Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2009 February ; 18(2): 541–550. doi: 10.1158/1055-9965.EPI-08-0347.

Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the INHANCE consortium

Mia Hashibe[1], **Paul Brennan**[1], **Shu-chun Chuang**[1], **Stefania Boccia**[2], **Xavier Castellsague**[3], **Chu Chen**[4], **Maria Paula Curado**[1,5], **Luigino Dal Maso**[6], **Alexander W. Daudt**[7], **Eleonora Fabianova**[8], **Leticia Fernandez**[9], **Victor Wünsch-Filho**[10], **Silvia Franceschi**[1], **Richard B. Hayes**[11], **Rolando Herrero**[12], **Karl Kelsey**[13,14], **Sergio Koifman**[15], **Carlo La Vecchia**[16], **Philip Lazarus**[17], **Fabio Levi**[18], **Juan J. Lence**[9], **Dana Mates**[19], **Elena Matos**[20], **Ana Menezes**[21], **Michael D. McClean**[22], **Joshua Muscat**[17], **Jose Eluf-Neto**[10], **Andrew F. Olshan**[23], **Mark Purdue**[11], **Peter Rudnai**[24], **Stephen M. Schwartz**[4], **Elaine Smith**[25], **Erich M. Sturgis**[26], **Neonilia Szeszenia-Dabrowska**[27], **Renato Talamini**[6], **Qingyi Wei**[26], **Deborah M. Winn**[10], **Oxana Shangina**[28], **Agnieszka Pilarska**[29], **Zuo-Feng Zhang**[30], **Gilles Ferro**[1], **Julien Berthiller**[1], and **Paolo Boffetta**[1]

[1] International Agency for Research on Cancer, Lyon, France [2] Institute of Hygiene, Università Cattolica del Sacro Cuore, Rome, Italy [3] Institut Català d'Oncologia, Barcelona, Spain [4] Fred Hutchinson Cancer Research Center, Seattle, WA, USA [5] Hospital Araujo Jorge, Goiania, Brazil [6] Aviano Cancer Centre, Aviano, Italy [7] Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil [8] Specialized State Health Institute, Banskà Bystrica, Slovakia [9] National Institute of Oncology and Radiobiology, Havana, Cuba [10] Universidade de Sao Paulo, Sao Paulo, Brazil [11] National Cancer Institute, Bethesda, MD, USA [12] Instituto de Investigación Epidemiológica, San José, Costa Rica [13] Harvard School of Public Health, Boston, MA [14] Brown University, Providence Rhode Island [15] Escola Nacional de Saude Publica, Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil [16] Istituto di Ricerche Farmacologiche Mario Negri, and University of Milan, Milan, Italy [17] Penn State College of Medicine, Hershey, PA, USA [18] Institut de médecine sociale et préventive, Université de Lausanne, Lausanne, Switzerland [19] Institut of Public Health, Bucharest, Romania [20] Institute of Oncology Angel H. Roffo, University of Buenos Aires, Argentina [21] Universidade Federal de Pelotas, Pelotas, Brazil [22] Boston University School of Public Health [23] UNC School of Public Health, Chapel Hill, NC, USA [24] National Institute of Environmental Health, Budapest, Hungary [25] College of Public Health, University of Iowa, Iowa City, IA, USA [26] UT-M.D. Anderson Cancer Center, Houston, Texas, USA [27] Institute of Occupational Medicine, Lodz, Poland [28] Cancer Research Centre, Moscow, Russia [29] 2nd Maxillofacial Surgery Clinic, Medical Academy, Warsaw, Poland [30] UCLA School of Public Health, Los Angeles, CA, USA

Abstract

Background—The magnitude of risk conferred by the interaction between tobacco and alcohol use on the risk of head and neck cancers is not clear, since studies have used various methods to quantify the excess head and neck cancer burden.

Methods—We analyzed individual-level pooled data from 17 European and American case-control studies (11,221 cases and 16,168 controls) participating in the International Head and

Corresponding author: Mia Hashibe, PhD, Lifestyle, Environment and Cancer Group, Genetics and Epidemiology Cluster, International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon, France, hashibe@iarc.fr, Fax: +33 (0) 4 72 73 83 20.

Neck Cancer Epidemiology (INHANCE) consortium. We estimated the multiplicative interaction parameter (ψ) and population attributable risks (PAR).

Results—A greater than multiplicative joint effect between ever tobacco and alcohol use was observed for head and neck cancer risk (ψ=2.15, 95%CI=1.53–3.04). The PAR for tobacco or alcohol was 72% (95%CI=61%–79%) for head and neck cancer, of which 4% was due to alcohol alone, 33% was due tobacco alone and 35% was due to tobacco and alcohol combined. The total PAR differed by subsite (64% for oral cavity cancer, 72% for pharyngeal cancer, 89% for laryngeal cancer), by sex (74% for men, 57% for women) by age (33% for cases <45 years, 73% for cases >60 years) and by region (84% in Europe, 51% in North America, 83% in Latin America).

