cases. Over 70% of cases and controls were white. The Italy Multicenter, US Multicenter, and North Carolina studies contributed the largest proportion of cases of both cancers combined. The US Multicenter provided cases of oral and pharyngeal cancer only. Cases of both cancers were more frequently and heavily exposed to tobacco and alcohol.

Table 3 gives separate ORs and the corresponding CIs for oral and pharyngeal and laryngeal cancers by quintile category of adjusted vitamin C intake. Mixed-effects estimates replaced the fixed-effects ones in the presence of heterogeneity among studies ($p<0.001$). Higher intakes of vitamin C were inversely related to oral and pharyngeal cancer, with an OR of

0.54 (95% CI: 0.45–0.65) for the fifth quintile compared to the first one (p-value for trend <0.001). Similarly, the OR for laryngeal cancer was 0.52 (95% CI: 0.40–0.68) for the last quintile category, with a significant p-value for trend (p=0.006). The extra adjustment for non-alcohol energy intake (either in continuum or in quintile categories of intake) did not substantially modify the ORs and the corresponding CIs. Mixed-effects models including quintiles of non-alcohol energy intake provided the following estimates for adjusted quintile categories of vitamin C intake and oral and pharyngeal cancer: OR=0.88 (95% CI: 0.73–1.05), 0.68 (95% CI: 0.58–0.78), 0.63 (95% CI: 0.53–0.74), 0.54 (95% CI: 0.45–0.64), and for laryngeal cancer: OR=0.83 (95% CI: 0.69–1.00), 0.65 (95% CI: 0.55–0.77), 0.60 (95% CI: 0.51–0.72), 0.52 (95% CI: 0.43–0.64), respectively (data not shown).

In addition, decreasing ORs with higher intakes of vitamin C were observed across strata of anatomical subsite for oral and pharyngeal cancer: OR=0.52 (95% CI: 0.38–0.72) for oral cavity, OR=0.53 (95% CI: 0.44–0.63) for oropharynx and hypopharynx combined, and OR=0.44 (95% CI: 0.30–0.63) for oral cavity or pharynx not otherwise specified, from random-effects models (p-value for heterogeneity among studies <0.001) (Supplemental Table 2). Separate analyses for oropharynx and hypopharynx cancer sites showed consistent results (OR=0.58, 95% CI: 0.48–0.70, for oropharynx, OR=0.52, 95% CI: 0.38, 0.72, for hypopharynx cancer sites, respectively) and, given the limited number of hypopharynx cancer sites, we decided to combine results for these subsites.

Table 4 shows the ORs of oral and pharyngeal cancer for adjusted vitamin C intake in strata of selected variables. No significant heterogeneity was detected for adjusted vitamin C intake across strata, with consistent inverse associations obtained from mixed-effects models for the fourth quintile category onwards for all the examined strata. However, an appreciable heterogeneity among studies emerged for several strata.

Table 5 shows the ORs of laryngeal cancer for adjusted vitamin C intake in strata of selected variables. Similarly to oral and pharyngeal cancer, an appreciable heterogeneity was observed among studies in several strata, but no significant heterogeneity was detected in general for adjusted vitamin C intake across strata. However, there was an appreciable heterogeneity across strata of geographic region, with a significant inverse association in the three European studies only.

Moreover, results from the fixed- and mixed-effects logistic regression models were comparable to each other in terms of the magnitude of the effect and significance (data not shown). Previous results were also comparable with the results derived from the random-effects meta-analyses [52] comparing each quintile category to the lowest one. Figure 1 shows the forest plots of the pooled and study-specific OR estimates for the associations between the highest versus the lowest quintile of adjusted vitamin C intake and oral and pharyngeal and laryngeal cancers, respectively. For oral and pharyngeal cancer, the pooled OR was 0.58 (95% CI: 0.45–0.76), with corresponding Cochrane's Q p-value equal to 0.001 and I^2 statistic equal to 68.6%. For laryngeal cancer, the pooled OR was 0.68 (95% CI: 0.46–0.99), with corresponding Cochrane's Q p-value equal to 0.011 and I^2 statistic equal to 61.5%. The ORs of oral and pharyngeal cancer were below unity in eight studies (significant in five) and above unity in one study (non significant); the ORs of laryngeal cancer were

below unity in six studies (significant in two) and above unity in two studies (non significant). Results from the influence analysis were reassuring, since the exclusion of one study at a time did not materially change the point estimates. For oral and pharyngeal cancer, the point estimates remained significant after the exclusion of any study, whereas, for laryngeal cancer, statistical significance was lost when individually excluding six of the eight studies from the meta-analysis.

Figure 2 shows the interaction between alcohol or tobacco consumption and adjusted vitamin C intake. For oral and pharyngeal cancer, compared to never and light drinkers (<1 drink/day) in the highest category of vitamin C intake, moderate (>= 1 to < 5 drinks/day) and heavy drinkers (>= 5 drinks/day) in either the low or the high vitamin C intake category had significantly higher ORs, with values ranging approximately from 2 to 12, for drinkers of 5 or more drinks per day in the lowest intake category. Moreover, compared to never smokers in the highest vitamin C intake category, former and current smokers in either the low or the high vitamin C intake category had significantly higher ORs, with values ranging approximately from 2 to 8, for current smokers of more than 20 cigarettes per day in the lowest intake category. Similarly, for laryngeal cancer, moderate and heavy drinkers or former and current smokers in either category of vitamin C intake had a significantly increased OR, with values of about 6 and 28 in the category with the highest exposure to smoking or alcohol and the lowest exposure to vitamin C.

