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Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium

Mia Hashibe, Paul Brennan, Simone Benhamou, Xavier Castellsague, Chu Chen, Maria Paula Curado, Luigino Dal Maso, Alexander W. Daudt, Eleonora Fabianova, Victor Wünsch-Filho, Silvia Franceschi, Richard B. Hayes, Rolando Herrero, Sergio Koifman, Carlo La Vecchia, Philip Lazarus, Fabio Levi, Dana Mates, Elena Matos, Ana Menezes, Joshua Muscat, Jose Eluf-Neto, Andrew F. Olshan, Peter Rudnai, Stephen M. Schwartz, Elaine Smith, Erich M. Sturgis, Neonilia Szeszenia-Dabrowska, Renato Talamini, Qingyi Wei, Deborah M. Winn, David Zaridze, Witold Zatonski, Zuo-Feng Zhang, Julien Berthiller, Paolo Boffetta

Background At least 75% of head and neck cancers are attributable to a combination of cigarette smoking and alcohol drinking. A precise understanding of the independent association of each of these factors in the absence of the other with the risk of head and neck cancer is needed to elucidate mechanisms of head and neck carcinogenesis and to assess the efficacy of interventions aimed at controlling either risk factor.

Methods We examined the extent to which head and neck cancer is associated with cigarette smoking among never drinkers and with alcohol drinking among never users of tobacco. We pooled individual-level data from 15 case-control studies that included 10244 head and neck cancer case subjects and 15227 control subjects, of whom 1072 case subjects and 5775 control subjects were never users of tobacco and 1598 case subjects and 4051 control subjects were never drinkers of alcohol. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. All statistical tests were two-sided.

Results Among never drinkers, cigarette smoking was associated with an increased risk of head and neck cancer (OR for ever versus never smoking = 2.13, 95% CI = 1.52 to 2.98), and there were clear dose-response relationships for the frequency, duration, and number of pack-years of cigarette smoking. Approximately 24% (95% CI = 16% to 31%) of head and neck cancer cases among nondrinkers in this study would have been prevented if these individuals had not smoked cigarettes. Among never users of tobacco, alcohol consumption was associated with an increased risk of head and neck cancer only when alcohol was consumed at high frequency (OR for three or more drinks per day versus never drinking = 2.04, 95% CI = 1.29 to 3.21). The association with high-frequency alcohol intake was limited to cancers of the oropharynx/hypopharynx and larynx.

Conclusions Our results represent the most precise estimates available of the independent association of each of the two main risk factors of head and neck cancer, and they exemplify the strengths of large-scale consortia in cancer epidemiology.

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Affiliations of authors: International Agency for Research on Cancer, Lyon, France (MH, P. Brennan, SF, JB, P. Boffetta); INSERM, U794, Evry, France (SB); Institut Català d'Oncologia, Barcelona, Spain (XC); Fred Hutchinson Cancer Research Center, Seattle, WA (CC, SMS); Hospital Araujo Jorge, Goiania, Brazil (MPC); Aviano Cancer Centre, Aviano, Italy (LDM, RT); Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil (AWD); Specialized State Health Institute, Banská Bystrica, Slovakia (EF); Universidade de Sao Paulo, Sao Paulo, Brazil (VWF, JEN); National Cancer Institute, Bethesda, MD (RBH, DMW); Instituto de Investigación Epidemiológica, San José, Costa Rica (RH); Escola Nacional de Saude Publica, Rio de Janeiro, Brazil (SK); Istituto di Ricerche Farmacologiche Mario Negri and University of Milan, Milan, Italy (CLV); Penn State College of Medicine, Hershey, PA (PL, JM); Institut de médecine sociale et préventive [IUMSP], Université de Lausanne, Lausanne, Switzerland (FL); Institute of Public Health, Bucharest, Romania (DM); Institute of Oncology Angel H. Roffo, University of Buenos Aires, Argentina (EM);

Universidade Federal de Pelotas, Pelotas, Brazil (AM); University of North Carolina School of Public Health, Chapel Hill, NC (AFO); National Institute of Environmental Health, Budapest, Hungary (PR); College of Public Health, University of Iowa, Iowa City, IA (ES); University of Texas M. D. Anderson Cancer Center, Houston, Texas (EMS, QW); Institute of Occupational Medicine, Lodz, Poland (NSD); Cancer Research Centre, Moscow, Russia (DZ); Maria Skłodowska Institute of Oncology, Warsaw, Poland (WZ); University of California, Los Angeles, School of Public Health, Los Angeles, CA (ZFZ).

Correspondence to: Mia Hashibe, PhD, Gene-Environment Epidemiology Group, International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon, France (e-mail: hashibe@iarc.fr)

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CONTEXT AND CAVEATS

Prior knowledge

Although at least 75% of head and neck cancers diagnosed in industrialized regions are attributable to the combination of cigarette smoking and alcohol drinking, the respective contributions of these risk factors to head and neck cancer risk are unclear because the two habits are strongly associated with each other.

Study design

A pooled analysis of data from 15 case-control studies of head and neck cancer risk and cigarette smoking among never drinkers and head and neck cancer risk and alcohol drinking among never users of tobacco.

Contribution

Among never drinkers, cigarette smoking was associated with an increased risk of head and neck cancer, and there were clear dose-response relationships for the frequency, duration, and number of pack-years of cigarette smoking. Among never users of tobacco, high-frequency alcohol consumption was associated with increased risks of cancers of the oropharynx/hypopharynx and larynx only.

Implications

Approximately one quarter of the head and neck cancers among the never drinkers were attributable to ever cigarette smoking, assuming a causal relationship. Only 7% of the head and neck cancers were attributable to alcohol drinking among the never users of tobacco, assuming a causal relationship.

Limitations

Misclassification of alcohol exposure, particularly exposure to hard liquors, and recall bias could have influenced the observed associations. Regional differences in social acceptance of tobacco habits and alcohol consumption may have influenced how a subject responded to questions about these practices in a face-to-face interview.

Head and neck cancers are a group of related neoplasms that arise in the oral cavity, pharynx, and larynx. Almost 600 000 new cases of head and neck cancer and 300 000 deaths occur worldwide each year (1). At least 75% of head and neck cancers diagnosed in Europe, the United States, and other industrialized regions are attributable to the combination of cigarette smoking and alcohol drinking (2,3). However, the respective contributions of these risk factors to head and neck cancer risk are difficult to study because these two habits are strongly associated with each other (4,5). A precise understanding of the independent associations between cigarette smoking and alcohol drinking and the risk of head and neck cancer has important implications for elucidating the mechanisms of head and neck carcinogenesis and for assessing the effects of interventions to modify these risk factors.

The etiologic factors for head and neck cancer in individuals who have never used tobacco products are not yet well understood. Of the head and neck cancer patients, 5%–30% are never smokers (6–19). Head and neck tumors in never smokers are thought to be distinct from those in smokers because they have fewer TP53 gene mutations, a lower frequency of loss of heterozygosity on chromosome arms 3p and 4q and at chromosome 11q13 (chromosomal sites at which loss of heterozygosity occurs during the progression

of oral cancer), and fewer microsatellite alterations than head and neck tumors that arise in smokers (20). Analyses of never users of tobacco are necessary to establish the etiologic role of risk factors other than tobacco use because tobacco use is the primary risk factor for head and neck cancer (21), and thus, residual confounding by tobacco use is difficult to rule out. Similarly, because alcohol drinking is a risk factor for head and neck cancer (22), analyses of nondrinkers are needed to rule out confounding by alcohol when estimating the effect of cigarette smoking. A pooled analysis within a consortium is a cost-effective method for generating a large sample size for the analysis of rare subgroups such as head and neck cancer patients who are never users of tobacco and never drinkers.