Conclusions—Our results confirm that the joint effect between tobacco and alcohol use is greater than multiplicative on head and neck cancer risk. However, a substantial proportion of head and neck cancers cannot be attributed to tobacco or alcohol use, particularly for oral cavity cancer, for head and neck cancer among women and among young onset cases.

Introduction

Over half a million head and neck cancer cases occur each year and is a significant cause of morbidity and mortality(1). The interaction between tobacco and alcohol use is important for head and neck cancer risk (2). Numerous epidemiologic studies have examined the interaction between tobacco and alcohol and the risk of head and neck cancers, but many reports assessed interactions only descriptively, without applying formal statistical testing (2). Some studies tested for the presence of interactions on the additive scale while others tested on the multiplicative scale, and different categories were used for tobacco use and alcohol use. These results are therefore difficult to compare across studies. Due to these limitations, the magnitude of head and neck cancer risk conferred by the interaction between tobacco and alcohol is not clear. Furthermore, it is unknown whether interactions differ by subsite, sex, age or geographic region. Finally, the proportion of cases which can be attributed to tobacco alone, alcohol alone, and tobacco and alcohol combined has not been estimated precisely. Better estimation of attributable risks for tobacco and alcohol may clarify the importance of other known or potential risk factors such as Human Papillomavirus (HPV), high body mass index (BMI) or family history of head and neck cancer.

To evaluate the interaction between tobacco and alcohol and the risk of head and neck cancer, we conducted a pooled analysis within the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Our aim was to (i) formally test the multiplicative model of interaction between alcohol and tobacco use with a very large sample size, (ii) to assess the population attributable risk (PAR) due to the effects of alcohol alone, tobacco alone and tobacco and alcohol combined, and (iii) to examine whether there is heterogeneity in the estimates for interactions by head and neck cancer subsite, as well as due to potential effect modifiers such as sex, age, and geographic region.

Methods

The International Head and Neck Cancer Epidemiology (INHANCE) Consortium (http://inhance.iarc.fr/) was established in 2004, based on the collaboration of research groups leading large epidemiology studies of head and neck cancer that are on-going or have been recently completed. We pooled the data from 18 individual case-control studies (version 1.1), including 12,282 cases and 17,189 controls (3–19). Compared to our previous publication (20), the current dataset added a Rome study(5), New York multicenter study(14) and Boston study(16). In this current analysis, we excluded from the analyses a

French study (323 cases and 234 controls) that was restricted to regular smokers (4) and the Sudan (106 cases and 151 controls) and India (576 cases and 582 controls) centers of the International Multicenter study(12) because of the small number of subjects to represent these regions for estimation of population attributable risks. Additionally in India, contrary to other countries, betel quid and areca nut chewing are major contributors to attributable fractions of oral cavity cancer.

Characteristics of the individual studies are presented in table 1 in the appendix. Most were hospital-based case-control studies and frequency matched their controls to the cases on age, sex and additional factors (study center, hospital, race/ethnicity). The Los Angeles study individually matched the control subjects to case subjects on age decade, gender and neighborhood, though in the 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 institutional review boards at each of the institutes involved. 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 and inconsistencies were resolved as necessary.

Cases and controls with missing data on age, sex, or race/ethnicity, and cases with missing information on the site of origin of their cancer were excluded (56 cases and 54 controls). Cases were included in this study if their tumor had been classified by the original study as an invasive tumor of oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified (NOS), larynx, or head and neck cancer unspecified. Subjects with cancers of the major salivary glands (parotid, submandibular, or sublingual glands; ICD-O-2 codes C07-C08), or of the nasal cavity/ear/paranasal sinuses (ICD-O-2 codes C30-C31) were excluded from the analysis. The ICD coding used for the classification into subsites was specified in detail previously(20). Thus the data for this analysis included 11,221 head and neck cancer cases and 16,168 controls from 17 studies. There were a total of 2,993 oral cavity cancer cases, 4,040 oropharyngeal and hypopharyngeal cancer cases (pharyngeal), 917 unspecified oral cavity/pharynx cases, 2,965 laryngeal cancer cases and 306 unspecified head and neck cancer cases. We focused our site-specific analyses on oral cavity, pharyngeal and laryngeal cancers. Three of the studies did not collect information on tumor histology. Of the studies that collected histology, 86.7% (8034/9265) of head and neck cancer cases were squamous cell carcinoma (SCC).

The questions about tobacco smoking and alcohol drinking in the 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 analysis (definitions for being a cigarette, cigar, or pipe smoker for each study are provided in the appendix). 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.