Finally, in the sensitivity analysis including one extra nutrient, the interaction model was selected over the corresponding additive one, from likelihood ratio tests, for fiber intake only, for both cancer sites (p-value=0.04, for oral and pharyngeal cancer, and p-value=0.006, for laryngeal cancer). For the remaining nutrients, the additive model was selected for seven (out of ten) nutrients for oral and pharyngeal cancer, whereas further adjustment for extra nutrients was not significant for laryngeal cancer in any of the fitted models. In either case, the point estimates and the statistical significance were generally in line with the ones from the main analysis. In the model including fiber intake, the ORs of the quintile categories of vitamin C intake were now close to the unity, whereas the ORs of the interaction terms between vitamin C and fiber intakes were generally below the unity, although not always significant, for both cancer sites (data not shown).

In the sensitivity analysis including quartile categories of total fruits or total vegetables, no significant interaction was found between vitamin C and total fruit or total vegetable intakes for either cancer site. The extra adjustment for total fruit or total vegetable intakes was suggested for oral and pharyngeal cancer only, with corresponding ORs for the last quintile category of vitamin C intake given by 0.71 (95% CI: 0.59–0.86) for the model including adjustment by total fruit, and 0.59 (95% CI: 0.50–0.71) for that including adjustment by total vegetable intake (data not shown).

Finally, in the sensitivity analysis including supplemental use of vitamin C, the interaction terms between natural and supplemental use of vitamin C intake were non significant for both cancer sites (p-values equal to 0.74, for oral and pharyngeal cancer, and 0.71 for laryngeal cancer). The extra adjustment for supplemental use of vitamin C intake was significant for oral and pharyngeal cancer only (p-value<0.001), with corresponding ORs

still in line with the ones from the main analysis (OR=0.54, 95% CI: 0.41–0.70 for the last quintile category of vitamin C, OR=0.87, 95% CI: 0.77–0.98 for supplemental use of vitamin C) (data not shown).

Discussion

The present analysis shows that, after study-specific adjustment for non-alcohol energy via the residual method, vitamin C intake was inversely and consistently related to oral and pharyngeal, and to laryngeal cancer risk. The identified associations were similar across oral and pharyngeal cancer subsites and in strata of major confounding and risk factors. In particular, these inverse associations were of similar magnitude in never, former, and current smokers, as well as across levels of alcohol drinking. Extra adjustment for potentially related nutrients, supplemental use of vitamin C intake, and non-alcohol energy intake did not materially change the point estimates and the statistical significance of the previous associations. A significant interaction effect with vitamin C intake was found for total fruit consumption and fiber intake, for both cancer sites, and for total vegetable consumption, for laryngeal cancer.

Among possible mechanisms of anti-cancer action, vitamin C has been hypothesized to counteract inflammation and subsequent oxidative damage to DNA, which play a role in the initiation and progression of cancer. Vitamin C may also function as cancer cells killer, due to its pro-oxidant capacity, although the killing of cancer cells is dependent on extracellular H2O2 formation with the ascorbate radical as an intermediate. Moreover, vitamin C may increase collagen synthesis and inhibit hyaluronidase and, on this way, it may prevent cancer spread by increasing extracellular matrix, thus walling in tumors [13, 58]. Finally, this nutrient may act synergistically with other biological antioxidants and radical scavengers in quenching different elements of a radical cascade. This might also justify the strongest evidence in favor of fruit and vegetables, as compared to that on nutrients. Similarly, we cannot exclude that a higher consumption of vitamin C or a more frequent consumption of fruit and vegetables may be a nonspecific indicator of a more affluent and healthy diet [59].

The major strength of our pooled analysis was the availability of a very large series of HNC patients and control subjects, which allowed us to compare vitamin C intake across populations, to examine related overall HNC risk and to explore differences in risks by cancer subsite, geographic region, and alcohol and tobacco consumption.

However, pooled analyses on dietary data pose several challenges. A first issue concerns the type of available dietary data. Nutrients are derived from the questionnaires through country-specific food composition databases. As compared to food-based analyses, this represents an extra step that may be responsible for heterogeneity among studies. Moreover, sources of nutrients may be different across countries. In the present case, a study based on the same FFQ administered in the Italy Multicenter, Milan (2006–2009), and Switzerland studies showed that vitamin C derived from different types of fruit and vegetables, with citrus fruits, kiwi, tomatoes, green salad, apples/pears representing the major sources [60]. In the Japanese 102-item FFQ from which the brief FFQ of the Japan study was derived, vitamin C was supplied by various vegetables and fruits, with spinach, Japanese persimmon,

mandarin orange, cabbage, potatoes, but also green tea [61] being relevant sources; however, similar sources ranked in a different way in a rural but otherwise comparable Japanese population, where miso soup was also a very important source of vitamin C [62]. In the Block FFQ used in the US Multicenter, Los Angeles, and MSKCC studies, the main sources of vitamin C were fruit juices, and fruit and vegetables. However, although fruit juices, tomatoes, oranges/tangerines, and potatoes were the leading dietary sources in all socio-demographic subgroups, fortified drinks and southern greens were the major contributors among the young and among the blacks, respectively [63, 64] (for a useful comparison of sources of vitamin C across different dietary questionnaires, see [62]). Keeping this in mind, we observe that, compared to other major nutrients, the validity of vitamin C is more likely to be satisfactory, because it derives from a few major sources, is assessed relatively well by a small number of foods, and these foods are generally consumed all over the world [29, 35]. Moreover, a selection of the top 20 foods contributing most to the total absolute intake accounted for a similar proportion of about 85% of total vitamin C intake from natural sources in the Willett and Block FFQs and in the Western New York FFQ which was used to develop the brief FFQ used in the Buffalo study [33, 64, 65].

