IJC
International Journal of Cancer

Vitamin or mineral supplement intake and the risk of head and neck cancer: pooled analysis in the INHANCE consortium

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Key words: vitamin supplement, mineral supplement, head and neck cancer

Abbreviations: CI: confidence interval; HNC: head and neck cancer; HPV: human papillomavirus; IARC: International Agency for Research on Cancer; INHANCE: International Head and Neck Cancer Epidemiology; MSKCC: Memorial Sloan-Kettering Cancer Center; NOS: not otherwise specified; OR: Odds ratios

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

Grant sponsors: NIH, NCI; **Grant number:** R03CA113157; **Grant sponsor:** NIDCR; **Grant number:** R03 DE016611; **Grant sponsor:** Swiss League against Cancer; **Grant number:** KFS1069-09-2000; **Grant sponsor:** Fribourg League gainst Cancer; **Grant number:** FOR381.88; **Grant sponsor:** Swiss Cancer Research; **Grant number:** AKT 617; **Grant sponsor:** Gustave-Roussy Institute; **Grant number:** 88D28; **Grant sponsor:** National Institutes of Health (NIH) US; **Grant numbers:** P01CA068384, K07CA104231; **Grant sponsor:** National Institutes of Health (NIH) US; **Grant numbers:** R01CA048896, R01DE012609; **Grant sponsor:** National Institutes of Health (NIH) US; **Grant number:** R01CA61188; **Grant sponsor:** National Institute of Environmental Health Sciences; **Grant number:** P30ES010126; **Grant sponsor:** National Institutes of Health (NIH) US; **Grant numbers:** P01CA068384, K07CA104231, R01DE13158; **Grant sponsor:** National Institute of Health (NIH) US; **Grant numbers:** P50CA90388, R01DA11386, R03CA77954, T32CA09142, U01CA96134, R21ES011667; **Grant sponsor:** Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center, IARC; **Grant sponsors:** National Institutes of Health (NCI) US and NIDCR intramural programs; **Grant sponsors:** Fondo para la Investigacion Cientifica y Tecnologica (FONCYT) Argentina, IMIM (Barcelona), Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP); **Grant number:** No 01/01768-2; **Grant sponsor:** European Commission; **Grant number:** IC18-CT97-0222; **Grant sponsor:** Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government; **Grant numbers:** FIS 97/0024, FIS 97/0662, BAE 01/5013; **Grant sponsors:** International Union Against Cancer (UICC) and Yamagiwa-Yoshida Memorial International Cancer Study Grant; **Grant sponsor:** National Institutes of Health (NIH) US; **Grant numbers:** R01CA078609, R01CA100679; **Grant sponsor:** The Intramural Program of the National Cancer Institute, National Institutes of Health, USA; **Grant sponsor:** NIH; **Grant number:** R01CA51845
DOI: 10.1002/ijc.27405
History: Received 5 Mar 2011; Accepted 18 Oct 2011; Online 15 Dec 2011

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Epidemiology

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To investigate the potential role of vitamin or mineral supplementation on the risk of head and neck cancer (HNC), we analyzed individual-level pooled data from 12 case–control studies (7,002 HNC cases and 8,383 controls) participating in the International Head and Neck Cancer Epidemiology consortium. There were a total of 2,028 oral cavity cancer, 2,465 pharyngeal cancer, 874 unspecified oral/pharynx cancer, 1,329 laryngeal cancer and 306 overlapping HNC cases. Odds ratios (OR) and 95% confidence intervals (CIs) for self reported ever use of any vitamins, multivitamins, vitamin A, vitamin C, vitamin E, and calcium, beta-carotene, iron, selenium and zinc supplements were assessed. We further examined frequency, duration and cumulative exposure of each vitamin or mineral when possible and stratified by smoking and drinking status. All ORs were adjusted for age, sex, race/ethnicity, study center, education level, pack-years of smoking, frequency of alcohol drinking and fruit/vegetable intake. A decreased risk of HNC was observed with ever use of vitamin C (OR = 0.76, 95% CI = 0.59–0.96) and with ever use of calcium supplement (OR = 0.64, 95% CI = 0.42–0.97). The inverse association with HNC risk was also observed for 10 or more years of vitamin C use (OR = 0.72, 95% CI = 0.54–0.97) and more than 365 tablets of cumulative calcium intake (OR = 0.36, 95% CI = 0.16–0.83), but linear trends were not observed for the frequency or duration of any supplement intake. We did not observe any strong associations between vitamin or mineral supplement intake and the risk of HNC.

Head and neck cancer (HNC) includes cancers originating in the oral cavity, the oropharynx, the hypopharynx and the larynx. Worldwide, more than half a million HNC cases and over 300,000 deaths due to HNC are estimated to occur each year.[1] Tobacco smoking and alcohol consumption are the predominant risk factors for HNC,[2,3] but the role of diet has been recognized. Increased fruit and vegetable consumption has been repeatedly shown to be associated with a reduced risk of HNC.[4–6] However, the mechanisms underlying these associations are complex. There are a large number of compounds in plant foods that may influence the risk of cancer, including both micronutrients for normal metabolism and other bioactive compounds with unknown metabolic significance. Therefore, whether dietary supplements containing micronutrients found in plant foods would be effective chemopreventive agents is of considerable public health interest.

Numerous *in vitro* studies and animal studies have suggested favorable effects of several vitamins and minerals on angiogenesis, immunity, cell differentiation, proliferation and apoptosis.[7–9] In epidemiologic studies, the precise nature and magnitude of the inverse relationships between multivitamin and mineral supplements and the risk of HNC, however, have not been clearly established because of inconsistent results.[10–20] In the early 1990s, case–control studies in the US suggested that vitamin E and vitamin C supplement intake was inversely associated with oral cavity and pharyngeal cancers.[13,14] Recently published meta-analysis of randomized trials suggest no association between cancer and vitamin or mineral supplement intake.[19–23] In a large randomized controlled trial, supplementation with alpha-tocopheryl acetate and beta-carotene were not associated with upper aerodigestive tract cancer incidence; however, a protective effect was suggested for early stage laryngeal cancers.[11]The results from the three secondary prevention trials for HNC, beta-carotene supplement had no significant effect for second primary HNC risk.[15–17] Therefore, this large pooled analysis was conducted to investigate the potential role of vitamin or mineral supplementation in the development of HNC.

We analyze pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium (http://inhance.iarc.fr) that was established in 2004 based on the collaboration of research groups leading large, molecular epidemiology studies of HNC. The primary goal of the consortium is to explore potential risk factors of HNC that are difficult to evaluate in individual studies.