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 Latin America, except in specific populations (e.g., Norway and Sweden) that were not included in the pooled dataset (definitions of ever chewing and ever use of snuff are provided in the appendix). 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. A combined tobacco frequency variable was created, where ever tobacco users were categorized as having used 1–20 cigarettes, 1–20 cigars, 1–20 pipes, 1–2 chewing products or 1–2 snuff units per day, or >20 cigarettes, >20 cigars, >20 pipes, >2 chewing products or >2 snuff units per day.

In the alcohol section of the study questionnaires, subjects were asked if they were alcohol drinkers (definitions by study in appendix); 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 aperitif). Details on the pooling of frequency and duration variables on alcohol are provided in the appendix.

Statistical methods

The interactions between tobacco and alcohol on the risk of head and neck cancer were assessed by estimating odds ratios (ORs) and 95% confidence intervals (95%CIs) using unconditional logistic regression models for each study. To assess interactions on the multiplicative scale, we estimated odds ratios for joint effects (OR_{11}= OR for ever tobacco/ever alcohol use, OR_{01}=OR for never tobacco/ever alcohol use, OR_{10} = OR for ever tobacco/never alcohol use). The multiplicative interaction parameters & 95%CIs [$\psi=OR_{11}/(OR_{01} * OR_{10})$] were also estimated by including variables for ever alcohol use, ever tobacco use and a product term (equivalent to the multiplicative interaction parameter) of those two variables in the logistic regression model. $\psi>1$ is suggestive of a joint effect that is greater than expected under the multiplicative model. When a joint effect greater than multiplicative was not observed, interactions on the additive scale were assessed with relative excess risk due to interaction (RERI), attributable proportion (AP, proportion of disease among those with both exposures that is attributable to their interaction) and synergy index (SI)(21). We estimated 95% confidence intervals for each of these measures. The null values of RERI and AP are 0, while the null value for SI is 1.

The logistic regression models included age (<40 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 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, other, Latin American), and study center to adjust for potential confounders. We tested for heterogeneity among the study ORs by conducting a likelihood ratio test comparing a model including the product terms between each study (other than the reference study) with the variable of interest and a model without the 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 these head and neck cancer subsites. Heterogeneity was detected consistently; therefore, to calculate the summary estimates of association, the study-specific estimates were included in a two-stage random effects logistic regression model with between-study variability and the common odds ratio being estimated using maximum likelihood estimation.

Information on ethnicity was not collected in the Central Europe and Latin America studies. In the Central Europe study, all subjects were classified as non-Hispanic White, since the large majority of these populations are expected to be White. In the Latin American study, we categorized subjects as Latin American. For the Latin America study only, study center was used as a proxy variable for race/ethnicity in all logistic regression models because each center had an expected predominant ethnic group distribution.

For subjects with missing data on education level (655 cases and 544 controls), we applied multiple imputation with the PROC MI procedure in SAS statistical software 9.1. We assumed that the education data were missing at random (MAR) with respect to unmeasured covariates; whether or not education level was missing did not depend on any other unobserved or missing values (22). We used a logistic regression model (23) to predict education level for each of the geographic regions separately (North America, Europe, Latin America) using age, sex, race/ethnicity, study, and case/control status as the covariates. The logistic regression results to assess summary estimates for cigarettes and alcohol drinking for five imputations were combined by using the PROC MIANALYZE procedure in SAS statistical software.

Stratified analyses were conducted by cancer site (oral, pharynx, larynx), sex, age (<45 years, 45–60 years, ≥60 years), education (<high school, ≥high school), geographic region (Europe, North America, Latin America), type of controls (hospital-based, population-based), study size (<500 cases, ≥500 cases), BMI 2 to 5 years before diagnosis (<18.5 kg/m^2, 18.5 –<25 kg/m^2, 25 – <30 kg/m^2, ≥30 kg/m^2) and BMI at age 20 or 30 and after restriction to squamous cell carcinoma cases.

The population attributable risks (PAR) were estimated based on the formula AF = p(ec) × (OR−1)/OR, where p(ec)is the proportion exposed among the cases (24). Odds ratios adjusted for potential confounding factors were used in these equations. The confidence intervals for the AFs were calculated from the lower and upper limit ORs. The PAR for tobacco and/or alcohol exposures (PAR_{total}) were estimated with the equation below where a_{00}=never tobacco/never alcohol users, a_{01}= never tobacco/ever alcohol users, a_{10}= ever tobacco/never alcohol users, and a_{11}=ever tobacco/ever alcohol users, m = total number of cases.

$$PAR_{total}=1-[((a_{11}/m)/OR_{11})+((a_{10}/m)/OR_{10})+((a_{01}/m)/OR_{01})+((a_{00}/m)/OR_{00})]$$

ORs from multivariate analysis were used. The PARs for the tobacco and alcohol were estimated as (31):

$$PAR_{\text{tobacco and alcohol combined}}=PAR_{\text{tobacco}}+PAR_{\text{alcohol}}-PAR_{\text{total}}$$
$$PAR_{\text{tobacco alone}}=PAR_{\text{tobacco}}-PAR_{\text{tobacco and alcohol combined}}$$
$$PAR_{\text{alcohol alone}}=PAR_{\text{alcohol}}-PAR_{\text{tobacco and alcohol combined}}$$

Results

Characteristics of cases and controls are shown in Table 1. The Latin America and New York multicenter studies contributed the largest proportion of cases. There were a higher proportion of men among cases compared to the controls. The majority of cases and controls were European in ethnic origin. Cases had completed lower levels of education than the controls.