Previous estimates of the independent associations among cigarette smoking, alcohol drinking, and the risk of head and neck cancer (23–28) were imprecise because of the small numbers of case subjects who were never drinkers or never tobacco smokers (typically fewer than 100). To overcome this limitation, we conducted a pooled analysis of cigarette smoking among never drinkers and alcohol drinking among never users of tobacco. This analysis was made possible by the establishment, in 2004, of the International Head and Neck Cancer Epidemiology (INHANCE) consortium as an international collaboration among research groups that were conducting large, ongoing (or recently completed) molecular epidemiology studies of head and neck cancer. The primary goal of the consortium is to address research questions—such as the independent associations among cigarette smoking, alcohol drinking, and head and neck cancer—that are difficult to answer in individual studies, which typically include 500–1000 case subjects and a comparable number of control subjects. Our goal was to examine whether cigarette smoking and alcohol drinking are each a risk factor in the absence of the other and to explore whether risk estimates differ by cancer site within the head and neck.

Methods

Studies

Investigators who had recently conducted molecular epidemiologic studies of head and neck cancers were invited to participate in the INHANCE consortium. The included studies had to have a protocol for the recruitment of case and control subjects and to have used a structured epidemiologic questionnaire that addressed both tobacco and alcohol use. We also invited investigators who had conducted high-quality, large-scale epidemiologic studies that lacked a molecular component to participate in the INHANCE consortium. The eligibility criteria for these studies were that they include more than 300 head and neck cancer case subjects and that information be available on demographic and tumor characteristics, alcohol consumption, and tobacco use habits (i.e., cigarettes, cigars, pipes, and, where relevant, snuff and chewing tobacco).

We initially pooled the data from 15 individual case-control studies (6–19) that included 10 302 head and neck cancer case subjects and 15 329 control subjects (data version 1.0). Case and control subjects with missing data on age, sex, or race/ethnicity and case subjects with missing information on the site of origin of their cancer (58 case subjects and 102 control subjects) were

excluded from this analysis. Thus, the data for this analysis included 10 244 head and neck cancer case subjects and 15 227 control subjects.

The characteristics of the individual studies included in the pooled data are shown in Table 1. The studies are referred to by location and by whether they are multicenter in study design. Most 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 (e.g., study center, hospital, and race/ethnicity). The Los Angeles study individually matched the control subjects to case subjects on age decade, sex, and neighborhood, although in the study analysis the matching was broken. Face-to-face interviews were conducted in all studies except for the Iowa study, in which subjects completed self-administered questionnaires. Written informed consent was obtained from all study subjects, and the investigations were approved by the institutional review board at each study center. Blank questionnaires were collected from all the 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 at the International Agency for Research on Cancer (IARC) with personal identifiers removed. Each data item was checked for illogical or missing values. Queries were sent to the investigators to resolve inconsistencies.

Case subjects were included in this analysis if their tumor had been classified by the original study as an invasive tumor of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, or larynx or head and neck cancer unspecified according to the International Classification of Diseases for Oncology, Version 2 [ICD-O-2; (29)] or the International Classification of Diseases, 9th [ICD-9; (30)] or 10th [ICD-10; (31)] Revision. Subjects with salivary gland cancers (ICD-O-2 codes C07–C08) were excluded from our analysis because the etiologic pattern of these cancers differs from that of head and neck cancers (32). For studies that used ICD-O-2 or ICD-10 classification (Central Europe, Iowa, Los Angeles, Seattle, Puerto Rico, and South America studies), tumors were assigned to one of the six categories as follows: 1) oral cavity (includes lip, tongue, gum, floor of mouth, and hard palate): codes C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, and C06.9; 2) oropharynx (includes base of tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx): codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, and C10.9; 3) hypopharynx (includes pyriform sinus and hypopharynx): codes C12.9, C13.0–C13.2, C13.8, and C13.9; 4) oral cavity, pharynx unspecified or overlapping: codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; 5) larynx (includes glottis, supraglottis, and subglottis): codes C32.0–C32.3 and C32.8–C32.9; and 6) head and neck cancer unspecified: defined as overlapping lesions when more than one ICD topographic code was available for each case subject and the multiple sites were not within one of the categories listed above.

For studies that classified tumor site data according to ICD-9 codes (Milan, Aviano, France, Italy Multicenter, Switzerland, North Carolina, Tampa, and International Multicenter studies), the assigned codes were converted to ICD-O-2 codes. For the Houston study, instead of the original ICD code, we received the

study surgeon's classification of subsites as oral cavity, oropharynx, hypopharynx, or larynx, consistent with the ICD-O-2 group designations listed above. There were 2854 case subjects with oral cavity cancer, 3358 with pharyngeal cancer (oropharyngeal or hypopharyngeal), 905 with oral cavity/pharynx not otherwise specified, 2821 with laryngeal cancer, and 306 with unspecified head and neck cancer.

Some studies (i.e., the France, North Carolina, Tampa, and Houston studies) restricted eligibility to case subjects with squamous cell carcinomas (SCC). For other studies that provided the ICD-O-2 histologic coding for each tumor (i.e., the Switzerland, Central Europe, Seattle, Los Angeles, Puerto Rico, and South America studies and the following centers in the International Multicenter study: Australia, Aviano, Barcelona, Canada, Cuba, Granada, Ireland, Milan, Poland, Sevilla, and Udine), we used the following codes to identify case subjects with SCC: 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8078/3, 8083/3, and 8084/3. The Iowa study provided a variable instead of ICD coding to specify which case subjects had SCC. For the Milan and Aviano studies, the Italy Multicenter study, and four centers in the International Multicenter study (i.e., Bangalore, Madras, and Trivandrum in India and Khartoum in Sudan), no data were available on histologic type. Of the 7613 head and neck cancer case subjects for whom histologic information was available, 7025 (92.3%) had SCC.

The questions about tobacco and alcohol use on study questionnaires were conceptually similar across studies, although the exact wording differed. The questions about tobacco and alcohol use were examined carefully for comparability before variables were created for this report. Each study subject was asked whether he or she had ever been a smoker of cigarettes, cigars, or pipes. However, the definitions of ever smoking varied widely among the individual studies (i.e., for cigarettes, ever smoking was defined as smoked ≥ 100 cigarettes in a lifetime [Central Europe, Los Angeles, North Carolina, Puerto Rico, Seattle, and Houston studies], as smoked one or more cigarettes per day for ≥ 1 year [International Multicenter, Tampa, South America, Milan, Aviano, Italy Multicenter, and Switzerland studies], as smoked one-half pack or more per week for ≥ 1 year [Iowa study], and as smoked "regularly" [France study]; for cigars and pipes, ever smoking was defined as smoked cigars or pipes for ≥ 6 months [Seattle, North Carolina, and Puerto Rico studies], as smoked one or more cigars or one or more pipefuls of tobacco per month for ≥ 6 months [Los Angeles study], as smoked one or more cigars or pipes per day for ≥ 1 year [Milan, Aviano, Italy, Switzerland, South America], as smoked cigars or pipes "regularly" [France and Central Europe studies], as ever used cigars or pipes [Houston study], as smoked at least one cigar or one pipeful of tobacco a week for ≥ 1 year [Iowa], as smoked daily for >1 year [International Multicenter study], and as smoked a cigar or pipe once a day for ≥ 1 year [Tampa study]. Variables on the frequency (i.e., number of cigarettes, cigars, or pipes smoked per day), duration (in years), and pack-years (i.e., cumulative smoking) of tobacco smoking were available in all studies. For several studies (i.e., the Central Europe, South America, France, and North Carolina studies), the frequency and duration variables were calculated centrally; for all other studies, we used the data calculated by the individual studies.