Material and Methods

Study subjects

Within version 1.3 of the INHANCE consortium pooled data set, 12 case–control studies from Europe, Latin America and the United States with information on vitamin supplementation included data on 7,085 HNC cases and 8,491 controls.[24–33] In this current analysis, we excluded the India center (576 cases and 582 controls), but not the other centers from the IARC multicenter study because information on vitamin supplementation was not available in the India center questionnaire. We also excluded 169 cases and 43 controls from Boston study because they had not been interviewed

Table 1. Demographic characteristics of the head and neck cases and controls

Demographic characteristics	Cases	(%)	Controls	(%)
Total	7002		8383	
Study				
France	323	4.61	234	2.79
New York Multicenter	497	7.10	271	3.23
Seattle, WA	191	2.73	400	4.77
North Carolina	180	2.57	202	2.41
Tampa, FL	207	2.96	897	10.70
Los Angeles, CA	417	5.96	1005	11.99
Puerto Rico	350	5.00	521	6.21
Latin America	2191	31.29	1706	20.35
IARC Multicenter	983	14.04	1094	13.05
Boston	415	5.93	616	7.35
US multicenter	1114	15.91	1268	15.13
Memorial Sloan-Kettering Cancer Center	134	1.91	169	2.02
Age				
<40	303	4.33	500	5.96
40_ <45	403	5.76	597	7.12
45_ <50	760	10.85	893	10.65
50_ <55	996	14.22	1347	16.07
55_ <60	1259	17.98	1455	17.36
60_ <65	1117	15.95	1244	14.84
65_ <70	950	13.57	1034	12.33
70_ <75	707	10.10	724	8.64
≥75	507	7.24	589	7.03
p for χ^2test	<0.0001			
Sex				
Men	5392	77.01	5791	69.08
Women	1610	22.99	2592	30.92
P for χ^2test	<0.0001			
Race/Ethnicity				
Nonhispanic white	3922	56.01	5406	64.49
Black	557	7.95	659	7.86
Hispanic/Latino	156	2.23	359	4.28
Asian/Pacific islanders	37	0.53	72	0.86
Others	139	1.99	181	2.16
Latin Americans[1]	2191	31.29	1706	20.35
P for χ^2test	<0.0001			
Education				
None	139	2.18	129	1.63
<Junior high school	2444	38.38	2073	26.17
Some high school	1185	18.61	1117	14.10
High school graduate	728	11.43	960	12.12
Vocational, some college	1224	19.22	2042	25.78
≥College	648	10.18	1601	20.21
Missing	634		461	
P for χ^2test	<0.0001			
HNC subtype				
Oral cavity	2028	0.29		
Pharynx	2465	0.28		
Oral/pharynx not otherwise specified	874	0.20		
Larynx	1329	0.19		
Overlapping head and neck cancer	306	0.04		

[1]Information on ethnicity was not collected in the Latin America study. We organized subjects as "Latin American." We adjusted for study center in all logistic regression models as a proxy variable for race/ethnicity because each center has an expected predominant ethnic group distribution.

with the vitamin supplementation questionnaire. Finally, subjects with missing data on age, sex or race/ethnicity and cases with missing information on the site of origin of their cancer were excluded (87 cases and 108 controls). Thus, the data for this analysis included 7,002 HNC cases and 8,383 controls.

Characteristics of the individual studies in the consortium are provided in Supporting Information Table 1. Most of the studies were hospital-based case–control studies, and in most studies, the control subjects were frequency matched to the case subjects on age, sex and additional factors (such as study center, hospital and race/ethnicity). Interviews in all studies were conducted face-to-face. Written informed consent was obtained from study subjects, and the investigations were approved by institutional review boards at each of the institutes involved. Questionnaires were collected from the individual studies to assess the comparability of the data and wording of interview questions. Each data item was checked for illogical or missing values. Queries were sent to investigators and inconsistencies were resolved.

Cases included patients with invasive tumors of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx or HNC unspecified as defined previously.[34] Cancers of salivary gland (International Classification of Diseases for Oncology version 2 C07-C08) were excluded from our analysis because of the different etiology from other HNC.[35] Studies provided tumor site data using either the International Classification of Diseases for Oncology version 2 or International Classification of Diseases, Ninth or Tenth Edition. In the overall dataset, there were a total of 2,028 oral cases, 2,465 pharyngeal cases (496 hypopharynx and 1,969 oropharynx), 874 unspecified oral/pharynx cases,

1,329 laryngeal cases and 306 overlapping head and neck cases.

In the 12 individual studies, each study subject was asked whether he or she had taken any vitamins or minerals. The definitions for ever use of vitamin or mineral supplements were: at least once a week for a year (New York multicenter and Tampa studies), at least once a week (Seattle study), at least once a month (Los Angeles study), on a regular basis for 6 months or longer (US multicenter study), on a regular basis (Puerto Rico, France, Boston, Memorial Sloan-Kettering Cancer Center (MSKCC) studies), before 1 year ago (North Carolina study) and in the last 2 years (IARC multicenter and Latin America studies). Variables on the type of vitamin supplementation were available in nine studies (New York multicenter, Seattle, North Carolina, Tampa, Los Angeles, Puerto Rico, Boston, MSKCC and US multicenter studies). Variables on the frequency of the type of vitamin supplementation were available in four studies (Seattle, Los Angeles, US multicenter and MSKCC studies). Variables on duration of vitamin supplementation were available in eight studies (France, New York multicenter, North Carolina, Tampa, Los Angeles, Puerto Rico, Boston and US multicenter studies). The lifetime number of tablets of vitamin supplementation was calculated based on the number of tablets per week or day and duration reported to estimate the cumulative and daily consumption in four studies (New York multicenter, Tampa, North Carolina and Puerto Rico studies). In short, for any vitamin and mineral supplement intake, three questions were included in the France, Latin America and IARC studies; ten questions were included in Seattle study; 15 questions were included in the MSKCC (14) and Tampa (16) studies; and more than 20 questions were included in New York multicenter (21), Puerto Rico (24), North Carolina (25), Los Angeles (27), US multicenter (28) and Boston (32).

Variables on pack-years of tobacco smoking and the frequency of alcohol drinking were available in all studies. The detailed description on the method used for pooling data on smoking and alcohol across different studies is provided in a previous paper.[34] Variables on dietary information included overall vegetables and fruit intake in quartiles based on center-specific controls.