The odds ratios were 2.37 (95%CI=1.66–3.39) for ever tobacco use among never alcohol drinkers, 1.06 (95%CI=0.88–1.28) for ever alcohol use among never tobacco users, and 5.73 (95%CI=3.62–9.06) for the joint effect according to the random effects model (results not shown). Thus, the joint effect between tobacco and alcohol was greater than expected under the multiplicative model for all head and neck cancers (ψ=2.15, 95%CI=1.53–3.04; Table 2). The ψ from the random effects model was not exactly equal to that calculated from the joint effects estimates (5.73/(2.37*1.06) = 2.28 ≠ 2.15), possibly due to the coefficient

allowing for unknown sources of heterogeneity in the random effects models. For the fixed effects model, the ORs were 2.17 for ever tobacco use among never alcohol drinkers, 0.98 for ever alcohol use among never tobacco users, 5.04 for the joint effect and 2.38 for the ψ. Thus the ψ calculated from the joint effects was similar to that of the ψ from the model (5.04/(2.17*0.98) = 2.37 ≈ 2.38).

By subsite, joint effects greater than multiplicative were observed for oral cavity cancer (ψ=3.09, 95%CI=1.82–5.23) and pharyngeal cancer (ψ=1.90, 95%CI=1.41–2.56; Table 2). For laryngeal cancer, the ψ was consistent with an interaction that is greater than multiplicative but the confidence interval included the null value (ψ=1.62, 95%CI=0.85–3.09). A more than additive interaction was detected between tobacco and alcohol for laryngeal cancer risk (RERI=4.97, 95%CI=3.16–6.78; AP=0.42, 95%CI=0.32–0.52; SI=1.85, 95%CI=1.50–2.26; data not shown). The study specific ψs are shown for head and neck cancer in Figure 1 and for the subsites in supplementary figures S1–S3. Statistically significant differences were not observed in the ψs for head and neck cancer, oral cavity cancer, pharyngeal cancer or laryngeal cancer, in the different strata of education, study size, source of controls or BMI (results not shown). The analysis restricted to SCCs (8034 cases) resulted in a ψ similar to the overall analysis (ψ=2.27, 95%CI=1.52–3.38). Adjustment for family history of head and neck cancer or ever passive smoking did not alter the magnitude of the iORs.

The population attributable risk (PAR) for tobacco and alcohol, alone and overlapped was 72% (95%CI=61–79) for head and neck cancer, of which 4% was for alcohol alone, 33% was for tobacco alone and 35% was for overlap between tobacco and alcohol (Table 2). Comparing across cancer subsites, the PAR for oral cavity cancer was lower (64%, 95%CI=45–75) than for laryngeal cancer (89%, 95%CI=82–92), while the PAR for pharyngeal cancer was intermediate to those of oral cavity and laryngeal cancer. For women, the PAR for head and neck cancer, appeared to be lower than for men. The overall PAR is probably closer to the PAR for men since the majority of cases and controls are men. The PARs due to the overlap of tobacco and alcohol were greater than the PARs due to the effects of tobacco alone on the risk of head and neck cancer among men, but not for women. The estimated PAR due to the effect of alcohol alone was negative for oral cavity, although as indicated by the CIs, this is consistent with either no effect of alcohol alone (PAR=0%) or a very small effect.

When stratified by age and by geographic region, the ψs were fairly similar across age strata, but the PARs were substantially lower among subjects <45 years of age compared to subjects who were 45 or older. The PARs were also lower in North America, relative to the PARs in Europe and Latin America.

In Table 3, the odds ratios and PARs for head and neck cancer by tobacco and alcohol frequency categories are shown. The cancer risk was greatest for individuals in the high frequency categories for tobacco and alcohol use. An interaction was suggested between the frequency of tobacco and alcohol use on the risk of head and neck cancer ($p<0.01$), oral cavity cancer ($p<0.01$), pharyngeal cancer ($p<0.01$), but not on the risk of laryngeal cancer ($p=0.63$). The PARs indicate that the greatest proportion of the head and neck cancers were attributable to heavy drinking (≥3 drinks/day) among smokers.

