RELATION OF ALLIUM VEGETABLES INTAKE WITH HEAD AND NECK CANCERS: EVIDENCE FROM THE INHANCE CONSORTIUM

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Abstract

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Scope—Only a few studies analyzed the role of allium vegetables with reference to head and neck cancers (HNC), with mixed results.

We investigated the potential favorable role of garlic and onion within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.

Methods and results—We analyzed pooled individual-level data from eight case-control studies, including 4590 cases and 7082 controls. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for associations between garlic and onion intakes and HNC risk. Compared with no or low garlic use, the ORs of HNC were 0.95 (95% CI 0.71–1.27) for intermediate and 0.74 (95% CI 0.55–0.99) for high garlic use (p for trend= 0.02). The ORs of HNC for increasing categories of onion intake were 0.91 (95% CI 0.68–1.21) for >1 to 3 portions per week, and 0.83 (95% CI 0.60–1.13) for >3 portions per week (p for trend= 0.02), as compared to <1 portion per week. We found an inverse association between high onion intake and laryngeal cancer risk (OR=0.69; 95% CI 0.54–0.88), but no significant association for other subsites.

Conclusions—The results of this pooled-analysis support a possible moderate inverse association between garlic and onion intake and HNC risk.

1) Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world [1]. The major recognized risk factors for HNC are tobacco and alcohol, with 5–10-fold higher risks for smokers as compared with nonsmokers [2] and for heavy drinkers as compared with abstainers or moderate drinkers [3–5]. In the International Head and Neck Cancer Epidemiology (INHANCE) database, the odds ratios (OR) for the highest alcohol drinking level (200 drinks-years versus 0) were 3.2 for oral cavity, 2.0 for pharyngeal and 1.8 for laryngeal cancer, and those for the highest smoking level (60 pack-years versus 0) were 10.1, 4.1 and 21.7, respectively [6]. The combined effect of heavy drinking and smoking led to an OR of 14.2 [7]. Thus, stopping drinking and smoking in the key factor to control HNC [8].

Selected other risk factors, including family history [9], human papillomavirus (HPV) infection for oropharyngeal cancer [10], and dietary and nutritional habits appear to play a role in the aetiology of these neoplasms [11]. The most convincing evidence on diet is a protective effect of non-starchy vegetables and fruit [12]. However, it is not yet clear which families of fruit or vegetables may exert a protective effect against HNC risk [13–16]. Previous studies reported that allium vegetables, in particular the most popular Allium sativum (garlic) and Allium cepa (onion), may have antioxidant and other anticancer properties [17, 18].

Several epidemiological investigations have suggested an inverse relation between allium vegetables intake and the risk of some cancers [19], in particular those of the digestive tract [20–23]. With reference to HNC, only a few studies analyzed the role of allium vegetables,

with mixed results. Five population based case-control studies were conducted in China. Those found a possible decrease in risk of cancer at selected anatomical sites of HNC for high allium vegetable intake [24–28]. Another case-control study, conducted in Uruguay, reported an inverse association between onion consumption and laryngeal cancer risk [29]. However, the EPIC cohort study, based on 352 HNC and esophageal cancer cases, found no association [30].

The INHANCE consortium is a collaboration of epidemiological studies of HNC with the aim to improve the understanding of the causes and mechanisms of HNC [31]. To date, the consortium includes more than 30 studies conducted worldwide, in areas with different smoking and drinking prevalence, and dietary patterns. The role of diet has been investigated using data from 22 studies with more than 14,500 cases and 22,000 controls [15]. The main result was that a diet rich in fresh vegetables and fruit and poor in red and processed meat was associated with a reduced HNC risk. In particular, a high intake of allium vegetables was associated with a reduction in HNC risk by 34% (OR for the highest versus the lowest quartile of intake = 0.66; based on 8 studies).

The aim of this report is to investigate more deeply the potential favorable role of the most consumed types of allium vegetables, i.e., garlic and onion. Thus, we analyzed them separately, in consideration of their different anticancer properties [32, 33], we considered their role according to subgroups of anatomical sites, and we examined the potential confounding/modifying effect of smoking and alcohol. The INHANCE dataset represents a unique opportunity to investigate this issue, since it includes patient-level data on allium vegetables consumption on more than 4500 cases and 7000 controls.