Table 1. Summary of individual studies in INHANCE consortium pooled data version 1.0, by region and study period*

Study location (referencet)	Case subjects					Control subjects†						
	Recruitment period	Source	Participation rate, %	Age eligibility, y	Total	No. of never drinkers	No. of never users of tobacco	Source	Participation rate, %	Total	No. of never drinkers	No. of never users of tobacco
Europe												
Milan, Italy (6)	1984–1989	Hospital	95§	<80	416	75	28	Hospital (unhealthy)	95§	1531	305	575
Aviano, Italy (7)	1984–1989	Hospital	>95§	>18	482	7	26	Hospital (unhealthy)	95§	855	57	277
Paris, France (8)	1987–1992	Hospital	95§	NA	323	12	0	Hospital (unhealthy)	95§	234	19	0
Italy (Aviano, Milan, Latina) (9)	1990–1999	Hospital	>95	18–80	1058	37	68	Hospital (unhealthy)	95	2579	246	987
Switzerland (10)	1991–1997	Hospital	95	<80	516	39	30	Hospital (unhealthy)	95	883	435	418
Central Europe (Banska Bystrica, Bucharest, Budapest, Lodz, Moscow) (11)	1998–2003	Hospital	96	≥15	762	14	49	Hospital (unhealthy)	97	907	62	308
North America												
Seattle, WA (12)	1985–1995	Cancer registry	54.4, 63.3¶	18–65	407	16	53	Random digit dialing	63, 61¶	607	45	192
Iowa (13)	1993–2006	Hospital	87	>17	546	137	106	Hospital (healthy)	92	759	335	285
North Carolina (14)	1994–1997	Hospital	88	>17	180	31	11	Hospital (unhealthy)	86	202	94	74
Tampa, FL (15)	1994–2003	Hospital	98	≥18	207	43	37	Cancer screening clinic (healthy)	90	897	351	345
Los Angeles, CA (16)	1999–2004	Cancer registry	49	18–65	417	70	115	Neighborhood	67.5	1005	250	453
Houston, TX (17)	2001–2006	Hospital	95	≥18	830	234	186	Hospital visitors	>80	865	396	374
South/Central America												
Puerto Rico (18)	1992–1995	Cancer registry	71	21–79	350	31	32	Residential records	83	521	112	211
South America (Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, São Paulo) (NA)	2000–2003	Hospital	95	15–79	2191	215	123	Hospital (unhealthy)	86	1706	495	506
International												
International (Italy, Spain, Ireland, Poland, Canada, Australia, Cuba, India, Sudan) (19)	1992–1997	Hospital	88.7	NA	1559	637	208	Hospital/Community	87.3	1676	849	770
Total					10244	1598	1072			15227	4051	5775

* INHANCE = International Head and Neck Cancer Epidemiology; NA = not applicable/not available.

† Representative publication in which study methods are described.

‡ All studies frequency matched control subjects to case subjects on age and sex. Additional frequency matching factors included study center (Italy, Central Europe, South America, and International Multicenter studies), hospital (France study), ethnicity (Tampa study), and neighborhood (Los Angeles study).

§ Participation rate was not formally assessed, estimated response rate reported.

|| Multicenter study.

¶ Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

Information about snuff use and chewing habits was collected by the Puerto Rico study, the International Multicenter studies, and all studies in North America. Snuff use and chewing are not common behaviors in Europe or South America, except in specific populations (e.g., Norway and Sweden) that were not included in the pooled dataset. For the Indian study population in the International Multicenter study, information on betel quid and areca nut chewing was collected. The definitions of ever chewing and ever use of snuff differed across studies (i.e., as ever use of snuff or chew for ≥ 6 months [Seattle, North Carolina, and Puerto Rico studies], as use of at least one small can of snuff or one pouch of chewing tobacco per week for ≥ 1 year [Iowa study], as use of chew or snuff at least once per day for ≥ 1 year [Tampa study], as daily chewing of tobacco, betel quid, areca nut, or pan masala or daily snuffing of tobacco for ≥ 1 year [International Multicenter studies], as at least one plug of tobacco or one pinch of snuff of tobacco per month for ≥ 6 months [Los Angeles study], and as ever use of snuff or dip or chewing tobacco [Houston study]). Frequency and duration variables for chewing and snuff use habits were pooled across relevant studies. For this study, never users of tobacco were defined as individuals who had not used cigarettes, cigars, pipes, snuff, or chewing products during their lifetimes.

In the alcohol section of the study questionnaires, subjects were asked if they were alcohol drinkers; for those who responded that they were, subsequent questions were asked about the frequency of drinking, the duration of drinking, and the different types of alcoholic beverages consumed (i.e., beer, wine, hard liquors, and/or aperitifs). The definitions of ever alcohol drinking were “ever” consumed alcohol (France, Central Europe, Aviano, Milan, Italy Multicenter, and Switzerland studies); consumed more than four drinks in a year (Seattle study); consumed one or more drinks per month for 6 or more months in a lifetime (Los Angeles study); consumed 12 or more drinks of any kind of alcohol in a lifetime (Puerto Rico study); consumed alcoholic beverages one or more times per month (International Multicenter and South America studies); consumed an average of one or more drinks per week for 1 or more years (Iowa study); consumed alcohol one or more times per week for 1 or more years (Tampa and Houston studies); and consumed beer, wine, or liquor four or more times per month (North Carolina study).

The volume specification for alcoholic beverages by type differed across studies. For example, a glass of wine was defined as 100–150 mL in the European studies, whereas the North American studies defined a wine glass as 3.6–5 ounces. To estimate cumulative alcohol consumption (milliliters of beverage over a lifetime) for each beverage type, we converted into milliliters the beverage volume specified in the questionnaire for the alcoholic beverage type and multiplied this value by the number of that beverage type consumed per week and the duration of beverage type consumption reported. We then multiplied the volume percentage of pure ethanol by beverage type (i.e., 5% for beer, 12% for wine, 40% for liquor, and 40% for aperitifs) to the beverage volume (33) to estimate the cumulative consumption of pure ethanol for each subject in milliliters. We then divided the cumulative consumption of pure ethanol by 15.6 mL, the mean volume of pure ethanol per drink across all alcoholic beverage types for the 15 studies, to calculate the lifetime number of standardized drinks consumed by each

subject (i.e., one standardized drink contains 15.6 mL of pure ethanol). Cumulative alcohol consumption was then expressed in drink-years. To obtain the frequency of consumption of each alcoholic beverage type, the cumulative consumption for each type of alcoholic beverage was divided by the corresponding duration. For the overall frequency of alcohol drinking (i.e., the number of drinks per day), the frequency of consumption of each alcoholic beverage type was weighted by the corresponding duration. For the France, Iowa, and Tampa studies, data on duration by type of alcoholic beverage were not available; thus, the average of the frequency of all alcoholic beverage types within those studies was used as the overall frequency.

Data on passive smoking exposure at home and at work (never/ever), which were available in six studies (Central Europe, Tampa, Los Angeles, Houston, Puerto Rico, and South America studies), were pooled. A variable representing the number of first-degree relatives who had head and neck cancer was also pooled across the 12 studies that had assessed this information (Milan, Aviano, Italy Multicenter, Switzerland, Central Europe, North Carolina, Tampa, Los Angeles, Houston, Puerto Rico, South America, and International Multicenter studies).