Discussion

Our results confirm a greater than multiplicative joint effect between tobacco and alcohol on head and neck cancer risk, particularly for oral and pharyngeal cancers. Heterogeneity in the multiplicative interaction parameters was not detected in the analysis stratified by anatomic

subsite, sex, education level, geographic region, or BMI. Tobacco smoking and alcohol drinking are responsible for a large proportion of oral and pharyngeal cancers, and an even greater proportion of laryngeal cancers. Additionally, tobacco smoking and alcohol drinking account for a higher proportion of head and neck cancers among men than among women. Generally for men, tobacco and alcohol combined accounted for a larger proportion of cases than smoking or drinking alone, while for women the effect of tobacco alone accounted for a larger proportion of cases than the overlap between tobacco and alcohol, or alcohol alone. Our estimates for PARs are consistent with previous estimates from a large-scale case-control study on oral and pharyngeal cancers (not included in current INHANCE dataset) which reported PARs of 80% for men, 61% for women and 74% overall (25). It will be important to determine the risk factors for at least 28% of head and neck cancer patients (42% for women, 26% for men) and specifically for at least 36% of oral cavity cancer patients, whose cancer cannot be attributed to tobacco or alcohol.

The differences observed for the multiplicative interaction parameter did not necessarily translate to differences in the PARs, or vice versa. The ψ appeared to be greater for oral cavity cancer than for laryngeal cancer, but the PAR for oral cavity cancer was lower than that of laryngeal cancer. The difference stemmed from the greater ORs observed for laryngeal cancer for subjects who smoked tobacco (regardless of whether they drank alcohol or not), relative to oral cavity and pharyngeal cancers. Similarly, although differences in the ψs were not observed by geographic region, we observed a statistically significant lower PAR for tobacco and alcohol in North America relative to Latin America and Europe. The source of this difference may be the larger proportion of cases that drank alcohol and smoked tobacco in Latin America and Europe in comparison to North America and the higher ORs observed for tobacco and tobacco and alcohol combined. The difference in risk for tobacco may reflect the differences in the types of cigarettes and tobacco used. This may point to a more important role for other risk factors in North America. Studies of HPV in North America provide some preliminary evidence that this may be true (26;27) in contrast to a study including cases mostly from Europe(12).

Tobacco and alcohol appeared to be responsible for a smaller proportion of the head and neck cancer cases in individuals who were younger (<45 years) compared to the older age groups. The number of cases and controls in subjects <45 years was limited (though larger than any previous study), as reflected in the odds ratio estimate for smoking tobacco. The younger subjects also had a lower proportion of cases that drank alcohol and smoked tobacco. It is possible that other head and neck cancer risk factors such as genetic susceptibility, human papillomavirus infection or some nutritional factors are more important risk factors in these groups, although further work is required to clarify this.

Though the PAR for the effect of alcohol alone was negative for oral cavity cancer and among young subjects, this should not be interpreted as evidence that alcohol prevented any cancers. The main effect OR for alcohol drinking overall and among never tobacco users were not <1 for head and neck cancer or any of the subsites. In our previous analysis, we showed that alcohol is an independent risk factor among never-tobacco users(20). The confidence intervals of the PAR for the effect of alcohol alone generally included the null value of 0%. These results suggest that either alcohol is acting only through its interaction effect with tobacco or that the PAR of alcohol alone is minimal and difficult to detect without greater statistical power. Significant PARs for the effect of alcohol alone were detected for the larger case groups of head and neck cancer and pharyngeal cancer, favoring the latter explanation.

There are several limitations in our pooled analysis. One potential source of bias is that regional differences in social acceptance of tobacco and alcohol habits may have influenced

how a subject responded to questions in a face-to-face interview. Our adjustment for study center may have partially addressed this limitation. Recall bias was also a potential limitation because in all of the studies the subjects knew their disease status when they were interviewed. We explored whether there were differences in the ψ by the type of control subjects (hospital-based or population-based), since hospital-based controls but not population-based controls could also have a recall similar to that of cases depending on the type of disease. The estimates by type of control were not different, suggesting a minimal role for recall bias.

Another limitation is that we are unable to adjust for unmeasured potential confounders such as HPV infection and nutritional factors. Low fruit and vegetable intake is a suspected risk factor of head and neck cancer (28). However, low fruit intake and low vegetable intake may increase risk by approximately 2 fold (29), which could not explain the magnitude of the ORs observed in some of the higher combination categories of tobacco and alcohol intake. It would be of interest to examine the three-way interaction for tobacco use, alcohol use and low fruit and vegetable intake on head and neck cancer risk. HPV infection is thought to be a stronger risk factor for oropharyngeal cancers (30), but the multiplicative interaction parameters were not particularly stronger for pharyngeal cancer. However, our pharyngeal group included hypopharyngeal cases in addition to oropharyngeal cases. Because hypopharyngeal cancer has very strong associations with tobacco and alcohol, this may have resulted in higher PARs than may have been seen for a pharyngeal group restricted to oropharyngeal cancers. In any case, we believe it is unlikely that our results are due to confounding by HPV. We hope to explore this area in the future when HPV data may be available with a standardized measure across the INHANCE studies.