2) Materials and methods

Studies and participants

The INHANCE consortium was established in 2004 and to date includes 35 HNC case-control studies providing data on 25,478 cases and 37,111 controls [31]. Cases included patients with histologically confirmed invasive tumors of the oral cavity, oropharynx, hypopharynx, larynx, oral cavity or pharynx not otherwise specified (NOS) or overlapping, as previously defined [34, 35]. Details on the case-control studies, harmonizing questionnaire data and data pooling methods for the INHANCE consortium have been previously described [31, 35]. All studies were performed according to the Declaration of Helsinki and were approved by the local ethics committees, according to the legislations of each country at the time of study conduction. Informed consent was obtained from all study participants.

Of the 35 epidemiological studies, 10 studies had some information on garlic and/or onion intakes and thus were included in this investigation. However, two studies among the ten were excluded for the following reasons: a) a study from France (1987–1992) provided only data on leek consumption and not on garlic or onion intake [36]; b) a study from Buffalo, US, provided more than 50% missing values on garlic and onion intake [37]. Therefore, eight studies providing information on garlic and/or garlic intakes were included in this investigation, for a total of 4590 cases and 7082 controls [38–45], data version 1.5. The

main characteristics of these studies are reported in Table 1. Among cases, 1040 were cancers of the oral cavity, 1703 cancers of the pharynx, 303 cancers of the oral cavity or pharynx NOS and 1544 were cancers of the larynx. In most hospital-based studies, controls were patients admitted for acute, non neoplastic diseases, not related to tobacco smoking or alcohol drinking. Questionnaires were obtained from individual studies to assess the comparability of the collected data and of the wording of interview questions among the studies. Data from individual studies were received with personal identifiers removed. Each data item was checked for illogical or missing values and inconsistencies were resolved as necessary. Food frequency questionnaires (FFQ) were designed by each individual study. More details on these FFQs were reported elsewhere [15].

Among the items in the FFQ considered in this investigation, six studies collected information on garlic intake measured in terms of frequency of use [38, 39, 42, 45] or number of servings per day (or per week) [41, 43]. Information across different studies was standardized into the variable "frequency of use" scored as 1 for none or low use (corresponding to less than 0.2 servings per day), 2 for intermediate use (corresponding to 0.2–1 serving per day), and 3 for high use (corresponding to more than 1 serving per day). Information on onion intake was collected in seven studies in terms of number of servings per day (or per week) [38, 39, 41–43] or frequency of use [44, 45]. Information across different studies was standardized into the variable "number of servings per week", by converting consumption "never or less than once a year" into 0, "less than once a month" into 0.2 portions per week, "less than once a week" into 0.5 portions per week, "1 or 2 times per week" into 1.5 portions per week, "3–5 times per week" into 4 portions per week and "every day" into 7 portions per week. For studies reporting usual portion size (small, medium, large), for which an intermediate portion corresponded to 80 grams of onion, we considered a small portion as 0.7 times an intermediate one, and a large portion as 1.3 times an intermediate one [38, 39, 42]. No study collected information on the type of garlic and onion consumed (fresh, powders or garlic supplements) and on manner of using (raw or cooked). Only a study from Puerto Rico collected information separately on use of cooked or raw onion [41].

Statistical analysis

The ORs of HNC, and the corresponding 95% confidence intervals (CIs), for different levels of garlic use (high, intermediate vs none or low) and onion intake (>3, >1 to 3 vs <1 portion per week) were derived using unconditional multiple logistic regression models. All models included terms for study center, age (5-year categories), gender, race/ethnicity (non-Hispanic white, black, Hispanic/Latino, other), education level (no formal education, less than junior high school, some high school, high school graduate, vocational/some college, college graduate/postgraduate; categorically), cigarette smoking (never, 1–10, 11–20, 21–30, 31–40, 41–50, >50 pack-years; categorically), duration of cigar smoking (continuously), duration of pipe smoking (continuously), alcohol drinking (nondrinkers, >0–1, >1–3, >3–8, >8–18, >18–40, >40–75, >75–115, >115–155, >155 ml per day; categorically) and body weight (quartiles; categorically). Information on ethnicity was not collected in the central Europe and Saarland studies and, since the majority of these populations is white, all study

subjects were classified as non-Hispanic whites. To impute the missing values of education, multiple imputations with the PROC MI procedure in SAS was applied.