Statistical methods

The association between HNC risk and vitamin supplementation was assessed by estimating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models for each case–control study. The model included age, sex, education, race/ethnicity, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous) and vegetable and fruit intake (quartiles of center-specific controls) to adjust to potential confounders. To calculate the summary estimates of association, the study-specific estimates were included in a two-stage random-effects logistic regression model with the maximum likelihood method, which allows for unexplained sources of heterogeneity between studies.[36] Pooled ORs were also estimated with a fixed-effects logistic regression models, adjusted for all the factors mentioned before and study center.

For subjects missing information on education level (634 cases and 461 controls), we applied multiple imputation with the PROC MI procedure in SAS. We assumed that the education data were missing at random, *i.e.*, whether or not education was missing did not depend on any other unobserved or missing values.[37] We used the logistic regression model[38] to predict education level using age, sex, race/ethnicity, study center and case/control status as the covariates within each of the geographic region.

We tested for heterogeneity between the study-specific ORs by conducting the likelihood ratio test, for the head and neck combined and for each of the subsites, by testing the difference between the log likelihood of a model with the product terms between study and the variable of interest, and that of a model with no such product terms, based on a X^2 distribution with a d*f* one less than the number of studies. If any heterogeneity was detected, we reported the random-effects estimates and examined whether the results from the two-stage random-effects model and the fixed-effects logistic regression model were comparable in magnitude of effect. Fixed-effects estimates are reported for all other models. We also conducted meta-regression analysis between studies, adjusting for some potential sources of heterogeneity, including case source(hospital *vs*. cancer registry), year of study (<=1990s *vs*. >=2000s), geographic location of the study (Europe, North America *vs*. South/central America) and sample size(<400 *vs*. >400 cases). We also conducted influence analysis, where each study was excluded one at a time to assure that the statistical significance and magnitude of the overall summary estimate was not dependent on any one study.

Results

Characteristics of studies and subjects

Selected demographic characteristics of cases and controls are shown in Table 1. The largest number of cases and controls were from the Latin America study (2,191 cases/1,706 controls), followed by the US multicenter study (1,114 cases/1,268 controls). There was a predominance of male cases (77%). The distributions of age, race/ethnicity and educational level were different between case and control groups.

Ever use of vitamin or mineral supplement intake

Table 2 presents the ORs of HNC according to select vitamin supplements. Ever use of any vitamin supplement was reported by 2,448 cases (37.6%) and 3,921 controls (48.3%), but not associated with the risk of HNC. For individual vitamin supplements, a decreased risk of HNC was observed with ever use of vitamin C (OR = 0.76, 95% CI 0.59–0.96) and with ever use of calcium supplements (OR = 0.64, 95% CI 0.42–0.97) after adjustment for age, sex, race/ethnicity, study center, education level, pack-years of smoking,

Table 2. Vitamin or mineral supplement use and risk of head and neck cancer, INHANCE pooled analysis

	Cases/controls	OR[1] (95% CI)	OR[2] (95% CI)
Any vitamins[3]			
Never	4016/4139	1.00	1.00
Ever	2448/3921	0.87 (0.71–1.06)	0.94(0.69–1.29)
Missing	41/52		
$p_{heterogeneity}$		<0.01	<0.01
Multiple vitamins[4]			
Never	1650/2702	1.00	1.00
Ever	1341/2351	0.99 (0.82–1.19)	1.04 (0.90–1.19)
Missing	17/25		
$p_{heterogeneity}$		0.12	0.10
Vitamin A[4]			
Never	2861/4772	1.00	1.00
Ever	130/281	1.04 (0.54–1.98)	1.20 (0.66–2.16)
Missing	17/25		
$p_{heterogeneity}$		<0.01	<0.01
Vitamin C[4]			
Never	2449/3787	1.00	1.00
Ever	542/1266	0.76 (0.59–0.96)	0.82 (0.65–1.02)
Missing	17/25		
$p_{heterogeneity}$		<0.01	<0.01
Vitamin E[4]			
Never	2574/3930	1.00	1.00
Ever	417/1123	0.71 (0.45–1.11)	0.83 (0.54–1.26)
Missing	17/25		
$p_{heterogeneity}$		<0.01	<0.01
Calcium[4]			
Never	1709/3164	1.00	1.00
Ever	171/624	0.64 (0.42–0.97)	0.67 (0.48–0.95)
Missing	14/22		
$p_{heterogeneity}$		0.01	<0.01
Beta-carotene[4]			
Never	1435/2406	1.00	1.00
Ever	50/92	1.35 (0.65–2.81)	1.45 (0.89–2.38)
Missing	11/15		
$p_{heterogeneity}$		0.33	0.35
Iron[4]			
Never	2445/3488	1.00	1.00
Ever	151/275	0.79 (0.54–1.16)	0.92 (0.69–1.23)
Missing	14/18		
$p_{heterogeneity}$		0.59	0.54
Selenium[4]			
Never	1100/1914	1.00	1.00
Ever	35/63	1.21(0.35–4.22)	1.22(0.67–2.24)
Missing	11/15		

Table 2. Vitamin or mineral supplement use and risk of head and neck cancer, INHANCE pooled analysis (Continued)

	Cases/controls	OR[1] (95% CI)	OR[2] (95% CI)
$p_{heterogeneity}$		0.73	0.74
Zinc[4]			
Never	1080/1860	1.00	1.00
Ever	55/17	0.88(0.34–2.26)	0.88(0.55–1.43)
Missing	11/15		
$p_{heterogeneity}$		0.74	0.72

[1]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous) and vegetable and fruit intake (quartiles of center-specific controls). [2]Additionally adjusted for other vitamins (Multiple vitamins, vitamin A, vitamin C and vitamin E). [3]New York study was not included in the model a; France, New York, Latin America and IARC studies were not included in the model b. So, in model b, there were 1,492 cases and 2,098 controls with never use of any vitamin supplementation; and 1,499 cases and 2,955 controls with the ever use of any vitamin supplementation. [4]Multiple vitamins, vitamin A, vitamin C and vitamin E do not include France, New York, Latin America, MSKCC and IARC studies; calcium does not include France, New York, Latin America, IARC, MSKCC and US multicenter studies; selenium and zinc include North Carolina, Los Angeles, Boston and MSKCC studies; iron includes North Carolina, Los Angeles, Puerto Rico, Boston, US multicenter and MSKCC studies; beta-carotene includes North Carolina, Los Angeles, Puerto Rico, Boston and MSKCC studies.