The major strength of our pooled analyses was the assembling of a very large series of head and neck cancer patients and control subjects, which allowed us to examine in detail the interaction between tobacco smoking and alcohol drinking, and explore differences in the interaction by cancer subsite, geographic region, and sex. Our results confirm that the joint effect between tobacco and alcohol is more than expected under the multiplicative model for head and neck cancer and the oral and pharyngeal subsites. Tobacco and alcohol are responsible for a large proportion of laryngeal cancers and head and neck cancer among men. However, a substantial proportion of head and neck cancers cannot be attributed to either tobacco or alcohol, particularly for oral cavity cancer, among women and below age 45.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the US National Institutes of Health, National Cancer Institute (R03CA113157). Dr. Shu-chun Chuang was supported by a Special Training Award from the International Agency for Research on Cancer.

The individual studies were funded by the following grants:

1. Milan study: Italian Association for Research on Cancer (AIRC)
2. Aviano and Italy Multicenter studies: Italian Association for Research on Cancer (AIRC), Italian League Against Cancer, Italian Ministry of Research
3. Swiss study: Swiss League against Cancer and the Swiss Research against Cancer/Oncosuisse (KFS-700 and OCS-1633)

4. Central Europe study: World Cancer Research Fund and the European Commission's INCO-COPERNICUS Program (Contract No. IC15-CT98-0332)
5. New York study: US NIH grants P01CA068384 and K07CA104231
6. Seattle study: US NIH grants R01CA048896 and R01DE012609
7. Boston study: US NIH grants R01CA078609 and R01CA100679
8. Iowa study: US NIH grants R01DE11979, R01DE13110, NIH FIRCA TW01500, and Veterans Affairs Merit Review Funds.
9. North Carolina study: US NIH grants R01CA61188 and P30ES010126
10. Tampa study: US NIH grants P01CA068384 and K07CA104231
11. Los Angeles study: US NIH grants P50CA90388, R01DA11386, R03CA77954, T32CA09142, U01CA96134, and R21ES011667, as well as the Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center
12. Houston study: US NIH grants R01ES11740 and R01CA100264
13. Puerto Rico study: jointly funded by NCI and NIDCR intramural programs.
14. Latin America study: FONCYT (Fondo para la Investigacion Cientifica y Tecnologica) Argentina, IMIM (Barcelona), Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP) No 01/01768-2, European Commission (IC18-CT97-0222)
15. IARC Multicenter study: Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government (FIS 97/0024, FIS 97/0662, and BAE 01/5013), International Union Against Cancer (UICC), Yamagiwa-Yoshida Memorial International Cancer Study Grant

Reference List

1. Ferlay, J.; Bray, F.; Pisani, P.; Parkin, DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide, Version 2.0. IARC Cancer Base No. 5. Lyon, France: IARC Press; 2004.
2. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1–1438. [PubMed: 15285078]
3. Baron AE, Franceschi S, Barra S, Talamini R, La Vecchia C. A comparison of the joint effects of alcohol and smoking on the risk of cancer across sites in the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 1993;2:519–23. [PubMed: 8268767]
4. Benhamou S, Tuimala J, Bouchardy C, Dayer P, Sarasin A, Hirvonen A. DNA repair gene XRCC2 and XRCC3 polymorphisms and susceptibility to cancers of the upper aerodigestive tract. Int J Cancer 2004;112(5):901–4. [PubMed: 15386379]
5. Boccia S, Cadoni G, Sayed-Tabatabaei FA, Volante M, Arzani D, De Lauretis A, Cattel C, Almadori G, van Duijn CM, Paludetti G, Ricciardi G. CYP1A1, CYP2E1, GSTM1, GSTT1, EPHX1 exons 3 and 4, and NAT2 polymorphisms, smoking, consumption of alcohol and fruit and vegetables and risk of head and neck cancer. J Cancer Res Clin Oncol 2007;134:93–100. [PubMed: 17611777]
6. Bosetti C, Gallus S, Trichopoulou A, et al. Influence of the Mediterranean diet on the risk of cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 2003;12(10):1091–4. [PubMed: 14578148]
7. Cui Y, Morgenstern H, Greenland S, et al. Polymorphism of Xeroderma Pigmentosum group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. Int J Cancer 2006;118(3):714–20. [PubMed: 16094634]
8. Elahi A, Zheng Z, Park J, Eyring K, McCaffrey T, Lazarus P. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis 2002;23(7):1229–34. [PubMed: 12117782]
9. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res 1990;50(20):6502–7. [PubMed: 2208109]
10. Hashibe M, Boffetta P, Zaridze D, Szeszenia-Dabrowski N, Mates D, Janout V, Fabianova E, Bencko V, Brennan P. Evidence for an important role of alcohol and aldehyde metabolizing genes

in head and neck cancer susceptibility. Cancer Epidemiol Biomarkers Prev 2006;15:696–703. [PubMed: 16614111]