Statistical Methods

The associations between head and neck cancer and cigarette smoking by drinking status and between head and neck cancer and alcohol drinking by tobacco use status were assessed by estimating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models for each case-control study. The models included age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, or ≥ 75 years), sex, education level (no formal education, less than junior high school, some high school, high-school graduate, vocational/some college, or college graduate/postgraduate), race/ethnicity (non-Hispanic white, black, Hispanic/Latino, Asian/Pacific Islander, Latin American, other), and study center. To calculate summary estimates of associations, the study-specific estimates were included in a two-stage random-effects logistic regression model that included the DerSimonian and Laird (34) estimator, which allows for unexplained sources of heterogeneity among studies. Pooled odds ratios were also estimated with a fixed-effects logistic regression model that adjusted for age, sex, education level, race/ethnicity, and study center. In addition, we adjusted for years of cigar smoking (as a continuous variable) and years of pipe smoking (as a continuous variable) when assessing cigarette smoking among never drinkers. We estimated odds ratios for cigarette smoking for both drinkers and nondrinkers in the same model for each study and odds ratios for alcohol drinking among tobacco users and never users of tobacco so that all the data could be used to estimate confounder relationships.

For subjects with a missing education level (17 case subjects and 80 control subjects among never users of tobacco, 56 case subjects and 108 control subjects among the never drinkers), we applied multiple imputation with the PROC MI procedure in SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC) so that these subjects could be included in the analyses. We assumed that the education data were missing at random, i.e., whether or not education level was missing did not depend on any other unobserved or missing values (35). We used a logistic regression model

(36) to predict education level for each of the geographic regions separately using age, sex, race/ethnicity, study center, and case-control status as the covariates. The logistic regression results to assess summary estimates for cigarettes and alcohol drinking for the five imputations were combined by using the PROC MIANALYZE procedure in SAS statistical software.

We tested for heterogeneity among the study odds ratios by conducting a likelihood ratio test comparing a model that included the product terms between each study (other than the reference study) with the variable of interest and a model without a product terms (degrees of freedom = number of studies - 1), for the risk of head and neck cancer combined and for the risk of each of the head and neck cancer subsites. We report the random-effects estimates for situations in which heterogeneity was detected consistently for assessments of the risk of head and neck cancers associated with cigarette smoking among never drinkers or with alcohol drinking among never users of tobacco. Fixed-effects estimates are reported for all other models. We examined whether the results from the two-stage random-effects model and from the fixed-effects logistic regression model were comparable to each other in terms of the magnitude of the effect. We also conducted an influence analysis, in which each study was excluded one at a time to ensure that the statistical significance and magnitude of the overall summary estimate were not dependent on any one study.

Analyses were stratified by cancer site (oral cavity, pharynx, oral cavity/pharynx not specified, and larynx), age category (≤ 45 , 46–50, 51–60, 61–70, and >70 years), sex, race/ethnicity, education level, source of control subjects (hospital based versus population based), and geographic region (Europe, North America, South/Central America, others). We also repeated the analysis restricting the cases to SCC histology within the set of studies that had collected histology information. All statistical tests were two-sided, and *P* value less than .05 was considered to be statistically significant.

The attributable fraction (AF) for cigarette smoking among never drinkers and for alcohol drinking among never users of tobacco was estimated using the formula $AF = p(ec) \times (OR - 1) / OR$, where *p(ec)* is the proportion exposed among the case subjects (4).

Results

Characteristics of Studies and Subjects

Approximately 15.6% of the case subjects and 26.6% of the control subjects in data version 1.0 were never drinkers and 10.5% of the case subjects and 37.9% of the control subjects were never users of tobacco (Table 1). The International Multicenter study contributed 39.9% of the case subjects and 21.0% of the control subjects who were never drinkers; the majority of these subjects (406 case subjects and 487 control subjects) were from India, where the prevalence of alcohol drinking is low. The International Multicenter and Houston studies contributed the largest proportions of case subjects who were never users of tobacco (19.4% and 17.4%, respectively). Characteristics of case and control subjects who were never drinkers or never users of tobacco are shown in Table 2. The case and control subjects among the never drinkers and among the never users of tobacco differed with respect to distributions of age, sex,

race/ethnicity, and education level. The never drinkers were more likely to be younger than 40 years or 75 years or older, female, and Asian/Pacific Islanders and had less education than the overall group of case subjects. The never users of tobacco were more likely to be younger than 40 years or 75 years or older and female and had completed a higher level of education than the overall group of case subjects.

Cigarette Smoking and Head and Neck Cancer Risk Among Never Drinkers

Cigarette smoking was associated with an increased risk of head and neck cancer among never drinkers, and there were clear dose-response relationships for smoking frequency, duration, and cumulative consumption (Table 3). Figure 1 shows a forest plot of the study-specific risk estimates for ever versus never cigarette smoking among never drinkers and the combined risk estimate (OR for ever versus never cigarette smoking = 2.13, 95% CI = 1.52 to 2.98). Seven studies (i.e., the Milan, Italy Multicenter, Switzerland, North Carolina, Houston, South America, and International Multicenter studies) reported a positive association between ever cigarette smoking and the risk of head and neck cancer in never drinkers. The Milan, Seattle, Iowa, and South America studies contributed the most to heterogeneity among the odds ratios (i.e., excluding them increased the *P* value for heterogeneity from $<.001$ to .208). When these four studies were not included in the summary estimate, the observed association (OR = 2.02, 95% CI = 1.61 to 2.53) was consistent with the results from the full analysis. The results also did not change substantially when we restricted the analysis to large-scale studies (i.e., those with more than 500 case subjects in the individual study). Because a large proportion of the never drinkers were from India, we also estimated the odds ratio after excluding this group of subjects and found that doing so did not change the odds ratio substantially (OR = 2.21, 95% CI = 1.54 to 3.18). The influence analysis showed that no one study was responsible for either the magnitude or the statistical significance of the summary estimate.

We next examined risks associated with specific head and neck cancer subsites. The risk of laryngeal cancer was strongly associated with cigarette smoking among never drinkers, whereas the risk of oral cavity and pharyngeal cancers was not as strong (Table 4). These differences and magnitudes of the risk estimates were not affected by excluding individuals who smoked cigars or pipes or who had chewing or snuff use habits. Exclusion of the subjects from India also did not change the heterogeneity in associations by cancer subsite. No strong differences among the strata were observed in the analysis of cigarette smoking among never drinkers stratified by age, race, ethnicity, education level, or study design (data not shown).

The association between ever smoking and the risk of head and neck cancer among never drinkers was slightly stronger for women (OR = 2.33, 95% CI = 1.56 to 3.49) than for men (OR = 1.65, 95% CI = 1.14 to 2.39), but this difference was not statistically significant; this sex difference was not apparent for associations with smoking frequency and duration categories (data not shown). Cigarette smoking was associated with greater risks of head and neck cancer among never drinkers for studies in Europe (OR for ever versus never smoking = 3.45, 95% CI = 1.90 to 5.89)

Table 2. Selected characteristics of head and neck cancer case subjects and control subjects who were never users of tobacco or never drinkers