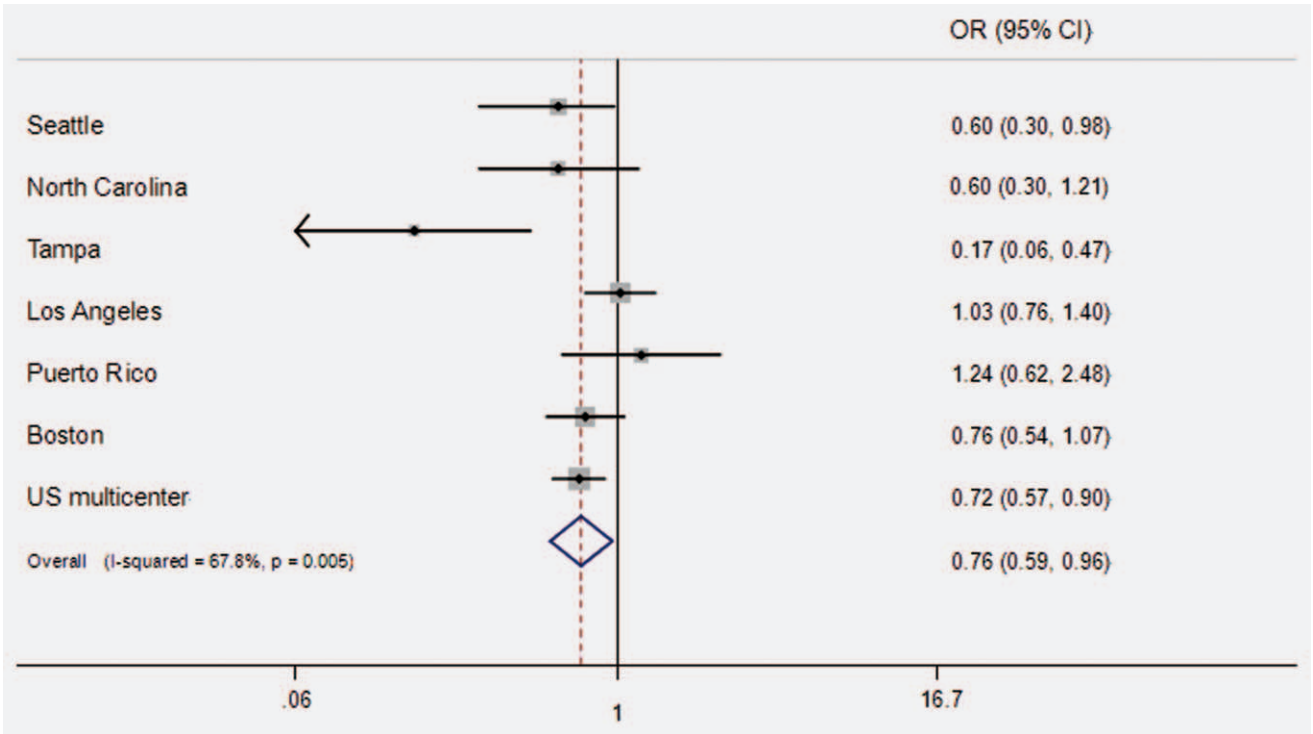

Figure 1. Study specific and pooled estimates for vitamin C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

frequency of alcohol drinking and fruit/vegetable intake. The inverse association with calcium supplement use persisted after adjustment for ever use of other vitamins (OR = 0.67, 95% CI 0.48–0.95). The ORs for vitamin C (OR = 0.75, 95% CI 0.55–0.95) did not change substantially when the analysis was restricted to the American studies (including Seattle, North Carolina, Tampa, Los Angeles, Puerto Rico, Boston, US multicenter and MSKCC studies; data not shown in the table).

Figures 1 and 2 show the study specific estimates for vitamin C and calcium supplements. The point estimates ranged between 0.60 and 1.24 for vitamin C and between 0.14 and 0.94 for calcium. For vitamin C, in 2 out of 7 studies the OR was above unity (Los Angeles and Puerto Rico). For calcium, ORs of all studies were below unity.

Heterogeneity was detected for the overall effect of vitamin C and calcium supplements and in a few strata. The random effect estimates, however, did not differ substantially

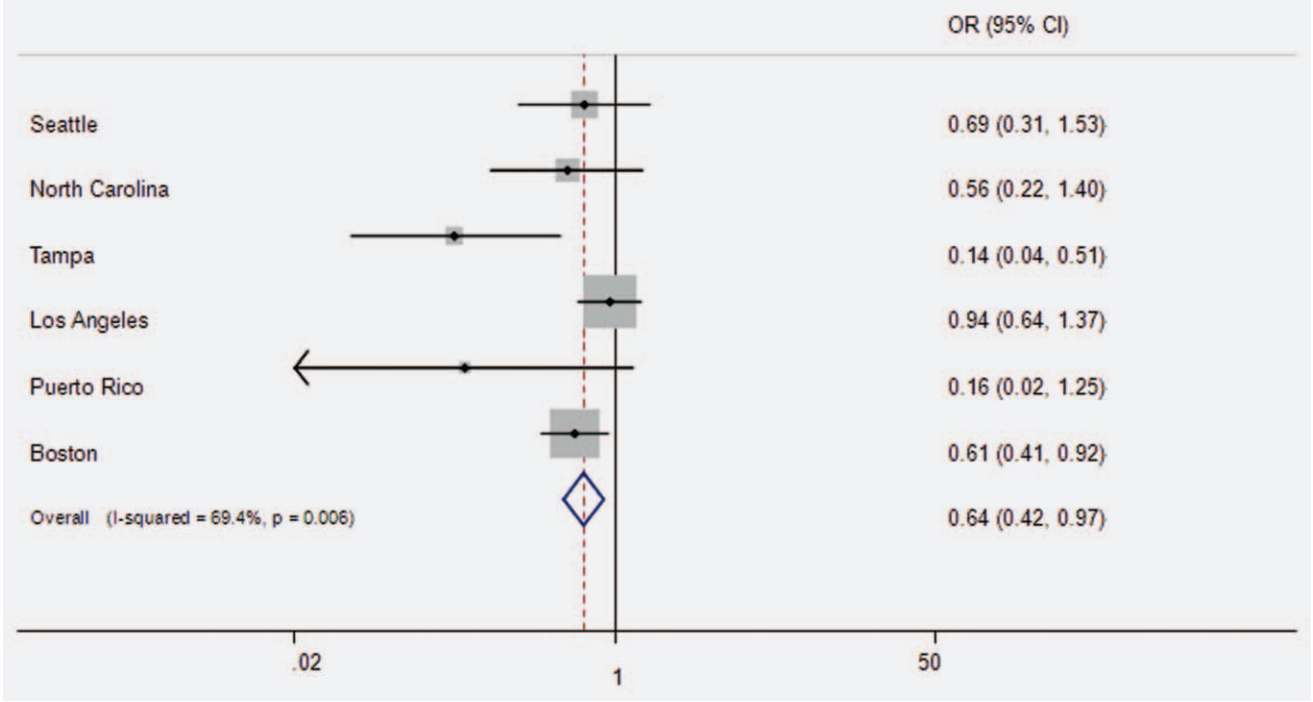

Figure 2. Study specific and pooled estimates for calcium supplement. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