11. Hayes RB, Bravo-Otero E, Kleinman DV, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. Cancer Causes Control 1999;10(1):27–33. [PubMed: 10334639]
12. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 2003;95(23): 1772–83. [PubMed: 14652239]
13. Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S, Monnier P. Food groups and risk of oral and pharyngeal cancer. Int J Cancer 1998;77:705–9. [PubMed: 9688303]
14. Muscat JE, Richie JP Jr, Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. Cancer Res 1996;56:5192–7. [PubMed: 8912856]
15. Olshan AF, Weissler MC, Watson MA, Bell DA. GSTM1, GSTT1, GSTP1, CYP1A1, and NAT1 polymorphisms, tobacco use, and the risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2000;9(2):185–91. [PubMed: 10698480]
16. Peters ES, McClean MD, Liu M, Eisen EA, Mueller N, Kelsey KT. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. Cancer Epidemiol Biomarkers Prev 2005;14(2):476–82. [PubMed: 15734975]
17. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res 2004;64(11):4049–54. [PubMed: 15173020]
18. Wang D, Ritchie JM, Smith EM, Zhang Z, Turek LP, Haugen TH. Alcohol dehydrogenase 3 and risk of squamous cell carcinomas of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14(3):626–32. [PubMed: 15767341]
19. Zhang Z, Shi Q, Liu Z, Sturgis EM, Spitz MR, Wei Q. Polymorphisms of methionine synthase and methionine synthase reductase and risk of squamous cell carcinoma of the head and neck: a case-control analysis. Cancer Epidemiol Biomarkers Prev 2005;14(5):1188–93. [PubMed: 15894670]
20. Hashibe M, Brennan P, Benhamou S, et al. 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. J Natl Cancer Inst 2007;99(10): 777–89. [PubMed: 17505073]
21. Lundberg M, Fredlund P, Hallqvist J, Diderichsen F. A SAS program calculating three measures of interaction with confidence intervals. Epidemiology 1996;7:655–6. [PubMed: 8899400]
22. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255–64. [PubMed: 7503045]
23. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John WIley and Sons, Inc; 1987.
24. Rothman, KJ.; Greenland, S.; Lash, TL. Modern Epidemiology. 3. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; 2008.
25. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48(11):3282–7. [PubMed: 3365707]
26. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356(19):1944–56. [PubMed: 17494927]
27. Smith EM, Ritchie JM, Pawlita M, et al. Human papillomavirus seropositivity and risks of head and neck cancer. Int J Cancer 2007;120(4):825–32. [PubMed: 17131312]
28. IARC. Fruits and Vegetables. Vol. 8. Lyon: IARC publications; 2003. Handbooks of Cancer Prevention.
29. Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. Am J Clin Nutr 2006 May; 83(5):1126–34. [PubMed: 16685056]
30. IARC Monogr Eval Carcinog Risks Hum. 2007. Human Papillomavirus; p. 90
31. Kleinbaum, DG.; Kupper, LL.; Morgenstern, H. Epidemiologic Research: Principles and Quantitative Methods. New York: Van Nostrand Reinhold; 1982.
32. Alcohol drinking. IARC Monogr Eval Carcinog Risks Hum; IARC Working Group; Lyon. 13–20 October 1987; 1988. p. 1-378.

Appendix

Definition of tobacco and alcohol use

For cigarettes, ever smoking was defined as smoked ≥100 cigarette in a lifetime [Central Europe, Los Angeles, North Carolina, Puerto Rico, Seattle, Houston and Boston studies]; smoked 1 cigarette/day for ≥1 year [International Multicenter, Tampa, Latin America, Milan, Aviano, Italy multicenter, and Switzerland studies]; smoked ½ pack/week for ≥1 year [Iowa study], once a day for one years time [New York]; ever smoked [Rome study].

For cigars and pipes, ever smoking was defined as smoked cigars or pipes for ≥6 months [Seattle, North Carolina, and Puerto Rico studies]; smoked 1 cigar or 1 pipeful of tobacco/month for ≥6 months [Los Angeles study]; smoked 1 cigar or pipe/day for ≥1 year [Milan, Aviano, Italy, Switzerland, Latin America]; smoked cigars or pipes “regularly” [Central Europe studies]; once a day for 1 years time [New York study]; ever used cigars or pipes [Houston study]); 1 cigar or 1 pipefuls of tobacco a week for ≥1 year [Iowa]; smoked daily for >1 year [International multicenter study]; smoked a cigar or pipe once a day for ≥1 year [Tampa study]; ever smoked 12 ounces of pipe tobacco or smoked 1 cigar/week for 1 year [Boston study] and ever smoked cigars or pipes [Rome study].