A second related issue is the comparability of nutrient intakes across studies. In our scenario, the analysis included only case-control studies, the selected studies were all based on FFQs, the FFQs showed a sufficient level of detail, and some of them were explicitly created to assess consumption of fruit and vegetables and related nutrients [66, 67, 20]. Moreover, we checked for consistency of vitamin C definitions and measurement units, and we excluded the contribution of supplements, whose consumption may represent an extra source of heterogeneity among studies. However, differences existed in the length of the questionnaires and in the wording and design of the questions, and in the food composition databases used to derive nutrient intakes. Moreover, in the Buffalo and Japan studies, diet was queried using brief FFQs, although both the FFQs were specifically designed to provide an assessment of foods providing good sources of vitamins C, and methods for the derivation of the regression weights used to calculate nutrient intakes were carefully examined and provided reassuring results [33, 35].

These differences may have created discrepancies in the study-specific empirical distributions of individual nutrients. To assess the burden of the problem, we carried out preliminary checks using descriptive statistics and a kernel density estimation plot comparing the study-specific empirical distribution of vitamin C intake across studies. We detected systematic differences in the empirical distribution across studies. To partially overcome the problem, we applied the Willett and Stampfer residual method [48] within each study before carrying out the analysis. The extra step of the application of the residual method, instead of the easier and more typical calculation of study-specific quintiles, is driven by the idea that separating out vitamin C from non-alcohol energy intake would allow isolation of the effect of this nutrient from that of total energy intake or energy balance and is suggested when dealing with quantile categories of nutrient intakes, as compared to the standard multivariate approach including both caloric intake and absolute nutrient intakes as terms in the multiple regression model [68]. However, we recognize that this solution may be rough - as between-studies differences are also likely driven by differences in

measurement protocols, instruments, study populations, and cultures - and therefore it may not completely solve the issue.

Given the mentioned difficulties in pooling dietary data, together with the different characteristics of the various populations, including variable exposure to alcohol and tobacco, a degree of heterogeneity among studies is to be expected. In our analysis, heterogeneity among studies emerged in the fixed-effects models overall and in several strata of interest, including subsites of oral and pharyngeal cancer. It was confirmed by mixed-effects models results in both GLMM and two-stage method approaches. Our inspection of study-specific findings, influence analyses, and subgroup analyses stratifying by study characteristics pointed to the presence of heterogeneity between European and American studies, especially for laryngeal cancer. However, it is difficult to disentangle the effect of control sources (hospital- versus population-based) from that of geographic region, as the three studies from Europe were all hospital-based and four out of the six American studies were population-based. The apparent heterogeneity cannot, therefore, be attributed beyond reasonable doubt to selection bias and to different types of controls,

In any case, selection bias may be strong in hospital-based case-control studies. since many diseases are related to diet; even population-based designs can be biased due to low or unsatisfactory participation of eligible persons in the source population, although selection bias should be minimized to the extent that participation is not related to the exposure of interest. Recall bias may be another limitation for our pooled analysis, because information about exposure was collected after the onset of HNC. However, diet was not a widely recognized risk factor for HNC, especially in the knowledge of the public at the time of the studies. Therefore, we would expect recall bias to be acceptable during dietary assessment and equally affecting cases and controls. Residual confounding by smoking and alcohol may still be a major issue for these cancers, given the overwhelming role of these risk factors as compared to diet. In the present study, we adjusted for status, intensity, and duration of cigarette smoking, for cigar and pipe use and drinking intensity, as well as for the interaction between cigarette and alcohol intensity. Thus, the residual confounding effect by these factors should have been minimized.

In pooled analyses of binary data, a two-stage method [52] is a simple, valid and practical alternative to a joint model, lending itself to flexibility with respect to differences in design, confounders and data collection across studies. Simulations indicate that, when the individual studies are large, two-stage methods produce nearly unbiased exposure estimates and standard errors of the exposure estimates from a GLMM [69]. However, it is unclear how well the two-stage method would perform if individual studies were smaller, especially when there are a few of them. In the present study, we fitted random-effects models both via GLMMs and the two-stage method, with reassuring results. While the GLMMs estimates are correct by definition, the two-stage method provides an immediate representation of study-specific and pooled risk estimates.

Some of the studies included in the present analysis already contributed to separate original reports on vitamin C intake or provided data for original publications on data partially overlapping with them [70, 67, 71, 72, 73, 24, 27]. Besides them, we are aware of at least

fourteen papers that have been reported in the literature to assess the association between vitamin C intake from natural sources and HNC and/or its subsites [5, 4, 3]. Among these, seven provided results on oral and/or pharyngeal cancer [74, 75, 76, 77, 78, 79, 80], four on laryngeal cancer [81, 82, 83, 84], one concerned UADTC and their subsites [85] and two UADTC overall [86, 87]. For oral cavity and/or pharyngeal cancer, significant inverse associations were found in four studies, with [80, 79, 75] or without a linear trend [76]. Some studies showed a weak but non significant protection for higher vitamin C intakes [78, 85, 77], and only one showed an increased but non significant risk [74]. For laryngeal cancer, two studies out of five [81, 84] found an association between low intakes of vitamin C and higher risk of laryngeal cancer, with a significant dose-response relationship, whereas the last three [82, 83, 85] found a weak-to-moderate non significant reduction in risk. For UADTC, in the Iowa Women's Health cohort, an inverse, but non significant, association was found for vitamin C intake in the original study [86] for cancers of the mouth/pharynx/esophagus combined, but no association was observed in its update for UADTC overall (including also a few cases of cancers of the nasopharynx, larynx, and stomach), after 14 years of follow-up [87]. Moreover, in a study from Uruguay, the overall UADTC risk was significantly lower (p for trend = 0.01) for higher intakes of vitamin C, although the protection was weak and non significant in oral and pharyngeal and laryngeal subsites [85].