from the fixed effect ones, although the CIs were wider. Meta-regression was conducted for the sources of heterogeneity between studies. The potential sources included the case source (hospital *vs.* cancer registry), year of study (≤1990s *vs.* ≥2000s), geographic location of the study (Europe, North America *vs.* South/central America) and sample size (<400 *vs.* >400 cases). The results showed that the geographic location of the study was the possible explanation for the heterogeneity of vitamin C supplement ($p = 0.047$). There did not appear to be any associations between HNC risk and ever use of multiple vitamins, vitamin A, beta-carotene, iron, selenium or zinc.

When the result was analyzed by gender, we did not observe any difference in the results stratified by gender. For calcium, the borderline protective effect was also observed for calcium supplement among female subjects (OR = 0.49, 95%CI = 0.24–1.00), and there was no significant association among male subjects (OR = 0.77, 95%CI = 0.55–1.09).

The analysis was further stratified by cancer subsite (Supporting Information Table 2). There was no difference in the reduction of risk associated with any vitamins, multiple vitamins, vitamin A, vitamin C, vitamin E and calcium supplement use by site of oral cavity, pharynx and larynx cancer. A 27% reduction in risk of oral cavity cancer was observed for vitamin E supplement use (OR = 0.73, 95% CI = 0.56–0.96).

Frequency, duration and cumulative consumption of vitamin or mineral supplement intake

Table 3 shows the association between HNC risk and frequency of various vitamins and mineral supplements. High frequency (7–13 tablets/week) of Vitamin E intake was associated with a decreased HNC risk (OR = 0.61, 95% CI = 0.37–0.98), but the association was not significant after the adjustment of dietary vitamin E intake (OR = 0.59, 95% CI = 0.22–1.61). For other vitamin or mineral supplement intake, no significant association was observed between the frequency of vitamin or mineral supplements and HNC risk in this pooled analysis.

We next examined whether there was a dose–response relationship between HNC risk and the years of supplement use (Table 4). Vitamin C supplementation for 10 or more years was associated with a reduced risk of HNC (OR = 0.72, 95% CI 0.54–0.97). However, statistical evidence of a dose–response relationship was not observed (p-trend = 0.46), and the associations did not persist after adjustment for other vitamins. The durations of other individual vitamin or mineral supplements were not significantly associated with risk of HNC.

We also explored dose–response relations for multiple vitamins, vitamin C, vitamin E and calcium, by cumulative consumption. Calcium supplement was associated inversely with the risk of HNC regardless of cumulative consumption level (OR for cumulative calcium <=365 tablets = 0.26, 95% CI = 0.07–0.94; OR for cumulative calcium >365 tablets = 0.36, 95% CI = 0.16–0.83), after adjustment for confounding factors, but no dose-response trend was apparent (p-trend = 0.75). There was no significant association between HNC risk and the cumulative consumption of other individual vitamin or mineral supplements (data not shown).

Table 3. Frequency of vitamin or mineral supplement use and risk of head and neck cancer, INHANCE pooled analysis

	Cases/controls	OR[1] (95% CI)	Cases/controls	OR[2] (95% CI)
Any vitamins				
None	896/1263	1.00	639/1103	1.00
1–6 tablets/week	84/281	0.71 (0.45–1.12)	60/266	0.64 (0.33–1.24)
7–13 tablets/week	404/686	0.79 (0.35–1.78)	207/593	0.74 (0.24–2.30)
≥14 tablets/week	32/55	1.30 (0.50–3.42)	18/52	1.26 (0.34–4.72)
Missing	9/6		4/6	
p_{trend}		0.80		0.70
$p_{heterogeneity}$		<0.01		<0.01
Multiple vitamins				
None	972/1594	1.00	694/1415	1.00
1–6 tablets/week	52/95	1.29 (0.68–2.45)	34/88	1.14 (0.31–4.14)
7–13 tablets/week	359/549	0.97 (0.54–1.72)	181/468	0.93 (0.42–2.06)
≥14 tablets/week	32/46	1.63 (0.61–4.34)	15/43	1.51 (0.39–5.78)
Missing	10/7		4/6	
p_{trend}		0.48		0.29
$p_{heterogeneity}$		<0.01		<0.01
Vitamin C				
None	1251/1821	1.00	832/1594	1.00
1–6 tablets/week	31/139	0.60 (0.31–1.17)	25/133	0.49 (0.18–1.35)
7–13 tablets/week	113/279	0.57 (0.27–1.12)	51/243	0.58 (0.30–1.12)
≥14 tablets/week	21/45	1.22 (0.45–3.30)	16/44	1.16 (0.34–3.95)
Missing	9/7		4/6	
p_{trend}		0.85		0.88
$p_{heterogeneity}$		<0.01		0.02
Vitamin E				
None	1307/1850	1.00	853/1610	1.00
1–6 tablets/week	25/145	0.59 (0.29–1.21)	22/144	0.52 (0.18–1.50)
7–13 tablets/week	76/265	0.61 (0.37–0.98)	43/237	0.59 (0.22–1.61)
≥14 tablets/week	8/24	1.71 (0.25–5.34)	6/23	1.33 (0.19–9.27)
Missing	9/7		4/6	
p_{trend}		0.17		0.76
$p_{heterogeneity}$		<0.01		0.02
Calcium				
None	1369/2029	1.00	899/1773	1.00
1–6 tablets/week	8/83	0.37 (0.10–1.44)	6/82	0.38 (0.14–1.01)
7–13 tablets/week	32/124	0.57 (0.28–1.17)	14/113	0.54 (0.19–1.53)
≥14 tablets/week	7/49	0.66 (0.13–3.38)	5/46	0.82 (0.10–7.13)
Missing	9/6		4/6	
p_{trend}		0.62		0.50
$p_{heterogeneity}$		0.02		0.20–›

[1]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous) and the frequency of alcohol drinking (continuous). All vitamins include New York, Seattle, North Carolina, Tampa and Puerto Rico studies. [2]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous) and vegetable and fruit intake (quartiles of center-specific controls). All vitamins include Seattle, North Carolina, Tampa and Puerto Rico studies.