The pooled effect estimates from all studies were estimated with fixed-effects and random-effects logistic regression models [46]. We tested for heterogeneity between the study-specific ORs by conducting a likelihood ratio test comparing a model that included the product terms between each study (other than the reference study) and the variable of interest with a model without product terms, for the risk of HNC combined and for that of each anatomical subsite. We used the random-effects [46] estimates when heterogeneity was detected (p<0.10), and the fixed-effects estimates otherwise. We quantified inconsistencies across studies and their impact on the analysis by using Cochrane's Q and the I^2 statistic [47, 48]. Stratified analyses were conducted according to anatomical site (oral cavity, pharynx, oral cavity/pharynx NOS and larynx) and *"a priori"* selected covariates, including age (<55, 55 years), gender, geographic region (Europe, America), education (<high school graduate, high school graduate), tobacco smoking (never users, light users defined as smokers of 20 pack-year equivalent, heavy users defined as >20 pack-year equivalent) and alcohol consumption (never/light to moderate drinkers defined as drinkers of <3 drinks per day of alcoholic beverages, heavy drinkers defined as 3 drinks per day), in order to identify possible sources of heterogeneity. We also conducted a sensitivity analysis, in which each study was excluded one at time to ensure that the magnitude of the overall estimates were not dependent on any specific study.

Analyses were performed using SAS 9.2 statistical software (SAS Institute, Cary, NC) and Stata Statistical Software: Release 11 (College Station, TX: StataCorp LP).

3) Results

The characteristics of the eight case-control studies from the INHANCE consortium included in this analysis were reported in Table 1. Five studies were conducted in Europe (65% of total cases and 75% of controls), 2 in North America (27% of total cases and 17% of controls) and 1 in Central America (8% of total cases and 8% of controls). Four studies were hospital-based and four were population-based studies.

The distribution of HNC cases and controls according to selected variables (age, gender, race/ethnicity, education cigarette smoking and alcohol drinking) is reported in Supplementary Table 1. Eighty-one percent of HNC cases were men and 95% were non-Hispanic whites. Patients with HNC were more frequently tobacco users and alcohol drinkers.

Table 2 shows the distribution of HNC cases (also by anatomical site) and controls, and the corresponding ORs and 95% CIs, according to garlic and onion intakes. Compared with no or low garlic use, on the basis of 6 studies, the ORs of HNC combined were 0.95 (95% CI 0.71–1.27) for intermediate use and 0.74 (95% CI 0.55–0.99) for high use (p for trend= 0.02). In the analyses by anatomical sites, the ORs for high garlic use were 0.77 (95% CI 0.49–1.21, p for trend= 0.29) for cancer of the oral cavity and pharynx combined, 0.84 (95% CI 0.56–1.27, p for trend=0.29) for cancer of the oral cavity, 0.62 (95% CI 0.40–0.97, p for trend= 0.07) for oro/hypopharyngeal cancer, and 1.18 (95% CI 0.60–2.30, p for trend=0.85)

for cancer of oral cavity/pharynx NOS. For laryngeal cancer, the corresponding OR for high garlic use, based on 5 studies, was 0.67 (95% CI 0.42–1.06, p for trend= 0.09). Information on onion intake derived from 7 studies for HNC and oral cavity and pharyngeal cancers combined, and from 6 studies for laryngeal cancer. The ORs for increasing categories of onion intake were 0.91 (95% CI 0.68–1.21) for >1 to 3 portions per week, and 0.83 (95% CI 0.60–1.13) for >3 portions per week (p for trend= 0.13) for HNCs combined. The ORs for the highest versus the lowest level of onion consumption were 0.88 (95% CI 0.67–1.15) for cancer of the oral cavity and pharynx combined, 0.95 (95% CI 0.67–1.35) for oral cavity cancer, 0.84 (95% CI 0.61–1.14) for oro/hypopharyngeal cancer, and 0.84 (95% CI 0.42–1.69) for cancer of oral cavity and pharynx NOS. The corresponding OR for laryngeal cancer was 0.69 (95% CI 0.54–0.88).