Our findings are consistent with evidence from a review on diet and oral and pharyngeal cancer [5], from previous results on food groups from the INHANCE consortium [16] and from the largest European case-control study on diet and UADTC [88], where fruit and vegetables were inversely related to those cancers. They provide extra evidence to integrate with findings from 'a priori' and 'a posteriori' dietary patterns [16, 17, 89].

In conclusion, clarification of the protective mechanisms of fruit and vegetables is important per se to our understanding of UADTC in general. Although several different factors probably act jointly, our findings suggest that vitamin C intake from foods may protect against cancers of the oral cavity and pharynx, and larynx, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence interval
DMV	Department of Motor Vehicles
FFQ	food-frequency questionnaire

GLMM	generalized linear mixed model
HNC	head and neck cancer
ICD	International Classification of Diseases
INHANCE	International Head and Neck Cancer Epidemiology
L	large
M	medium
MSKCC	Memorial Sloan Kettering Cancer Center
NA	not available
NCI	National Cancer Institute
NE	Not estimable
NIH	National Institutes of Health
OR	odds ratio
REML	restricted maximum likelihood
S	small
UADTC	upper aerodigestive tract cancer.

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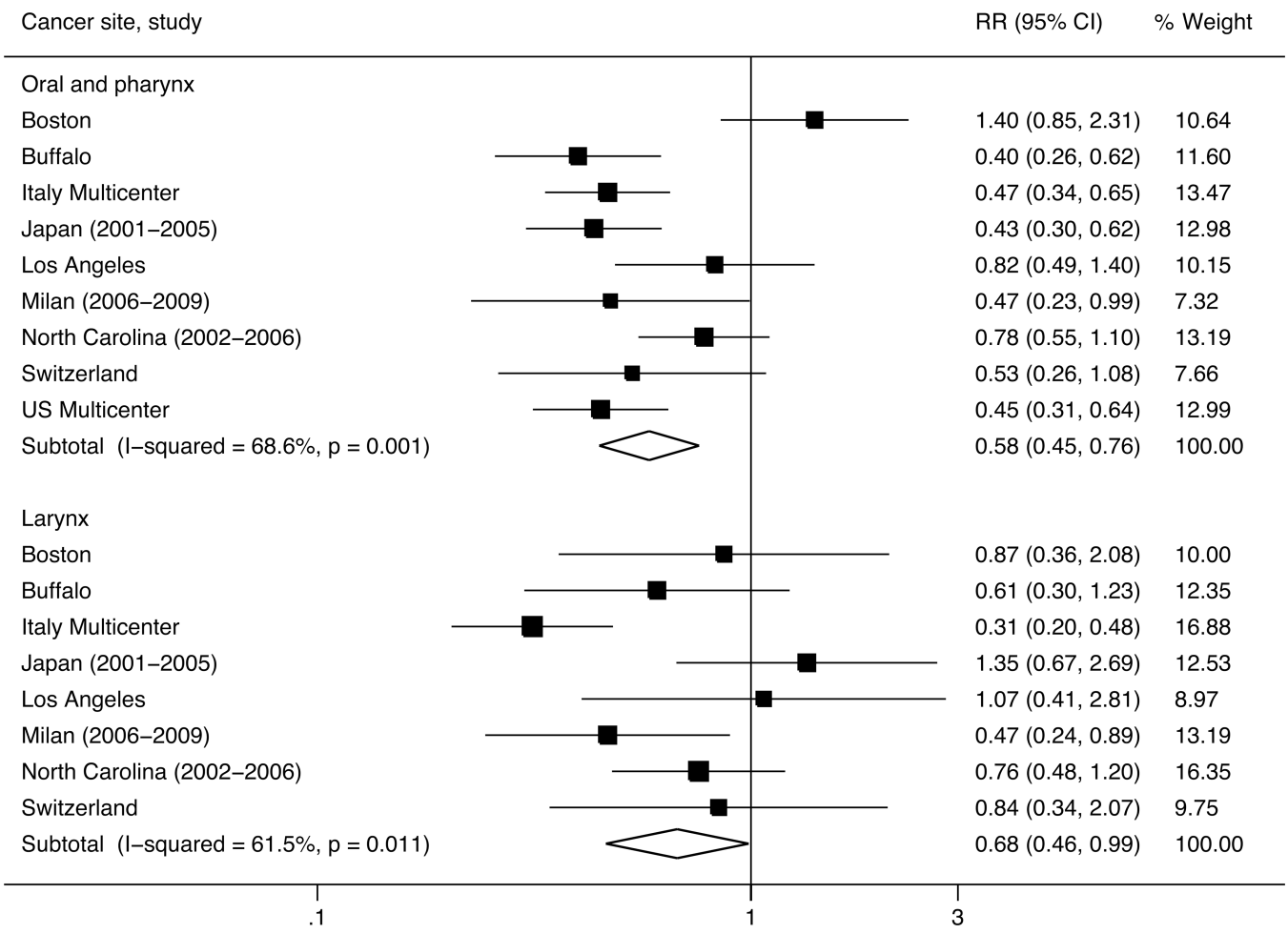

Figure 1.