Table 4. Duration of vitamin or mineral supplement use and risk of head and neck cancer, INHANCE pooled analysis

	Cases/controls	OR[1] (95% CI)	Cases/controls	OR[2] (95% CI)
Any vitamins				
None	1601/2015	1.00	1333/1832	1.00
<1 year	664/1136	0.84(0.67–1.07)	617/1094	0.84(0.60–1.16)
1–9 years	374/684	0.89(0.58–1.37)	367/676	1.01(0.72–1.43)
10+ years	354/893	0.75(0.54–1.05)	353/892	0.84(0.57–1.26)
Missing	13/15		13/15	
p_{trend}		0.02		0.93
$p_{heterogeneity}$		<0.01		<0.01
Multiple vitamins				
None	1453/2347	1.00	1453/2347	1.00
<1 year	397/688	0.87(0.68–1.11)	397/688	0.87(0.68–1.12)
1–9 years	379/641	1.00(0.82–1.22)	379/641	1.06(0.87–1.30)
10+ years	441/818	1.03(0.86–1.24)	441/818	1.11(0.91–1.35)
Missing	13/15		13/15	
p_{trend}		0.74		0.33
$p_{heterogeneity}$		0.12		0.21
Vitamin C				
None	2193/3393	1.00	2193/3393	1.00
<1 year	156/355	0.80(0.58–1.10)	156/355	0.83(0.58–1.18)
1–9 years	154/292	0.88(0.61–1.27)	154/292	0.97(0.67–1.14)
10+ years	167/454	0.72(0.54–0.97)	167/454	0.80(0.57–1.14)
Missing	13/15		13/15	
p_{trend}		0.46		0.52
$p_{heterogeneity}$		<0.01		<0.01
Vitamin E				
None	2297/3477	1.00	2297/3477	1.00
<1 year	129/359	0.79(0.57–1.11)	129/359	0.87(0.60–1.26)
1–9 years	131/312	0.74(0.38–1.41)	131/312	0.80(0.39–1.65)
10+ years	113/346	0.77(0.41–1.42)	113/346	0.89(0.52–1.50)
Missing	13/15		13/15	
p_{trend}		0.77		0.75
$p_{heterogeneity}$		<0.01		<0.01
Calcium				
None	1404/2658	1.00	1404/2658	1.00
<1 year	56/205	0.72(0.48–1.07)	56/205	0.71(0.47–1.07)
1–9 years	61/194	0.69(0.46–1.02)	61/194	0.71(0.47–1.07)
10+ years	38/172	0.71(0.45–1.10)	38/172	0.68(0.43–1.08)
Missing	10/12		10/12	
p_{trend}		0.79		0.76
$p_{heterogeneity}$		0.06		0.05

[1]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous) and vegetable and fruit intake (quartiles of center-specific controls). Any vitamins include France, North Carolina, Tampa, Los Angeles, Puerto Rico, Boston and US multicenter studies; multiple vitamins, vitamin A, vitamin C and vitamin E include North Carolina, Tampa, Los Angeles, Puerto Rico, Boston and US multicenter studies; calcium includes North Carolina, Tampa, Los Angeles, Puerto Rico and Boston studies. [2]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous), vegetable and fruit intake (quartiles of center-specific controls) and other vitamins (Multiple vitamins, vitamin A, vitamin C and vitamin E). Any vitamins, multiple vitamins, vitamin A, vitamin C and vitamin E include North Carolina, Tampa, Los Angeles, Puerto Rico, Boston and US multicenter studies; calcium includes North Carolina, Tampa, Los Angeles, Puerto Rico and Boston studies.

Table 5. Vitamin or mineral supplement use and the risk of HNC, stratified on smoking and alcohol status, INHANCE pooled analysis

	Ever tobacco users		Never tobacco users		Ever alcohol users		Never alcohol users		Ever tobacco/alcohol users		Never tobacco/alcohol users	
	Cases/ controls	OR[1] (95% CI)	Cases/ controls	OR[1] (95% CI)	Cases/ controls	OR[2] (95% CI)	Cases/ controls	OR[2] (95% CI)	Cases/ controls	OR[3] (95% CI)	Cases/ controls	OR[4] (95% CI)
Multiple vitamins[5]												
None	1223/1404	1.00	230/939	1.00	1297/1714	1.00	1551/631	1.00	1158/1185	1.00	90/144	1.00
Ever	989/1291	0.96 (0.81–1.14)	228/855	1.07 (0.80–1.44)	1113/1755	1.07 (0.92–1.24)	103/391	0.81 (0.19–3.47)	938/1171	0.98 (0.77–1.24)	53/271	0.76 (0.42–1.37)
<1 year	334/425	0.86 (0.64–1.15)	63/263	0.78 (0.47–1.32)	353/563	0.85 (0.65–1.11)	44/124	0.81 (0.42–1.56)	312/374	0.85 (0.62–1.16)	22/74	0.89 (0.35–2.30)
1–9 years	307/385	1.00 (0.79–1.15)	72/255	1.13 (0.75–1.72)	351/513	1.12 (0.91–1.39)	31/139	1.14 (0.62–2.11)	294/354	1.05 (0.81–1.35)	15/96	1.01 (0.42–2.40)
10+ years	348/481	1.02 (0.81–1.28)	93/337	1.26 (0.87–1.83)	409/679	1.15 (0.94–1.40)	2/8	0.83 (0.45–1.55)	332/443	1.01 (0.80–1.29)	16/101	0.77 (0.33–1.82)
Missing	12/5		1/6		11/4				10/2		0/5	
p_{trend}		0.78		0.13		0.44		0.69		0.98		0.54
$p_{heterogeneity}$		0.06		0.51		0.23		0.69		0.03		0.21
Vitamin C[5]												
None	1846/2021	1.00	347/1367	1.00	1975/2557	1.00	216/833	1.00	1746/1742	1.00	117/556	1.00
Ever	366/674	0.83 (0.63–1.10)	111/427	1.22 (0.53–2.80)	435/912	0.83 (0.64–1.08)	42/189	0.82 (0.36–1.89)	350/614	0.86 (0.64–1.16)	26/129	0.99 (0.41–2.42)
<1 year	121/210	0.86 (0.58–1.26)	35/145	1.01 (0.60–1.67)	144/291	0.87 (0.61–1.25)	11/64	0.68 (0.26–1.76)	116/187	0.93 (0.62–1.41)	7/41	1.26 (0.33–4.80)
1–9 years	118/187	0.86 (0.57–1.30)	36/105	1.84 (1.08–3.15)	135/240	0.89 (0.60–1.31)	19/52	1.10 (0.41–2.95)	111/170	0.90 (0.58–1.40)	12/35	1.36 (0.37–4.99)
10+ years	127/277	0.78 (0.53–1.15)	40/177	0.93 (0.57–1.52)	156/381	0.78 (0.55–1.11)	11/73	0.84 (0.32–2.20)	123/257	0.82 (0.54–1.25)	7/35	0.67 (0.15–3.03)
Missing	12/5		1/6		11/4		2/8		10/12		0/5	
p_{trend}		0.13		0.88		0.53		0.28		0.60		0.43
$p_{heterogeneity}$		<0.01		0.02		<0.01		0.12		<0.01		0.28
Vitamin E[5]												
None	1934/2070	1.00	363/1402	1.00	2083/2653	1.00	213/821	1.00	1839/1799	1.00	118/552	1.00
Ever	278/625	0.74 (0.46–1.18)	95/392	1.04 (0.53–2.04)	327/816	0.76 (0.49–1.18)	45/201	1.13 (0.59–2.16)	257/1557	0.73 (0.48-1.12)	25/133	1.63 (0.68–3.95)
<1 year	93/213	0.79 (0.49–1.28)	36/146	1.33 (0.67–2.63)	114/282	0.78 (0.53–1.15)	15/77	1.23 (0.35–4.30)	89/188	0.77 (0.49–1.21)	11/52	1.80 (0.48–6.77)
1–9 years	100/192	0.71 (0.41–1.23)	31/120	1.24 (0.26–6.01)	111/251	0.72 (0.37–1.40)	20/61	2.43 (0.71–8.35)	91/168	0.71 (0.42–1.22)	11/37	5.31 (1.43–19.76)
10+ years	85/220	0.77 (0.49–1.21)	28/126	0.96 (0.31–2.98)	102/283	0.82 (0.50–1.36)	10/63	1.08 (0.15–7.78)	77/201	0.71 (0.44–1.14)	3/44	1.69 (0.23–12.54)
Missing	12/5		1/6		11/4		2/8		10/2		0/5	
p_{trend}		0.16		0.89		0.77		0.55		0.44		0.73
$p_{heterogeneity}$		<0.01		0.04		<0.01		0.06		0.01		0.28