Stratified-analyses are presented in Figure 1. Panel A shows stratified results for high garlic use and Panel B those for high onion consumption. No significant heterogeneity was found across strata of age, gender, geographical region, education, tobacco and alcohol consumption. However, an apparently stronger inverse association emerged in men for high garlic use (p for heterogeneity between strata p=0.34), and in heavy tobacco users (i.e., smokers of >20 pack-year equivalent) for high onion intake (p=0.38).

4) Discussion

In this pooled analysis of 8 case-control studies included in the INHANCE consortium, there was an inverse relation between garlic consumption and HNC risk. The pattern of risk was similar for onion, though the inverse association was significant for larynx only. In particular, high garlic use was associated with a significant risk reduction of overall HNC and oro/hypopharyngeal cancers by 26% and 38%, respectively. Further, consuming more than 3 portions of onion per week was associated with a significant reduction of laryngeal cancer risk by more than 30%.

The combination of garlic and onion is difficult to interpret, given the different measures used to collect information on the two intakes in various studies. We therefore presented details of the two separate items only in the present analysis. A previous publication related to food and HNC in the INHANCE database, based on 8 studies and about 4000 cases [15], tried to derive a summary measure of all allium vegetables. The ORs for subsequent quartiles were 0.98, 0.86 and 0.66, and the test for trend was significant. Thus, the early analysis is broadly consistent with the present more detailed one.

The inverse association between allium vegetables and the risk HNC may be related to various components of garlic and onion. Allium vegetables contain many chemicals with potential antioxidant and anticancer activity, including organosulfur compounds, flavonoids, minerals and vitamins [49]. In particular, garlic contains around 33 sulfur compounds. When its clove's membrane is disrupted, alliin is metabolize to produce allicin (diallyl thiosulfinate), which is further metabolized to diallyl sulfide (DAS), diallyl disulfide, diallyl trisulfide (DATS), and other compounds such as ajoene. Onions contain several sulfoxides, mainly S-propenylcysteine sulfoxide, S-propylcysteine sulfoxide and S-methylcysteine sulfoxide [50]. Many experimental studies have suggested a protective effect of

organosulfur compounds in *'in vitro'* and *'in vivo'* models against different types of cancer [50], and cancer chemopreventive effects may be related to various biological mechanisms, including modulation of metabolizing enzymes, and regulation of cell proliferation and apoptosis [17]. In particular for HNC, *S*-allylcysteine, a water-soluble organosulfur compound present in garlic, significantly suppressed 7,12-dimethylbenz[a]anthracene-induced buccal pouch carcinogenesis in hamsters by modulating lipid peroxidation and enhancing the level of reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione *S*-transferase (GST)[51]. *N*-acetylcysteine, another organosulfur compound, tested in two human tongue squamous carcinoma cell lines and in a human oral squamous cell carcinoma xenograft mouse model, inhibited cell proliferation and induced apoptosis by the regulation of Epidermal Growth Factor Receptor (EGFR)/Akt/HBP1signaling pathway [52]. Flavonoids, present in garlic and onions, may also contribute to the anticancer effects through their antioxidant activity. In particular, flavonoids have been inversely related with laryngeal cancer risk [53]. The anticancer effect of quercetin, a very abundant flavonol in onions, was also evaluated in *'in vitro'* studies. In particular, the growth of a human laryngeal cancer cell line (Hep-2) was significantly inhibited by quercetin probably through apoptosis [54], as members of the MAPK pathways seem to be involved. Support for a real inverse association between garlic and HNC and between onion and cancer of the larynx comes from the significant inverse dose-risk relation, and from the consistent relation reported across strata of potential confounders and effect modifiers.

Our data of a significant inverse relation of onion intake with laryngeal cancer risk are in agreement with those of an Uruguayan case-control study not included in the INHANCE consortium, which found an OR of 0.50 (95% CI 0.31–0.80) for an increment of onion consumption of 3.4 g per day [29].