Characteristic	Never drinkers*				Never users of tobacco†			
	Case subjects (N = 1598)		Control subjects (N = 4051)		Case subjects (N = 1072)		Control subjects (N = 5775)	
	n	%	n	%	n	%	n	%
Age, y								
<40	120	7.5	339	8.4	128	11.9	499	8.6
40–44	90	5.6	344	8.5	79	7.4	463	8.0
45–49	144	9.0	449	11.1	117	10.9	663	11.5
50–54	215	13.5	608	15.0	134	12.5	896	15.5
55–59	248	15.5	638	15.7	149	13.9	960	16.6
60–64	216	13.5	580	14.3	126	11.8	841	14.6
65–69	190	11.9	493	12.2	98	9.1	698	12.1
70–74	183	11.5	349	8.6	116	10.8	481	8.3
≥75	192	12.0	251	6.2	125	11.7	274	4.7
<i>P</i> ‡								
Sex								
Female	910	56.9	2117	52.3	531	49.5	2735	47.4
Male	688	43.1	1934	47.7	541	50.5	3040	52.6
<i>P</i> ‡								
Race/ethnicity§								
Non-Hispanic white	795	49.7	2586	63.8	763	71.2	4397	76.1
Black	111	6.9	233	5.8	62	5.8	238	4.1
Hispanic/Latino	40	2.5	152	3.8	45	4.2	170	2.9
Asian/Pacific Islander	421	26.3	530	13.1	70	6.5	393	6.8
Other	16	1.0	55	1.4	9	0.8	71	1.2
Latin American	215	13.5	495	12.2	123	11.5	506	8.8
<i>P</i> ‡								
Education level								
No formal education	319	20.0	205	5.1	62	5.8	156	2.7
Less than junior high school	520	32.5	1262	31.2	321	29.9	2317	40.1
Some high school	154	9.6	534	13.2	108	10.1	650	11.3
High-school graduate	197	12.3	653	16.1	150	14.0	641	11.1
Vocational school, some college	183	11.5	633	15.6	171	16.0	889	15.4
College graduate/postgraduate	169	10.6	656	16.2	243	22.7	1042	18.0
Missing	56	3.5	108	2.7	17	1.6	80	1.4
<i>P</i> ‡								

* The definitions of ever alcohol drinking were 1) ever consumed alcohol (France, Central Europe, Aviano, Milan, Italy Multicenter, and Switzerland studies), 2) more than four drinks in a year (Seattle study), 3) one or more drinks per month for 6 or more months in a lifetime (Los Angeles study), 4) 12 or more drinks of any kind of alcohol in a lifetime (Puerto Rico study), 5) one or more times per month (Multicenter, South America studies), 6) average of one or more drinks per week for 1 or more years (Iowa study), 7) one or more times per week for 1 or more years (Tampa and Houston studies), and 8) four or more times per month of beer, wine, or liquor (North Carolina study).

† The definitions of ever cigarette smoking were 1) smoked 100 or more cigarettes in a lifetime (Central Europe, Los Angeles, North Carolina, Puerto Rico, Seattle, and Houston studies), 2) smoked one cigarette/day for 1 or more years (International Multicenter, Tampa, South America, Milan, Aviano, Italy Multicenter, and Switzerland studies), 3) smoked one-half pack per week for 1 or more years (Iowa study), and 4) smoked “regularly” (France study). The definitions of ever cigar and pipe smoking were smoked cigars or pipes for 6 or more months (Seattle, North Carolina, and Puerto Rico studies), smoked one cigar or one pipeful of tobacco per month for 6 or more months (Los Angeles study), smoked one cigar or pipe/day for 1 or more years (Milan, Aviano, Italy, Switzerland, and South America studies), smoked cigars or pipes “regularly” (France and Central Europe studies), ever used cigars or pipes (Houston study), one cigar or one pipeful of tobacco a week for 1 or more years (Iowa), smoked daily for 1 or more years (International Multicenter study), and smoked a cigar or pipe once a day for 1 or more years (Tampa study). The definitions of ever chewing and ever use of snuff differed across studies (i.e., ever use of snuff or chew for ≥6 months [Seattle, North Carolina, and Puerto Rico studies], one small can of snuff or one pouch of chewing tobacco per week for ≥1 year [Iowa study], use chew or snuff once per day for ≥1 year [Tampa study], chewed daily tobacco, betel quid, areca nut, or pan masala or snuffed tobacco daily for ≥1 year [International Multicenter studies], one plug of tobacco or one pinch of snuff of tobacco per month for ≥6 months [Los Angeles study], and ever use of snuff or chew [Houston study]).

‡ Chi-square test (two-sided).

§ Information on ethnicity was not collected in the Central Europe and South America studies. In the Central Europe study, all subjects were classified as non-Hispanic white because the large majority of these populations were white. All subjects in the South American study were categorized as Latin American. We adjusted for study center in all logistic regression models as a proxy variable for race/ethnicity because each center had an expected predominant ethnic group distribution.

|| Information on education level was collected in each study as highest degree earned (Houston, Puerto Rico, Tampa, North Carolina, and Seattle studies), years of education (Iowa, Los Angeles, Italy Multicenter, Aviano, Milan, Switzerland, International Multicenter, and South America studies), or age at last formal education (Central Europe study). The French study did not collect information on education level. In the analysis, for subjects with missing information on education level, we applied multiple imputation (n = 5 imputations), by using a logistic regression model, with age, sex, race/ethnicity, case-control status, and study as predictors for education level, within geographic region.

Table 3. Cigarette smoking among never drinkers and the risk of head and neck cancer*

Smoking variable	Never drinkers		
	Case subjects	Control subjects	OR† (95% CI)
Cigarette smoking			
Never	854	2577	1.00 (referent)
Ever	720	1425	2.13 (1.52 to 2.98)
Missing	24	49	
<i>P</i> for heterogeneity‡			<.001
Frequency, cigarettes/day			
Never smokers	854	2577	1.00 (referent)
1–10	202	481	1.82 (1.28 to 2.59)
11–20	281	601	2.36 (1.60 to 3.47)
21–30	119	154	3.58 (2.09 to 6.16)
31–40	72	102	4.46 (2.54 to 7.83)
>40	37	60	2.69 (1.21 to 5.98)
Missing	33	76	
<i>P</i> _{trend}			<.001
<i>P</i> for heterogeneity‡			<.001
Duration, y			
Never smokers	854	2577	1.00 (referent)
1–10	63	200	1.45 (1.04 to 2.03)
11–20	59	269	1.10 (0.75 to 1.61)
21–30	133	362	1.79 (1.20 to 2.67)
31–40	202	324	3.61 (2.26 to 5.75)
>40	255	249	4.83 (3.18 to 7.33)
Missing	32	70	
<i>P</i> _{trend}			<.001
<i>P</i> for heterogeneity‡			<.001
Cumulative smoking, py			
Never smokers	854	2577	1.00 (referent)
1–10	139	407	1.58 (1.13 to 2.22)
11–20	108	291	1.85 (1.08 to 3.16)
21–30	109	219	2.75 (1.71 to 4.43)
31–40	91	152	4.06 (2.33 to 7.09)
41–50	70	101	3.46 (1.97 to 6.09)
>50	193	219	5.40 (3.06 to 9.53)
Missing	34	85	
<i>P</i> _{trend}			<.001
<i>P</i> for heterogeneity‡			<.001

* OR = odds ratio; CI = confidence interval; py = pack-years; dy = drink-years.

† Random-effects model used. Study-specific odds ratios were adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking (continuous), and years of pipe smoking (continuous).

‡ Two-sided test for heterogeneity among studies.

and South America (OR = 3.58, 95% CI = 1.24 to 10.30) than for studies in India and Sudan (OR = 1.17, 95% CI = 0.78 to 1.76) and North America (OR = 1.20, 95% CI = 0.86 to 1.67). Dose–response trends for the frequency, duration, and pack-years of cigarette smoking were apparent for studies in Europe, South America, and North America, but not for studies in India and Sudan (data not shown).