Forest plots of pooled and study-specific odds ratios (ORs) for the associations between the highest versus the lowest quintile categories of non-alcohol energy-adjusted vitamin C intake and oral and pharyngeal, and laryngeal cancers, respectively. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

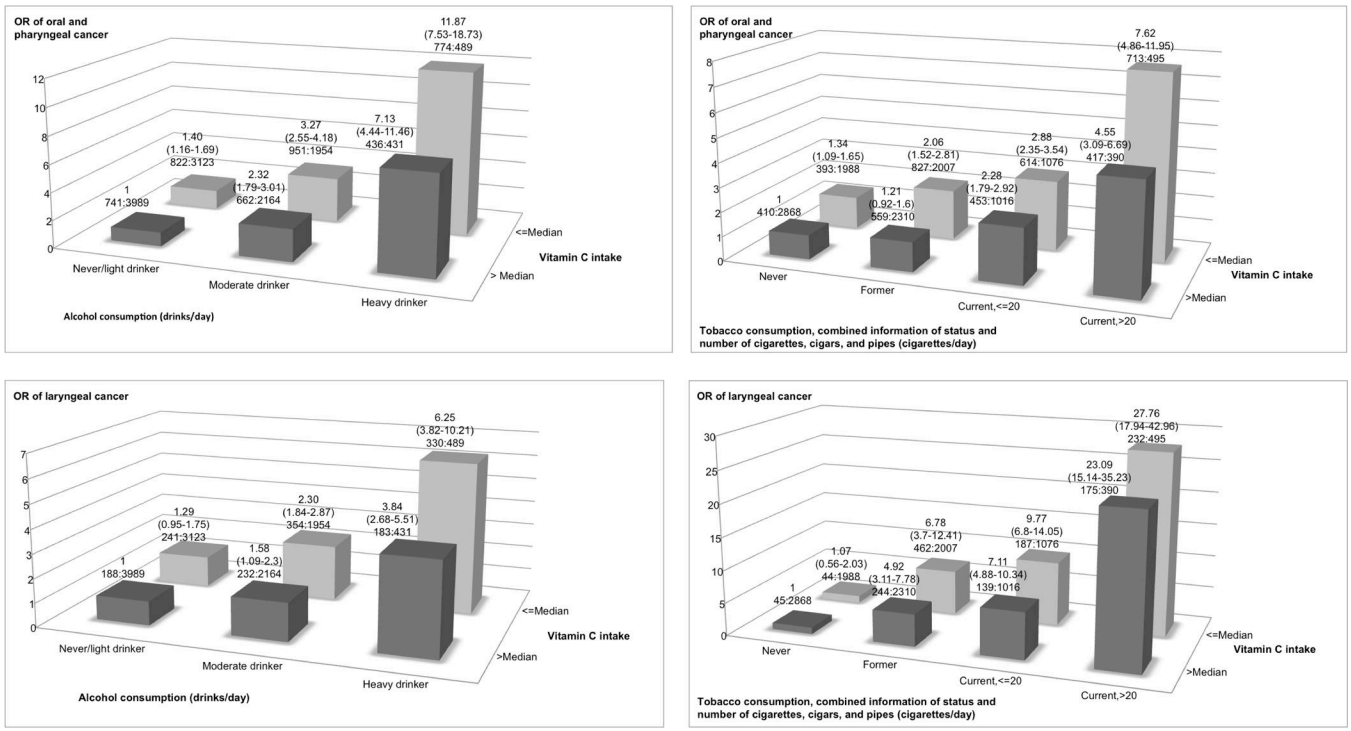

Figure 2.

Odds ratios (ORs)[a,b,c] of oral and pharyngeal, and laryngeal cancers, and corresponding confidence intervals (95% CIs), according to alcohol or tobacco consumption and 'non-alcohol energy-adjusted' vitamin C 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 odds ratio as: "number of cases : number of controls".

[c] The never/light drinker category included never drinkers and subjects who drinks less than 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 1

Descriptive statistics on raw values of vitamin C intake (mg/day) across studies and in all the studies combined. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Study name	20%	Median	Mean	80%
Boston	67.95	122.00	135.60	190.95
Buffalo	95.93	168.90	188.00	263.44
Italy Multicenter	82.34	128.10	141.30	189.85
Japan (2001–2005)	60.26	86.60	91.45	118.65
Los Angeles	43.78	70.53	82.51	120.72
Milan (2006–2009)	78.63	124.80	139.40	192.46
MSKCC	76.08	133.30	148.40	208.34
North Carolina (2002–2006)	74.95	118.90	128.80	174.62
Switzerland	61.24	102.00	133.80	190.35
US Multicenter	77.48	145.80	166.80	231.37
All studies combined	68.08	113.70	133.40	183.97

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

Table 2

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

	Oral and pharyngeal cases	**(%)**	**Controls**	**(%)**	**Laryngeal cases**	**(%)**	**Controls**	**(%)**
Age (years)								
<40	208	4.7	681	5.6	26	1.7	681	5.6
40–44	194	4.4	563	4.6	45	2.9	563	4.6
45–49	446	10.1	949	7.7	123	8.0	949	7.7
50–54	645	14.6	1731	14.1	188	12.2	1731	14.1
55–59	816	18.5	2079	17.0	271	17.5	2079	17.0
60–64	713	16.2	2029	16.6	290	18.8	2029	16.6
65–69	658	14.9	1931	15.8	279	18.1	1931	15.8
70–74	474	10.7	1540	12.6	227	14.7	1540	12.6
≥75	260	5.9	743	6.1	96	6.2	743	6.1
Missing values	0	0.0	2	0.0	0	0.0	2	0.0
X^2 (*p-value*) [a]	*42.0 (<0.001)*				*66.5 (<0.001)*			
Sex								
Female	1187	26.9	3541	28.9	244	15.8	3541	28.9
Male	3223	73.0	8702	71.0	1300	84.1	8702	71.0
Missing values	4	0.1	5	0.0	1	0.1	5	0.0
X^2 (*p-value*)[a]	*6.3 (0.012)*				*117.8 (<0.001)*			
Race								
Black	387	8.8	535	4.4	116	7.5	535	4.4
Others (with Asian)	463	10.5	3089	25.2	101	6.5	3089	25.2
White (with Hispanic)	3555	80.5	8596	70.2	1324	85.7	8596	70.2
Missing values	9	0.2	28	0.2	4	0.3	28	0.2
X^2 (*p-value*)[a]	*491.5 (<0.001)*				*281.7 (<0.001)*			
Study name								
Boston	313	7.1	611	5.0	71	4.6	611	5.0
Buffalo	396	9.0	1190	9.7	168	10.9	1190	9.7