Among the strengths of the study are the uniquely large sample size, the involvement of many populations with different dietary and lifestyle habits, particularly alcohol drinking and diet, and the proper allowance for the major confounding factors, including tobacco smoking and alcohol drinking. In a sensitivity analysis, exclusion of each study from the pooled-analysis did not materially change the summary estimates, indicating that the results were not driven by any single study. Recall of dietary intake has been shown satisfactorily reproducible in most of studies [15], and should not be different on the basis of the disease status or among various types of controls, as allium vegetables is not commonly known to affect HNC risk.

There was significant heterogeneity across studies. Potential sources of heterogeneity include differences among populations in dietary correlates, patterns of smoking and alcohol drinking, and other covariates of HNC risk, and the way of consumption and cooking of garlic and onion in various countries.

An important limitation of this analysis included the paucity of information on the modalities of garlic and onion consumption (in particular no distinction between raw and cooked allium vegetables was made in studies, except for a study from Puerto Rico [41]), as there may be differences in the composition, concentration, and activities of bioactive compounds according to the modalities of cooking [55, 56]. The modalities of consumption

(raw or cooked) and the cooking methods (boiled, fried and temperature of oven heating) of allium vegetables are responsible of their bioavailability and the activity of their bioactive components. Indeed, it was reported a reduction of about 30% in quercetin content by boiling onions, and boiled allium vegetables lose much of their antioxidant activity. In particular, cooking garlic may inactivate the enzyme alliinase, which is responsible for converting allicin to allicin, which in turn yields all other bioactive compounds. [57].

With reference to confounding, we were able to control for several risk factors for HNC. In particular, we paid attention to adjust for alcohol and tobacco, which are also the major risk factors for HNC [2–5], inversely related to high vegetables and fruit intake [58]. No information was available in the INHANCE data version 1.5 on HPV – a recognized risk facror for oropharyngeal cancer – and total energy intake. We adjusted for body weight to address this limitation because weight would reflect the energy intake in middle-aged adults [59]. In addition, the risk estimates did not materially change after adjustment for vegetable and fruit intake, which has been favorably related to HNC and may correlate with allium vegetables intake. For instance, in the Mediterranean diet, onion and garlic are often eaten or cooked in combination with other foods, such as tomato sauces for pasta, various vegetables and raw olive oil and tomatoes in salads, and some studies reported a synergistic favorable effect of garlic and tomatoes on cancer [60, 61]. We cannot however exclude some reverse causation as the presence of preneoplastic lesions, mainly in the oral cavity/pharynx, or symptoms of these diseases may have led to a reduction of allium vegetables intake among cases.

The results of this pooled-analysis of case-control studies support the hypothesis of a moderate inverse association between allium vegetables intake and the risk of HNC, and provide a quantitative estimate of the effect, even if some bias, confounding, and reverse causality cannot be excluded. In conclusion, although the most effective strategy for HNC prevention involves alcohol and tobacco control, selected dietary advices, including a vegetable rich diet, specifically with a high allium vegetable intake, may reduce the occurrence of this neoplasm with high incidence and low survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

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CI	Confidence Interval
HNC	Head and Neck Cancers
HPV	Human PapillomaVirus
INHANCE	International Head and Neck Cancer Epidemiology
NOS	Not Otherwise Specified
OR	Odds Ratio