Table 5. Vitamin or mineral supplement use and the risk of HNC, stratified on smoking and alcohol status, INHANCE pooled analysis (Continued)

	Ever tobacco users		Never tobacco users		Ever alcohol users		Never alcohol users		Ever tobacco/alcohol users		Never tobacco/alcohol users	
	Cases/ controls	OR[1] (95% CI)	Cases/ controls	OR[1] (95% CI)	Cases/ controls	OR[2] (95% CI)	Cases/ controls	OR[2] (95% CI)	Cases/ controls	OR[3] (95% CI)	Cases/ controls	OR[4] (95% CI)
Calcium[5]												
None	1145/1552	1.00	259/1101	1.00	1214/1946	1.00	188/709	1.00	1057/1315	1.00	101/474	1.00
Ever	111/321	0.67 (0.43–1.04)	44/250	0.73 (0.37–1.44)	133/422	0.75 (0.49–1.14)	22/149	0.39 (0.16–0.94)	102/267	0.75 (0.45–1.24)	13/95	0.44 (0.14–1.40)
<1 year	38/100	0.86 (0.44–1.66)	18/105	0.75 (0.38–1.46)	45/146	0.80 (0.51–1.26)	11/59	0.48 (0.15–1.61)	33/82	0.90 (0.54–1.50)	6/41	0.34 (0.08–1.48)
1–9 years	46/117	0.74 (0.32–1.75)	15/77	0.87 (0.42–1.81)	54/137	0.86 (0.56–1.33)	7/57	0.33 (0.05–2.05)	44/95	0.79 (0.49–1.28)	5/35	0.50 (0.05–4.60)
10+ years	27/104	0.63 (0.30–1.32)	11/68	0.72 (0.33–1.57)	34/139	0.75 (0.46–1.22)	4/33	1.11 (0.20–6.05)	25/90	0.70 (0.40–1.22)	2/19	2.93 (0.19–44.76)
Missing	10/5		0/6		8/4		2/8		8/2		0/5	
p_{trend}		0.13		0.48		0.65		0.47		0.79		0.28
$p_{heterogeneity}$		<0.01		<0.01		0.02		0.28		0.01		0.32

[1]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, the frequency of alcohol drinking (continuous) and vegetable and fruit intake (quartiles of center-specific controls), and other vitamins (Multiple vitamins, vitamin C and vitamin E). [2]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous), vegetable and fruit intake (quartiles of center-specific controls) and other vitamins (Multiple vitamins, vitamin C and vitamin E). [3]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking (continuous), the frequency of alcohol drinking (continuous), vegetable and fruit intake (quartiles of center-specific controls) and other vitamins (Multiple vitamins, vitamin C and vitamin E). [4]Odds ratio adjusted for age, sex, race/ethnicity, study center, educational level, vegetable and fruit intake (quartiles of center-specific controls) and other vitamins (Multiple vitamins, vitamin C and vitamin E). [5]Multiple vitamins, vitamin C and vitamin E include North Carolina, Tampa, Los Angeles, Puerto Rico, Boston and US multicenter studies; calcium includes North Carolina, Tampa, Los Angeles, Puerto Rico and Boston studies.

Stratification by smoking and drinking status

Finally, the analysis was further stratified on smoking and drinking status (Table 5). Among never alcohol users (212 cases and 866 controls), calcium intake was associated with reduced HNC risk (OR = 0.39, 95% CI = 0.16–0.94). Ever use of vitamin E supplement were reported by 25 cases (17.1%) and 133 controls (18.2%) among never users of tobacco and alcohol but not associated with the risk of HNC. However, increased HNC risk was observed with the use of vitamin E supplement for 1 to 9 years but the CI was so wide (OR = 5.31, 95% CI 1.43–19.76) because of the small number of subjects with vitamin E intake of 1 to 9 years (11 cases and 37 controls). For the supplements of multiple vitamins and vitamin C, there was no significant association with HNC risk when stratified by smoking or drinking status.