	Oral and pharyngeal cases	(%)	Controls	(%)	Laryngeal cases	(%)	Controls	(%)
Italy Multicenter								
Milan	169	3.8	621	5.1	24	1.6	621	5.1
Pordenone	471	10.7	1528	12.5	409	26.5	1528	12.5
Latina	95	2.2	425	3.5	0	0.0	425	3.5
Japan (2001–2005)	407	9.2	3002	24.5	86	5.6	3002	24.5
Los Angeles	246	5.6	828	6.8	60	3.9	828	6.8
Milan (2006–2009)	131	3.0	691	5.6	200	12.9	691	5.6
MSKCC	74	1.7	123	1.0	32	2.1	123	1.0
North Carolina (2002–2006)	687	15.6	1120	9.1	374	24.2	1120	9.1
Switzerland	367	8.3	877	7.2	121	7.8	877	7.2
US Multicenter								
Atlanta	129	2.9	134	1.1	0	0.0	134	1.1
New Jersey	467	10.6	459	3.7	0	0.0	459	3.7
Los Angeles	398	9.0	501	4.1	0	0.0	501	4.1
San Francisco	64	1.4	138	1.1	0	0.0	138	1.1
X^2 (*p-value*)[a]	*1121.5 (<0.001)*				*1092.0 (<0.001)*			
Education								
<= Junior high school	863	19.6	2723	22.2	603	39.0	2723	22.2
Some high school	885	20.0	1240	10.1	258	16.7	1240	10.1
High school graduate	588	13.3	1267	10.3	237	15.3	1267	10.3
Technical school, some college	1174	26.6	2305	18.8	214	13.9	2305	18.8
>= college graduate	491	11.1	1703	13.9	145	9.4	1703	13.9
Missing	413	9.4	3010	24.6	88	5.7	3010	24.6
X^2 (*p-value*)[a]	*766.2 (<0.001)*				*503.7 (<0.001)*			
Smoking status								
Never	806	18.3	4868	39.7	90	5.8	4868	39.7
Former	1387	31.4	4330	35.4	707	45.8	4330	35.4
Current	2210	50.1	2986	24.4	735	47.6	2986	24.4
Missing	11	0.2	64	0.5	13	0.8	64	0.5
X^2 (*p-value*)[a]	*1139.6 (<0.001)*				*755.3 (<0.001)*			

	Oral and pharyngeal cases	(%)	Controls	(%)	Laryngeal cases	(%)	Controls	(%)
Cigarette intensity (cigarettes/day)								
Never smoker	806	18.3	4868	39.7	91	5.9	4868	39.7
0to<=10	471	10.7	1949	15.9	149	9.6	1949	15.9
10to<=20	1466	33.2	3169	25.9	628	40.6	3169	25.9
>20	1633	37.0	2137	17.4	661	42.8	2137	17.4
Missing	38	0.9	125	1.0	16	1.0	125	1.0
X^2 (*p-value*)[a]	*1111.2 (<0.001)*				*1015.8 (<0.001)*			
Duration of cigarette smoking (years)								
Never smoker	806	18.3	4868	39.7	91	5.9	4868	39.7
0to<=20	443	10.0	2166	17.7	102	6.6	2166	17.7
>20	3132	71.0	5123	41.8	1343	86.9	5123	41.8
Missing	33	0.7	91	0.7	9	0.6	91	0.7
X^2 (*p-value*)[a]	*1116.8 (<0.001)*				*1133.7 (<0.001)*			
Cigar smoking								
Never cigar user	3583	81.2	8545	69.8	1323	85.6	8545	69.8
Ever smoked >=100 cigars in a lifetime	394	8.9	636	5.2	118	7.6	636	5.2
Missing values	437	9.9	3067	25.0	104	6.7	3067	25.0
X^2 (*p-value*)[a]	*33.7 (0.008)*				*2.8 (0.093)*			
Pipe smoking								
Never pipe user	3579	81.1	8327	68.0	1325	85.8	8327	68.0
Ever smoked>=100 pipes in a lifetime	399	9.0	864	7.1	115	7.4	864	7.1
Missing values	436	9.9	3057	25.0	105	6.8	3057	25.0
X^2 (*p-value*)[a]	*1.2 (0.027)*				*2.8 (0.094)*			
Alcohol consumption (drinks/day)								
Never drinker	548	12.4	3156	25.8	187	12.1	3156	25.8
<1	1030	23.3	4022	32.8	250	16.2	4022	32.8
>=1to3	973	22.0	2934	24.0	344	22.3	2934	24.0
>=3to5	647	14.7	1215	9.9	250	16.2	1215	9.9
>=5	1216	27.5	921	7.5	514	33.3	921	7.5

	Oral and pharyngeal cases	(%)	Controls	(%)	Laryngeal cases	(%)	Controls	(%)
X^2 (*p-value*)[a]		*1442.0 (<0.001)*				*1155.2 (<0.001)*		

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center.

[a]Missing values were not considered in the calculation of the Chi-square test.

Table 3

Odds ratios (ORs)[a] for oral and pharyngeal, and laryngeal cancers, and corresponding confidence intervals (95%CIs), on non-alcohol energy-adjusted vitamin C intake quintiles. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Controls	Oral and pharyngeal cases	OR (95% CI)[b]	$P_{studies}$[c]	Laryngeal cases	OR (95% CI)[b]	$P_{studies}$[c]
I Quintile[d]	1359	995	1[e]		431	1[e]	
II Quintile[d]	1768	892	0.86 (0.71–1.03)		288	0.64 (0.46–0.89)	
III Quintile[d]	1945	730	0.66 (0.58–0.77)	<0.001	252	0.53 (0.39–0.72)	<0.001
IV Quintile[d]	1956	666	0.62 (0.53–0.74)		210	0.48 (0.38–0.62)	
V Quintile[d]	1968	611	0.54 (0.45–0.65)		221	0.52 (0.40–0.68)	
$p_{for\ trend}$[f]			<0.001			0.006	

[a] Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study center, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and the interaction between cigarette intensity and alcohol drinking intensity.