Alcohol Drinking and Head and Neck Cancer Risk Among Never Users of Tobacco

Among never users of tobacco, there was no association between ever drinking alcohol and the risk of head and neck cancer (OR = 1.18, 95% CI = 0.93 to 1.50; Table 3). Heterogeneity among the study estimates was indicated for ever alcohol drinking (*P* for heterogeneity <.001), for categories of frequency (*P* for heterogeneity =

.006), and for duration (*P* for heterogeneity <.001) of alcohol consumption. In an influence analysis, individual exclusions of the Italy Multicenter study (OR = 1.23, 95% CI = 0.99 to 1.53), the Seattle study (OR = 1.24, 95% CI = 0.99 to 1.54), or the Iowa study (OR = 1.23, 95% CI = 1.01 to 1.51) resulted in borderline statistically significant associations for ever drinking. No dose–response relationship was apparent for the duration of alcohol use and the risk of head and neck cancer among never users of tobacco. However, consuming an increasing number of drinks per day was associated with a greater risk of head and neck cancer among never users of tobacco (*P*_{trend} = .001; Table 5). More specifically, never users of tobacco who consumed three or more alcoholic drinks per day had approximately twice the risk of head and neck cancer as never drinkers (OR = 2.04, 95% CI = 1.29 to 3.21; Fig. 1). The influence analysis confirmed that the increased risk of head and neck cancer associated with consuming three or more drinks per day was not due to any one study. The odds ratios for alcohol drinking did not change substantially when the analysis was restricted to relatively large studies (i.e., those with more than 500 case subjects in the original study). Adjustment for family history of cancer or for passive smoking also did not change the odds ratio for alcohol drinking substantially (data not shown).

An analysis of never users of tobacco stratified by cancer subsite revealed a dose–response relationship, with monotonic increasing risks for the frequency of alcohol consumption on the risks of pharyngeal and laryngeal cancers (Table 6). For pharyngeal cancer, increased risks were observed for subjects who drank one to two drinks per day (OR = 1.66, 95% CI = 1.18 to 2.34), whereas for laryngeal cancer, an increased risk was observed for drinking five or more drinks per day (OR = 2.98, 95% CI = 1.72 to 5.17). Monotonic increasing risks were not observed for the duration of alcohol consumption, even though the *P*_{trend} was statistically significant for all cancer subsites. Differences in risk associated with alcohol consumption were not observed when the analyses of never users of tobacco were further stratified by age, sex, race/ethnicity, education level, study region, or source of control subjects.

Attributable Fractions

Approximately 24% (95% CI = 16% to 31%) of the cases of head and neck cancer among the never drinkers were attributable to ever cigarette smoking, assuming a causal relationship. Among the never users of tobacco, 7% (95% CI = –4% to 16%) of the cases of head and neck cancer were attributable to alcohol drinking, assuming a causal relationship.

Discussion

The results of this pooled analysis confirm previous findings that cigarette smoking is a strong risk factor for head and neck cancer independent of alcohol drinking. Seven of the 15 studies we included showed a statistically significant association between ever having smoked cigarettes and the risk of head and neck cancer in never drinkers, including dose–response relationships for smoking frequency and duration. Based on an earlier review of epidemiologic studies reviewed in the IARC monograph (21), the magnitude of average relative risks for tobacco smoking were 4.0–5.0 for oral cavity cancers, 4.0–5.0 for oro- and hypopharyngeal cancers, and

Fig. 1. The risk of head and neck cancer associated with cigarette smoking in never drinkers of alcohol (left) and with alcohol drinking in never users of tobacco (right), overall and by study, using International Head and Neck Cancer Epidemiology consortium pooled data version 1.0. Odds ratios (ORs) for ever versus never cigarette smoking in never drinkers were adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking, and years of pipe smoking. Odds ratios for drinking three or more alcoholic drinks per day versus never drinking in never users of tobacco were adjusted for age, sex, race/ethnicity, education level, and study center. Study-specific estimates for the Paris, France, study were not available because none of the subjects were never users of tobacco and, among the never drinkers, none of the control subjects were never cigarette smokers. **Squares** = study-specific odds ratios; **size of the square** = the weight given to this study (inverse of the variance of the log odds ratio) when estimating the summary odds ratio; **horizontal lines** = study-specific confidence intervals (CIs); **diamond** = summary estimate combining the study-specific estimates with a random-effects model; **solid vertical line** = odds ratio of 1; **dashed vertical line** = summary odds ratio.

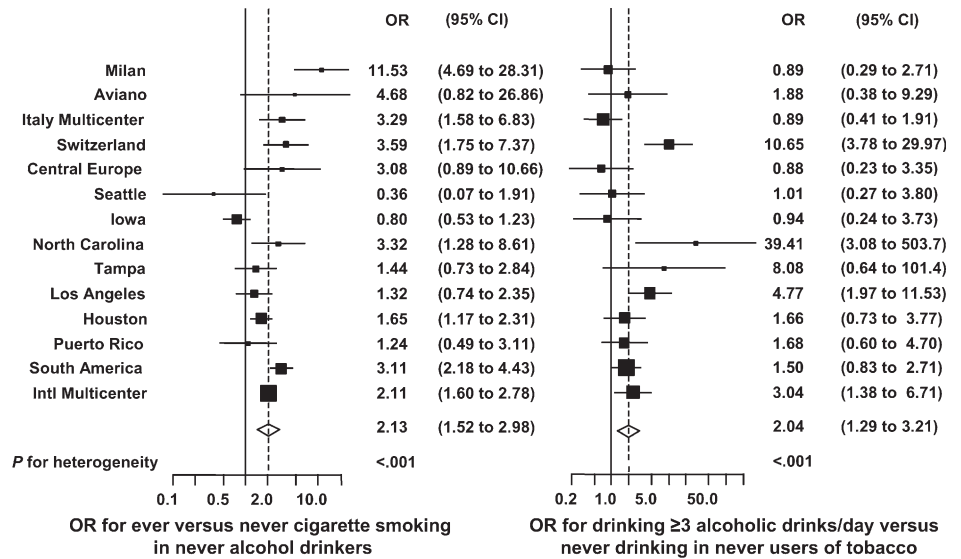


Table 4. Cigarette smoking and the risk of head and neck cancer by subsite among never drinkers*

Variable	Oral cavity† (717 case subjects/4051 control subjects)		Oropharynx/hypopharynx‡ (380 case subjects/3989 control subjects)		Oral cavity/pharynx NOS§ (174 case subjects/3554 control subjects)		Larynx¶ (286 case subjects/3045 control subjects)	
	No. of case subjects/No. of control subjects	OR (95% CI)	No. of case subjects/No. of control subjects	OR (95% CI)	No. of case subjects/No. of control subjects	OR (95% CI)	No. of case subjects/No. of control subjects	OR (95% CI)
Cigarette smoking								
Never	505/2577	1.00 (referent)	168/2530	1.00 (referent)	115/2268	1.00 (referent)	41/1822	1.00 (referent)
Ever	206/1425	1.35 (0.90 to 2.01)	206/1411	2.02 (1.34 to 3.05)	57/1240	1.07 (0.50 to 2.28)	235/1175	6.84 (4.25 to 11.01)
Missing	6/49		6/48		2/46		10/48	
P for heterogeneity¶¶		.019		<.001		.012		<.001
Frequency, cigarettes/day								
Never smokers	505/2577	1.00 (referent)		1.00 (referent)	115/2268	1.00 (referent)	41/1822	1.00 (referent)
1–10	67/481	1.38 (0.80 to 2.38)	168/2530	2.55 (1.59 to 4.10)	21/424	1.55 (0.86 to 2.79)	42/365	5.72 (3.41 to 9.60)
11–20	82/601	1.43 (0.85 to 2.38)	67/473	2.15 (1.38 to 3.34)	17/500	1.08 (0.39 to 2.99)	101/530	8.36 (5.18 to 13.51)
21–30	31/154	1.61 (0.31 to 8.47)	75/596	3.86 (1.80 to 8.25)	11/148	2.68 (1.25 to 5.78)	44/116	14.38 (8.47 to 24.43)
31–40	15/102	2.92 (0.91 to 9.44)	31/154	4.82 (2.42 to 9.60)	4/94	5.46 (0.92 to 33.47)	32/91	18.38 (7.14 to 47.31)
>40	6/60	1.40 (0.30 to 6.61)	18/101	3.10 (1.43 to 6.69)	4/59	6.00 (1.48 to 24.29)	14/47	11.02 (4.92 to 24.72)
Missing	11/76		13/60		2/61		12/74	
P trend		.044		<.001		.001		<.001
P for heterogeneity¶¶		.051		<.001		.003		<.001
Duration, y								
Never smokers	505/2577	1.00 (referent)	168/2530	1.00 (referent)	115/2268	1.00 (referent)	41/1822	1.00 (referent)
1–10	27/200	1.37 (0.84 to 2.23)	19/199	1.69 (1.00 to 2.88)	5/192	1.71 (0.62 to 4.74)	8/171	4.33 (1.13 to 16.62)
11–20	22/269	1.16 (0.64 to 2.10)	17/267	1.18 (0.61 to 2.28)	7/228	2.35 (0.69 to 7.96)	12/233	3.48 (1.61 to 7.50)
21–30	45/362	1.32 (0.92 to 1.91)	32/357	1.47 (0.94 to 2.31)	12/295	2.14 (0.94 to 4.86)	42/298	5.75 (2.94 to 11.23)
31–40	46/324	2.28 (1.19 to 4.37)	65/320	3.74 (2.61 to 5.38)	13/278	2.07 (0.88 to 4.84)	73/271	9.30 (5.40 to 16.02)
>40	62/249	3.23 (1.54 to 6.77)	71/247	4.84 (2.22 to 10.54)	20/226	2.56 (1.29 to 5.07)	98/182	16.32 (9.58 to 27.79)
Missing	10/70		8/69		2/67		12/68	
P trend		.001		<.001		<.001		<.001
P for heterogeneity¶¶		.023		<.001		.030		<.001