Discussion

This study, based on a large pooled dataset, examined associations of vitamin or mineral supplements with HNC risk. Ever supplemental intake of vitamin C and calcium were associated with a reduced risk of HNC in this large pooled analysis of case–control study, but linear trends were not observed for the frequency or duration of any supplement intake. There did not appear to be any association between the HNC risk and ever use of any vitamins, multiple vitamins, vitamin A, beta-carotene, iron, selenium and zinc.

To date, only a handful of studies evaluated the association of supplemental vitamins and HNC. In a study focusing on pharyngeal cancer, Rossing *et al.* reported increasing cancer risk with decreasing use of vitamin C supplement.[12] Another case–control study by Barone *et al.*, reported that vitamin C was not associated with the risk of oral cancer.[13] Vitamin C is thought to play a role in cancer chemoprevention by stimulating immune function, inhibiting nitrosamine formation, blocking the metabolic activation of carcinogens and preventing oxidative stress.[39]

In our study, a 24% reduction in HNC risk was associated with ever use of vitamin C supplement (95% CI = 0.59–0.96). The inverse association was also observed with the long term intake of supplemental vitamin C (more than 10 years). Our results are in agreement with earlier case–control studies. However, we note that dose–response relations were not observed.

An inverse association between calcium supplement and the HNC risk was detected in our pooled analysis, even after adjustment for fruit and vegetable intake and other potential confounding factors. Cumulative calcium intake was also significantly associated with HNC risk. When stratified on smoking and drinking status, the significant association was stronger among never alcohol users. The finding may be explained by the fact that calcium is required for optimal activity of vitamin D and has been found to participate in regulating apoptosis, cell proliferation and differentiation.[40] In animal and epidemiological studies, calcium intake has been suggested to have protective effects against many cancer types, including colorectal,[41] breast,[42] endometrial,[43] prostate and ovarian.[40,41] However in our study, there was no dose–response relationship between calcium supplement and the risk of HNC.

Vitamin E is a strong intracellular antioxidant,[44] which has been shown to confer a cancer-inhibiting effect in animal studies.[45] Topical application of this nutrient has been reported to inhibit the development of tumors in the hamster buccal pouch.[46] Lower serum levels of alpha-tocopherol were related to a low oral cancer risk in some epidemiological studies.[47,48] Two case–control studies also provide modest evidence for an inverse association between vitamin E supplements and oral and pharyngeal cancers.[12,13] However, results from systematic review and meta-analysis do not provide support for vitamin E supplementation on the reduced risk of HNC.[11,20] In addition, Bairati *et al.* found vitamin E supplementation statistically significantly increased the risk of second primary cancers among HNC patients in a multicenter, double-blind, placebo-controlled, randomized chemoprevention trial.[17,18] In our pooled analysis, the high frequency of vitamin E intake was associated with a reduced the risk of HNC, especially oral cancer. However, increased HNC risk was observed with the vitamin E supplement for 1 to 9 years use, although the CI was wide.

There did not appear to be any association with HNC risk and other vitamin or mineral supplements in our study, such as beta-carotene, selenium, iron and zinc. In a large randomized controlled trial, beta-carotene was observed to possibly be protective against early stage laryngeal cancer.[11] However, the results from the three prevention trials for HNC, beta-carotene supplement had no significant effect for second primary risk among HNC patients.[15–17] Systematic reviews have reported that beta-carotene might increase overall mortality and cardiovascular mortality.[20–23] Selenium given singly or in combination with other supplements seemed to significantly decrease mortality.[22,49] However, few studies have investigated the relation of mineral supplements and HNC. One possible explanation for the null associations in our study is the low prevalence of use of individual supplements.

In this analysis, there was significant heterogeneity between studies for some vitamins, such as vitamin C. Given the different characteristics of the various populations, variation in assessment in exposure and the study design, a degree of heterogeneity across studies is to be expected. Meta-regression analysis showed that the geographic location of the studies might explain the source for the heterogeneity across studies. It is possible that the prevalence of susceptibility genes varies in different populations. For example, for vitamin C supplement, the five studies for which the point estimate was below 1 were from North America. Another explanation for the source of heterogeneity is that the case subtype distribution may differ by geographic location or hospital type/specialty. A few studies did not include cases of the larynx (Seattle, US multicenter, New York multicenter, Puerto

Rico and IARC studies) since all of the studies recruited eligible HNC patients sequentially. Moreover, the different types of questions and the different number of questions were across the studies.

There are several limitations in our pooled analysis. A potential limitation with regards to pooling data on ever use of vitamin or mineral supplements is the difference of definition of ever use. Accordingly, individuals with low vitamin or mineral supplement use might have been categorized as a "never user of vitamin or mineral supplements" in the analysis because of the wording on the questionnaires used to establish the "unexposed" group in the studies. The studies with the highest thresholds for classifying an individual as unexposed were the New York multicenter and Tampa studies (never users were defined as an individual who took any vitamins or minerals at least once a week for a year) and the US multicenter study (never users were defined as an individual who took any vitamins on a regular basis less than for 6 months). However, the ORs for these studies with higher thresholds were not necessarily toward the null, if inclusion of these minimal users had an impact on the association.

Recall bias is a potential limitation in retrospective studies because the subjects knew their disease status when they were interviewed. Supplemental vitamin use is not an established protective factor specifically for HNC, especially in the knowledge of the public at the time of the studies. Therefore, we would expect recall bias to be minimal during the interview for vitamin or mineral supplements assessment.

Another limitation is our inability to adjust for other potential confounding factors, such as micronutrients from dietary intake and HPV infection. We adjusted on fruit and vegetable intake as confounding factors in our study because most antioxidant vitamins are from fruit and vegetables. HPV would not be expected to result in major confounding because an association between vitamin or mineral supplements and HPV infection has not been established. It would be of interest to explore this area in the future when HPV data may be available with a standardized measure across the INHANCE studies.

Furthermore, although the pooled data provided large sample size for the investigation on vitamin or mineral supplements and HNC risk, the statistical power of analysis was limited for beta-carotene, iron, selenium and zinc because the prevalence of these supplements was low in the study population. It was difficult to analyze the duration and frequency of these supplements because of small sample size.

The major strength of our pooled analyses was assembly of a very large series HNC patients and control subjects, which allowed us to examine HNC risks in detail and to explore differences in risks by cancer subsites, smoking and alcohol status. To our knowledge, the estimates we present are the most precise available for the relationship of vitamin supplement and HNC risk. In summary, though some associations were suggested for vitamin C and calcium supplement use, dose-response trends were not observed.

Acknowledgements

The work reported in this article was undertaken during the tenure of a Postdoctoral Fellowship awarded by the IARC (postdoctoral fellowship, Q. Li).

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