[b] As heterogeneity among studies was detected (p<0.1), we reported the mixed-effects estimates derived from the corresponding generalized linear mixed model.

[c] P for heterogeneity among studies.

[d] The quantile cut-offs were the following ones:−0.779, −0.367, 0.055,and 0.683.

[e] Reference category.

[f] P for linear trend.

Table 4

Odds ratios (ORs)[a,b] for oral and pharyngeal cancer and corresponding confidence intervals (95% CIs) on non-alcohol energy-adjusted vitamin C intake quintiles, in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$p_{studies}$[c]
Age (years)					
<55	0.83 (0.65–1.05)	0.58 (0.45–0.76)	0.55 (0.41–0.73)	0.65 (0.47–0.90)	0.001
≥ 55	0.84 (0.69–1.03)	0.69 (0.57–0.83)	0.63 (0.52–0.77)	0.49 (0.39–0.63)	< 0.001
p_{strata}[d]			0.087		
Sex					
Female	0.88 (0.67–1.16)	0.59 (0.44–0.79)	0.59 (0.45–0.78)	0.54 (0.37–0.79)	< 0.001
Male	0.84 (0.68–1.04)	0.69 (0.59–0.81)	0.63 (0.52–0.76)	0.53 (0.45–0.63)	< 0.001
p_{strata}[d]			0.514		
Education					
≤high school graduate	0.84 (0.69–1.02)	0.65 (0.53–0.81)	0.64 (0.52–0.80)	0.52 (0.42–0.66)	0.002
≥some college	0.90 (0.70–1.18)	0.72 (0.58–0.88)	0.62 (0.50–0.77)	0.61 (0.49–0.76)	0.014
p_{strata}[d]			0.578		
Geographic region[e]					
Europe	0.93 (0.71–1.22)	0.57 (0.45–0.73)	0.56 (0.40–0.77)	0.46 (0.35–0.61)	0.085
America	0.82 (0.65–1.03)	0.70 (0.59–0.82)	0.64 (0.54–0.76)	0.57 (0.45–0.73)	< 0.001
Asia	0.72 (0.52–1.00)	0.67 (0.48–0.94)	0.57 (0.41–0.79)	0.43 (0.30–0.62)	NE
p_{strata}[d]			0.573		
Body mass index					
<25 kg/m^2	0.80 (0.65–0.98)	0.62 (0.50–0.75)	0.53 (0.43–0.65)	0.52 (0.42–0.64)	0.016
≥25 kg/m^2	0.89 (0.70–1.14)	0.71 (0.59–0.86)	0.68 (0.54–0.85)	0.57 (0.45–0.71)	0.002
p_{strata}[d]			0.254		
Tobacco consumption					
Never user	1.03 (0.67–1.59)	0.74 (0.51–1.08)	0.67 (0.49–0.91)	0.60 (0.40–0.92)	< 0.001
Former user	0.77 (0.59–0.99)	0.75 (0.59–0.97)	0.59 (0.45–0.76)	0.56 (0.43–0.74)	0.560
Current user	0.78 (0.64–0.95)	0.61 (0.49–0.75)	0.65 (0.48–0.88)	0.62 (0.49–0.80)	0.051

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$p_{studies}$ [c]
p_{strata} [d]			0.887		
Alcohol consumption [f]					
Never/light drinker	0.97 (0.75–1.24)	0.69 (0.56–0.85)	0.61 (0.48–0.78)	0.64 (0.50–0.82)	< 0.001
Moderate drinker	0.82 (0.62–1.09)	0.73 (0.59–0.91)	0.73 (0.58–0.93)	0.49 (0.37–0.64)	0.051
Heavy drinker	0.74 (0.54–1.02)	0.49 (0.35–0.69)	0.42 (0.29–0.59)	0.46 (0.33–0.65)	0.835
p_{strata} [d]			0.107		
Tobacco and alcohol consumption combined [f]					
Never/former user -Never/light drinker	1.08 (0.72–1.61)	0.78 (0.60–1.02)	0.64 (0.49–0.83)	0.69 (0.53–0.89)	0.001
Current user- Never/light drinker	0.79 (0.55–1.13)	0.57 (0.38–0.84)	0.59 (0.35–1.01)	0.76 (0.46–1.25)	0.024
Never/former user -Moderate drinker	0.62 (0.44–0.89)	0.66 (0.47–0.93)	0.62 (0.44–0.87)	0.41 (0.26–0.65)	0.055
Current user -Moderate drinker	0.86 (0.62–1.18)	0.70 (0.50–0.96)	0.70 (0.50–0.99)	0.53 (0.37–0.77)	0.476
Never/former user - Heavy drinker	1.02 (0.63–1.65)	0.64 (0.38–1.09)	0.42 (0.24–0.74)	0.49 (0.29–0.83)	0.694
Current user -Heavy drinker	0.68 (0.46–1.01)	0.60 (0.40–0.91)	0.51 (0.32–0.80)	0.55 (0.35–0.87)	0.866
p_{strata} [d]			0.307		

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center; NE: Not estimable.

[a] Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study center, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and the interaction between cigarette intensity and alcohol drinking intensity, when appropriate.

[b] The I Quintile category was considered as the reference one.