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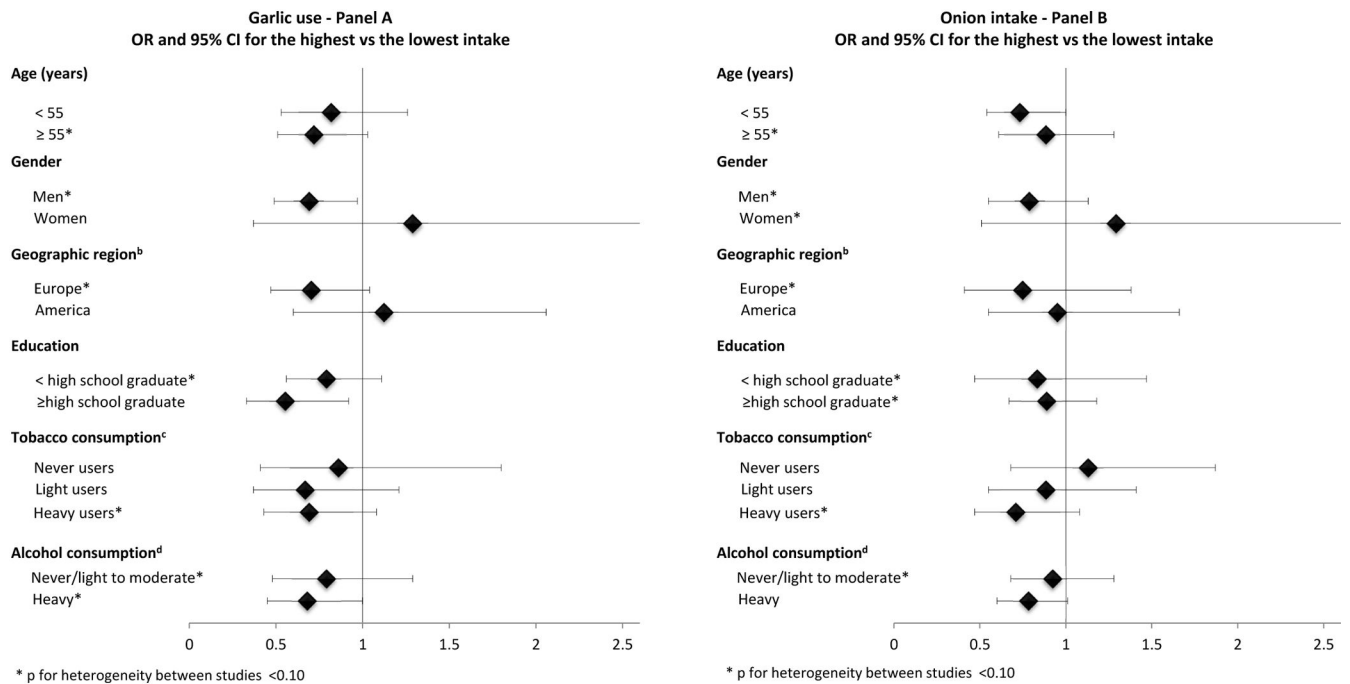
Figure 1.

Odds ratios (OR)[a] and 95% confidence intervals (CI), according to highest intake of garlic (Panel A) and onion (Panel B) versus the lowest one in strata of selected covariates. INHANCE Consortium

[a]ORs from random effects estimates when significant heterogeneity (p<0.10) was detected and the fixed-effects estimates otherwise. Adjusted for age, gender, race/ethnicity, education, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake and body weight. The reference category was the lowest intake of garlic (i.e., no/low use) or onion (<1 portion/week) in each stratum.

[b]Europe included two studies from Italy [38, 39], one from Switzerland [42], one from Germany [45], and one from Central Europe [40]. America included two studies from USA [43, 44] and one from Puerto Rico [41].

[c]Light tobacco users were smokers of ≤20 pack-year equivalent (combination of pack-years of cigarettes and equivalent amount of cigars or pipe). Heavy tobacco users were smokers of >20 pack-year equivalent.

[d]Never/Light to moderate drinkers were drinkers of <3 drinks per day of alcoholic beverages and heavy drinkers were those consuming ≥3 drinks per day.

TABLE 1

Characteristics of individual studies of the International Head and Neck Cancer Epidemiology (INHANCE) consortium pooled analysis including information on allium vegetables intake