* Random-effects model used for all odds ratios. NOS = not otherwise specified; OR = odds ratio; CI = confidence interval.

† Adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking (continuous), and years of pipe smoking (continuous).

‡ Does not include the Central Europe study.

§ Does not include the Switzerland and Central Europe studies.

¶ Does not include the International Multicenter, Seattle, and Puerto Rico studies.

¶¶ Two-sided test for heterogeneity.

Table 5. Alcohol drinkers among never users of tobacco and the risk of head and neck cancer*

Drinking variable	Never users of tobacco		
	Case subjects	Control subjects	OR† (95% CI)
Alcohol drinking			
Never	541	2482	1.00 (referent)
Ever	523	3290	1.18 (0.93 to 1.50)
Missing	8	3	
<i>P</i> for heterogeneity‡			<.001
Frequency, drinks/day			
Never drinkers	541	2482	1.00 (referent)
<1	164	899	1.04 (0.79 to 1.38)
1–2	202	1324	1.30 (0.94 to 1.80)
3–4	59	536	1.82 (1.10 to 2.99)
≥5	65	389	2.81 (1.49 to 5.27)
Missing	41	145	
<i>P</i> _{trend}			.001
<i>P</i> for heterogeneity‡			<.001
Duration, y			
Never drinkers	541	2482	1.00 (referent)
1–10	59	211	1.56 (1.11 to 2.19)
11–20	70	447	1.22 (0.87 to 1.71)
21–30	121	774	1.27 (0.87 to 1.87)
31–40	138	919	1.17 (0.84 to 1.62)
>40 years	106	813	1.05 (0.65 to 1.68)
Missing	37	129	
<i>P</i> _{trend}			.319
<i>P</i> for heterogeneity‡			<.001
Cumulative drinking, dy			
Never drinkers	541	2482	1.00 (referent)
1–10	147	747	1.07 (0.82 to 1.39)
11–20	64	339	1.31 (0.86 to 1.98)
21–30	42	260	1.33 (0.73 to 2.42)
31–40	33	219	1.31 (0.86 to 2.01)
41–50	23	190	1.15 (0.70 to 1.90)
>50	179	1391	1.87 (1.27 to 2.75)
Missing	43	147	
<i>P</i> _{trend}			.003
<i>P</i> for heterogeneity‡			<.001

* OR = odds ratio; CI = confidence interval; py = pack-years; dy = drink-years.

† Random-effects model used. Study-specific odds ratios were adjusted for age, sex, race/ethnicity, education level, and study center.

‡ Two-sided test for heterogeneity among studies.

10.0 for laryngeal cancers (21,37). We did not expect our estimates among never drinkers to be the same as the estimates by Vineis et al. (37), whose analyses were not restricted to never drinkers. Of interest, however, is our finding that the risk was stronger for laryngeal cancer than for oral cavity and pharyngeal cancers, which is consistent with the Vineis estimates. For example, in the review by Vineis et al. (37), the average relative risk of laryngeal cancer was 10-fold higher for ever cigarette users versus never users across 25 case-control studies and five cohort studies, which was similar to the sevenfold increase in risk we observed among never drinkers in our pooled analysis of 15 case-control studies. We estimated increased risks of 1.4-fold for oral cavity cancers and twofold for oro- and pharyngeal cancers, for ever versus never smokers among never drinkers of alcohol. The difference in risk by subsite observed in our study was independent of associations with the use of cigars,

pipes, chewing tobacco, or snuff; exclusion of subjects who had these other tobacco habits from the analysis did not change the differences observed in risk by subsite. These results suggest that the larynx is the organ within the head and neck that is most susceptible to the effects of cigarette smoking. However, the mechanism for this increased susceptibility is unclear.

We also detected heterogeneity by geographic region for the association between cigarette smoking and the risk of head and neck cancer in never drinkers: a higher risk was observed for studies in Europe and South America than for studies in North America. This difference may reflect the fact that cigarettes from different countries and regions differ with respect to their content of nitrosamines, polycyclic aromatic hydrocarbons, and other tobacco carcinogens (38). The content of these compounds in cigarettes is also known to change over time (38). Patterns of smoking, such as the depth of inhalation, were not captured in most of the included studies and may also have varied across and between regions. In addition, sociologic differences among societies may have led to different smoking and drinking practices; for example, because there were fewer smokers who were also never drinkers in the United States than in other countries, the precision of our estimates was decreased for some studies. Additional sources of heterogeneity for the association with cigarette smoking in never drinkers may include the differences across study centers in terms of the relative proportions of case subjects with cancers at different anatomic subsites.

Our results suggest that, in the absence of tobacco use, the association between alcohol consumption and the risk of head and neck cancer is weak and is apparent only at high doses and only for pharyngeal and laryngeal cancers. Dose-response trends for both the frequency and duration of alcohol drinking were strongest for cancers of the pharynx, which suggests that it is the organ within the head and neck that is most sensitive to the carcinogenicity of alcoholic beverages. The finding of an increased cancer risk only at high levels of alcohol intake in never smokers is consistent with results from two studies that were not included in this pooled dataset, one on oral cavity cancer in the United States (26) and the other on head and neck cancers in Brazil (28). There are several possible mechanisms for how alcoholic beverages might exert a carcinogenic effect in the head and neck, including ethanol acting as a solvent for carcinogens, ethanol or its metabolite acetaldehyde damaging DNA, and constituents other than ethanol in alcoholic beverages acting as carcinogens.

Our study has several limitations. First, we applied a global value for the percentage of ethanol found in each alcoholic beverage type (wine, beer, hard liquors). Although the ethanol content of wine and beer is likely to be relatively consistent across countries and regions in the world (33), there is considerable potential for variation in ethanol content among hard liquors that we did not take into account in this study. Case subjects were more likely than control subjects to drink hard liquors; thus, misclassification of alcohol exposures may have been more severe for case subjects than for control subjects, which could have biased the results away from the null. However, this potential misclassification would not affect our estimates for the duration of drinking or for ever drinking, for which we observed associations with the risk of pharyngeal cancer, because we did not apply a global value for the percentage of ethanol for these variables.