[c] P for heterogeneity among studies. When the p-value was less than 0.1 within strata, we reported the mixed-effects estimates derived from the corresponding generalized linear mixed model.

[d] P for heterogeneity across strata. When, for a single stratification variable, fixed- and mixed-effects models were estimated within different strata, likelihood ratio tests for heterogeneity across strata were 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.

[e] Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, MSKCC, 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 among studies in the Asia stratum.

[f] The never/light drinker category included never drinkers and subjects who drinks less than 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 5

Odds ratios (ORs)[a,b] for laryngeal cancer and corresponding confidence intervals (95% CIs) on non-alcohol energy-adjusted vitamin C intake quintiles, in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$p_{studies}$[c]
Age (years)					
<55	0.63 (0.44–0.92)	0.44 (0.28–0.70)	0.39 (0.25–0.61)	0.48 (0.32–0.71)	0.281
≥ 55	0.62 (0.43–0.88)	0.55 (0.39–0.78)	0.52 (0.41–0.67)	0.53 (0.39–0.72)	< 0.001
p_{strata}[d]			0.729		
Sex					
Female	0.76 (0.47–1.24)	0.57 (0.34–0.95)	0.42 (0.23–0.77)	0.69 (0.35–1.34)	0.002
Male	0.60 (0.41–0.86)	0.52 (0.39–0.70)	0.48 (0.39–0.61)	0.48 (0.38–0.62)	0.002
p_{strata}[d]			0.716		
Education					
≤high school graduate	0.56 (0.38–0.82)	0.47 (0.32–0.70)	0.53 (0.34–0.82)	0.48 (0.35–0.67)	< 0.001
≥some college	0.78 (0.52–1.17)	0.57 (0.32–1.02)	0.53 (0.35–0.80)	0.58 (0.38–0.90)	0.119
p_{strata}[d]	0.325				
Geographic region[e]					
Europe	0.55 (0.33–0.9)	0.36 (0.24–0.54)	0.33 (0.24–0.44)	0.36 (0.21–0.63)	< 0.001
America	0.80 (0.54–1.20)	0.91 (0.68–1.22)	0.76 (0.56–1.02)	0.77 (0.57–1.04)	0.459
Asia	0.82 (0.39–1.75)	1.54 (0.81–2.92)	0.50 (0.22–1.14)	1.35 (0.67–2.69)	NE
p_{strata}[d]			0.006		
Body mass index					
<25 kg/m^2	0.71 (0.53–0.97)	0.52 (0.34–0.79)	0.38 (0.25–0.60)	0.47 (0.3–0.74)	0.005
≥25 kg/m^2	0.60 (0.39–0.90)	0.50 (0.33–0.75)	0.57 (0.41–0.79)	0.52 (0.34–0.79)	< 0.001
p_{strata}[d]			0.210		
Tobacco consumption					
Never user	0.45 (0.18–1.08)	0.38 (0.15–0.98)	0.60 (0.27–1.34)	0.68 (0.32–1.46)	0.185
Former user	0.58 (0.41–0.82)	0.64 (0.43–0.96)	0.43 (0.29–0.62)	0.66 (0.47–0.92)	0.144
Current user	0.55 (0.41–0.73)	0.59 (0.39–0.90)	0.49 (0.35–0.68)	0.55 (0.41–0.72)	< 0.001

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$p_{studies}$[c]
p_{strata}[d]			0.845		
Alcohol consumption[f]					
Never/light drinker	0.65 (0.39–1.09)	0.72 (0.45–1.16)	0.61 (0.43–0.87)	0.76 (0.54–1.08)	0.227
Moderate drinker	0.51 (0.31–0.84)	0.38 (0.24–0.61)	0.43 (0.30–0.61)	0.39 (0.28–0.54)	0.004
Heavy drinker	0.55 (0.37–0.81)	0.43 (0.28–0.65)	0.35 (0.22–0.54)	0.38 (0.25–0.59)	0.831
p_{strata}[d]			0.308		
Tobacco and alcohol consumption combined[f]					
Never/former user -Never/light drinker	0.61 (0.34–1.06)	0.53 (0.28–0.99)	0.40 (0.23–0.71)	0.71 (0.44–1.16)	0.043
Current user- Never/light drinker	0.58 (0.31–1.09)	0.73 (0.39–1.38)	0.62 (0.39–0.99)	0.79 (0.49–1.28)	0.100
Never/former user -Moderate drinker	0.49 (0.28–0.86)	0.55 (0.27–1.12)	0.59 (0.34–1.00)	0.63 (0.38–1.06)	0.011
Current user -Moderate drinker	0.47 (0.31–0.72)	0.41 (0.23–0.73)	0.40 (0.24–0.66)	0.42 (0.22–0.84)	<0.001
Never/former user - Heavy drinker	0.52 (0.29–0.94)	0.49 (0.27–0.92)	0.24 (0.11–0.51)	0.55 (0.29–1.06)	0.626
Current user -Heavy drinker	0.57 (0.34–0.95)	0.70 (0.33–1.46)	0.47 (0.20–1.08)	0.48 (0.26–0.90)	0.024
p_{strata}[d]			0.907		

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center; NE: Not estimable.

[a] Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study center, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and the interaction between cigarette intensity and alcohol drinking intensity, when appropriate.

[b] The I Quintile category was considered as the reference one.

[c] P for heterogeneity among studies. When the p-value was less than 0.1 within strata, we reported the mixed-effects estimates derived from the corresponding generalized linear mixed model.

[d] P for heterogeneity across strata. When, for a single stratification variable, fixed- and mixed-effects models were estimated within different strata, likelihood ratio tests for heterogeneity across strata were 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.

[e] Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, MSKCC, 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 among studies in the Asia stratum.

[f] The never/light drinker category included never drinkers and subjects who drinks less than 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.