Study name[a]	Study location	Recruitment period	Source of controls	Participation rate of cases and controls (%)	Information on		Total oral cavity/pharynx			Larynx	Controls
					Garlic	Onion	Oral cavity	Oropharynx/ hypopharynx	Oropharynx NOS		
Europe											
Italy Multicenter [38]	Aviano, Milan, Latina	1990–2005	HB	>95, >95	Yes	Yes	209	502	90	460	2716
Switzerland [42]	Lausanne	1991–1997	HB	>95, >95	Yes	Yes	138	247	7	124	883
Central Europe [40]	Central Europe	1998–2003	HB	96, 97	No	Yes	196	150	32	384	907
Germany [45]	Saarland	2001–2003	PB	94, -	Yes	No	15	43	9	27	94
Italy [39]	Milan	2006–2009	HB	>95, >95	Yes	Yes	66	58	18	229	755
North America											
USA (Seattle-Leo) [44]	Seattle	1983–1987	PB	81, 75	No	Yes	183	212	47	209	547
USA (Boston) [43]	Boston	1999–2003	PB	88.7, 48.7	Yes	Yes	139	291	43	111	659
Central America											
Puerto Rico [41]	Puerto Rico	1992–1995	PB	71, 83	Yes	Yes	94	200	57	-	521
Total subjects							1040	1703	303	1544	7082[b]

HB: Hospital based; NOS: not otherwise specified; PB: Population based

[a] Representative publications in which study methods are available.

[b] The total number of controls for the analyses on laryngeal cancer was 6561, as one study was not included [41].

TABLE 2

Distribution of cases of head and neck cancers (HNC) combined and by anatomical site, and of controls, and corresponding odds ratios[a] (OR) and 95% confidence intervals (CI), according to garlic and onion intake. INHANCE Consortium

	Garlic use[b] OR (95% CI)			Onion intake[c] (portions/week) OR (95% CI)			
	No/Low	Moderate	High	<1	>1 – 3	> 3	
HNC combined	1[d]	0.95 (0.71–1.27)	0.74 (0.55–0.99)	1[d]	0.91 (0.68–1.21)	0.83 (0.60–1.13)	
Cases:Controls	1293:2325	1061:1888	207:530	2010:3660	482:764	920:1347	
p for trend	0.02			0.13			
p for heterogeneity between studies	0.02			<0.01			
Total oral cavity and pharynx cancer	1[d]	0.91 (0.74–1.12)	0.77 (0.49–1.21)	1[d]	0.82 (0.56–1.19)	0.88 (0.67–1.15)	
Cases:Controls	871:2325	732:1888	132:530	1221:3660	270:764	679:1347	
p for trend	0.29			0.15			
p for heterogeneity between studies	0.05			<0.01			
Oral cavity	1[d]	0.99 (0.76–1.27)	0.84 (0.56–1.27)	1[d]	0.91 (0.58–1.43)	0.95 (0.67–1.35)	
Cases:Controls	248:2325	199:1888	41:530	376:3660	94:764	261:1347	
p for trend	0.29			0.58			
p for heterogeneity between studies	0.31			0.07			
Oropharynx/hypopharynx	1[d]	0.92 (0.71–1.19)	0.62 (0.40–0.97)	1[d]	0.77 (0.53–1.11)	0.84 (0.61–1.14)	
Cases:Controls	555:2325	459:1888	75:530	740:3660	151:764	355:1347	
p for trend	0.07			0.10			
p for heterogeneity between studies	0.04			0.02			
Oral cavity/pharynx NOS	1[d]	0.94 (0.60–1.45)	1.18 (0.60–2.30)	1[d]	1.30 (0.59–2.89)	0.84 (0.42–1.69)	
Cases:Controls	68:2325	74:1888	16:530	105:3660	25:764	63:1347	
p for trend	0.85			0.10			
p for heterogeneity between studies	0.20			0.03			
Larynx	1[d]	1.07 (0.56–2.05)	0.67 (0.42–1.06)	1[d]	1.15 (0.88–1.49)	0.69 (0.54–0.88)	
Cases:Controls	422:2235	328:1522	75:502	789:3556	212:716	241:1015	
p for trend	0.09			0.04			
p for heterogeneity between studies	<0.01			0.15			

[a]ORs from random effects estimates when significant heterogeneity (p<0.10) was detected and from the fixed-effects estimates otherwise. Adjusted for age, gender, race/ethnicity, education, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake and body weight. The sum does not add up to the total because of some missing information

[b]Includes 6 studies for HN and OP cancers [38, 39, 41–43, 45] and 5 studies for laryngeal cancer [38, 39, 42, 43, 45]

[c]Includes 7 studies for HN and OP cancers [38–44] and 6 studies for laryngeal cancer [38–40, 42–44]

[d]Reference category.