Table 6. Alcohol drinking and the risk of head and neck cancer by subsite among never users of tobacco*

Variable	Oral cavity† (383 case subjects/5775 control subjects)		Oropharynx/hypopharynx‡ (369 case subjects/5775 control subjects)		Oral cavity/pharynx NOST,§ (155 case subjects/4983 control subjects)		Larynx¶, (121 case subjects/4602 control subjects)	
	No. of case subjects/ No. of control subjects	OR (95% CI)	No. of case subjects/ No. of control subjects	OR (95% CI)	No. of case subjects/ No. of control subjects	OR (95% CI)	No. of case subjects/ No. of control subjects	OR (95% CI)
Alcohol consumption								
Never	243/2482	1.00 (referent)	153/2482	1.00 (referent)	80/1982	1.00 (referent)	40/1788	1.00 (referent)
Ever	137/3290	1.17 (0.92 to 1.48)	216/3290	1.38 (0.99 to 1.94)	72/2998	1.09 (0.77 to 1.54)	79/2812	1.21 (0.82 to 1.79)
Missing	3/3		0/3		3/3		2/2	
<i>P</i> for heterogeneity¶¶		.087		<.001		.141		.193
Frequency, drinks/day								
Never drinker	243/2482	1.00 (referent)	153/2482	1.00 (referent)	80/1982	1.00 (referent)	40/1788	1.00 (referent)
<1	44/899	1.14 (0.8 to 1.63)	73/899	1.39 (0.99 to 1.96)	25/834	1.08 (0.67 to 1.75)	15/724	0.92 (0.5 to 1.69)
1–2	60/1324	1.64 (1.19 to 2.25)	83/1324	1.66 (1.18 to 2.34)	26/1171	1.24 (0.77 to 1.99)	28/1155	1.26 (0.77 to 2.07)
3–4	10/536	1.11 (0.57 to 2.15)	24/536	2.33 (1.37 to 3.98)	13/495	2.32 (1.24 to 4.34)	11/480	1.24 (0.62 to 2.45)
≥5	8/389	1.23 (0.59 to 2.57)	29/389	5.50 (2.26 to 13.36)	4/382	0.77 (0.27 to 2.18)	22/349	2.98 (1.72 to 5.17)
Missing	18/145		7/145		7/119		5/106	
<i>P</i> _{trend}		.032		<.001		.891		<.001
<i>P</i> for heterogeneity¶¶		.913		<.001		.202		.006
Duration, y								
Never drinker	243/2482	1.00 (referent)	153/2482	1.00 (referent)	80/1982	1.00 (referent)	40/1788	1.00 (referent)
1–10	21/211	2.36 (1.43 to 3.88)	18/211	1.76 (0.99 to 3.14)	13/181	2.59 (1.38 to 4.86)	7/185	2.61 (1.14 to 5.98)
11–20	17/447	1.09 (0.65 to 1.85)	28/447	1.34 (0.81 to 2.11)	11/394	1.09 (0.56 to 2.11)	9/375	1.63 (0.78 to 3.43)
21–30	19/774	0.81 (0.49 to 1.33)	63/774	1.95 (1.37 to 2.77)	18/697	1.26 (0.73 to 2.17)	18/673	1.40 (0.79 to 2.48)
31–40	35/919	1.29 (0.88 to 1.9)	61/919	1.44 (0.78 to 2.66)	14/853	0.86 (0.47 to 1.57)	21/797	1.10 (0.64 to 1.89)
>40	32/813	1.15 (0.77 to 1.73)	37/813	1.51 (0.68 to 3.37)	13/773	0.92 (0.49 to 1.71)	21/677	1.00 (0.58 to 1.73)
Missing	16/129		9/129		6/103		5/107	
<i>P</i> _{trend}		<.001		.003		.014		<.001
<i>P</i> for heterogeneity¶¶		.419		<.001		.585		.350

* NOS = not otherwise specified; OR = odds ratio; CI = confidence interval.

† Fixed-effects model, adjusted for age, sex, race/ethnicity, education level, and study center.

‡ Random-effects model. Study-specific odds ratios adjusted for age, sex, race/ethnicity, and education level.

§ Does not include the Switzerland and Texas studies.

|| Does not include the International Multicenter, Seattle, and Puerto Rico studies.

¶¶ Two-sided test for heterogeneity.

Second, some individuals who had minimal levels of tobacco or alcohol use might have been included in the “never user of tobacco” and “never drinker” categories in the analysis because of the wording on the questionnaires used to establish the “unexposed” groups in some of the studies. The studies with the highest thresholds for classifying an individual as unexposed were the North Carolina study (in which a never drinker was defined as an individual who consumed three or fewer drinks per month), the Iowa study (in which a never cigarette smoker was defined as an individual who smoked less than one-half pack of cigarettes per week for <1 year), and the Tampa or Houston studies (in which a never drinker was defined as an individual who consumed alcohol one or more times per week for one or more years), and the International Multicenter study (in which never use of cigars, pipes, chewing tobacco, or snuff was defined as smoking cigars or pipes, chewing, or snuffing less than daily for <1 year). However, the odds ratios for these studies with the highest thresholds were not substantially higher than would be expected if inclusion of these minimal users had an impact on the associations.

Third, although we excluded the possibility of residual confounding by tobacco in the assessment of alcohol drinking and by alcohol in the assessment of cigarette smoking, we did not adjust for other potential confounders that are associated with the risk of the head and neck cancer, such as human papillomavirus (HPV) infection (19) and diet and nutrition (39,40). However, a recent analysis (41) of data from the International Multicenter study (which were included in this pooled analysis) did not show an inverse association between fruit and vegetable intake and the risks of oral cavity or oropharyngeal cancers among never users of tobacco or never drinkers of alcohol, which suggests that our results are unlikely to be due to confounding by fruit and vegetable intakes. Although HPV infection appears to be an important risk factor for oral cavity and oropharyngeal cancers for never users of tobacco (19), no association between cigarette smoking and HPV infection in the general population or source population of never users of tobacco has been established (42,43). In addition, according to several survey studies (44,45), it seems unlikely that alcohol drinking is associated with HPV infection in either the general

population or in never users of tobacco. Because the criterion that a confounder should be associated with the exposure of interest in the source population is not met, we would not expect HPV to be a major confounder.

Fourth, regional differences in social acceptance of tobacco habits and alcohol consumption may have influenced how a subject responded to questions about these practices in a face-to-face interview. Our adjustment for study center may have partially addressed this limitation, however. Fifth, recall bias was also a potential limitation because in all the studies the subjects knew their disease status when they were interviewed. We explored whether there were differences in the odds ratios by the source of control subjects (hospital based or population based) because hospital-based control subjects could have had similar recall bias to case subjects depending on the type of disease for which they were being treated, but no difference was observed. Thus, we do not believe that recall bias could explain our results.

The major strength of our pooled analyses was assembly of a very large series of never users of tobacco and never drinkers among head and neck cancer patients and control subjects, which allowed us to examine head and neck cancer risks in detail and to explore differences in risks by cancer subsite, geographic region, and sex. To our knowledge, the estimates we present are the most precise estimates available for the independent associations of each of the two main risk factors of head and neck cancer. In summary, cigarette smoking was confirmed as a risk factor for head and neck cancer among never drinkers, and the highest risk was for laryngeal cancer. If the never drinkers had not smoked cigarettes, approximately one-quarter of the head and neck cancers in this group would have been prevented. Alcohol drinking at high frequency was also confirmed as an independent risk factor for head and neck cancers, but the association was limited to cancers of the oropharynx/hypopharynx and larynx.

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