The definitions of ever chewing and ever use of snuff differed across studies: ever use of snuff or chew for ≥6 months [Seattle, North Carolina, and Puerto Rico studies]; 1 small can of snuff or 1 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, pan massala or snuffed tobacco daily for ≥1 year [International Multicenter studies]; 1 plug of tobacco or 1 pinch of snuff of tobacco/month for ≥6 months [Los Angeles study]; at least once a week for at least one year [New York]; ever use of snuff or chew [Houston and Rome studies] and ever chewed smokeless tobacco [Boston study].

The definitions of ever alcohol drinking were: ‘ever’ consumed alcohol [Central Europe, Aviano, Milan, Italy Multicenter, Switzerland, New York, Boston and Rome studies]; >4 drinks in a year [Seattle study]; ≥1 drink/month for ≥6 months in a lifetime [Los Angeles study); ≥12 drinks of any kind of alcohol in a lifetime [Puerto Rico study]; ≥once/month (Multicenter, Latin America studies); average ≥1 drink/week for ≥1 year [Iowa study]; once/week for ≥1 year [Tampa & Houston study]; ≥4 times/month of beer, wine or liquor (North Carolina study).

Pooling alcohol variables

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 (mL 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 beverage type consumed per week and the duration of beverage type consumption reported. We then applied the volume percentage of pure ethanol by beverage type [5% for beer, 12% for wine, 40% for liquor and 40% for aperitifs to the beverage volume(32)], to estimate the cumulative consumption of pure ethanol for each subject in mL. 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 for each subject (ie, one standardized drink contains 15.6 mL of pure ethanol). For the overall frequency of alcohol drinking (i.e., the number of drinks/day), the frequency of consumption of each alcoholic beverage type was weighted by the corresponding duration. For the 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.

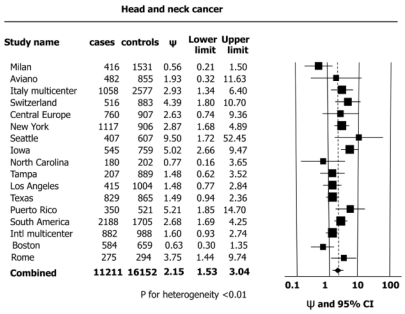

Figure 1.

Multiplicative interaction parameters (ψ) for tobacco (cigarette, cigar, pipe, snuff, chewing tobacco) and alcohol study and combined, using INHANCE pooled data version 1.1. ORs used to calculate ψ were adjusted for age, sex, race/ethnicity, education level.

Table 1

Selected characteristics of head and neck cancer cases and controls

	Cases		Controls	
	n	%	n	%
TOTAL	**11221**		**16168**	
Study				
Milan	416	3.7	1531	9.5
Aviano	482	4.3	855	5.3
Italy Multicenter	1058	9.4	2579	16.0
Switzerland	516	4.6	883	5.5
Central Europe Multicenter	762	6.8	907	5.6
Rome	275	2.5	294	1.8
New York Multicenter	1118	10.0	906	5.6
Seattle	407	3.6	607	3.8
Iowa	546	4.9	759	4.7
North Carolina	180	1.6	202	1.2
Tampa	207	1.8	897	5.5
Los Angeles	417	3.7	1005	6.2
Texas	829	7.4	865	5.4
Boston	584	5.2	659	4.1
Puerto Rico	350	3.1	521	3.2
Latin America Multicenter	2191	19.5	1706	10.6
IARC Multicenter[1]	883	7.9	992	6.1
Age				
<40	415	3.7	1023	6.3
40–44	629	5.6	1151	7.1
45–49	1223	10.9	1800	11.1
50–54	1714	15.3	2487	15.4
55–59	2096	18.7	2801	17.3
60–64	1901	16.9	2531	15.7
65–69	1555	13.9	2064	12.8
70–74	1024	9.1	1517	9.4
≥75	664	5.9	794	4.9
Sex				
Women	2256	20.1	4557	28.2
Men	8965	79.9	11611	71.8
Race/ethnicity				
White	8272	73.7	13358	82.6
Black	403	3.6	485	3.0
Hispanic	164	1.5	350	2.2
Asian/Pacific Islanders	53	0.5	86	0.5
Other	138	1.2	183	1.1

	Cases		Controls	
	n	%	n	%
Latin American	2191	19.5	1706	10.6
Education				
None	93	0.8	106	0.7
<Junior high school	4347	38.7	6169	38.2
Some high school	1576	14.0	1784	11.0
High School Graduate	1765	15.7	2163	13.4
Vocational, some college	1368	12.2	2514	15.5
≥College	1417	12.6	2888	17.9
Missing	655	5.8	544	3.4
Subtype				
Oral	2993	26.7		
Pharynx	4040	36.0		
Oral/Pharynx NOS	917	8.2		
Larynx	2965	26.4		
H&N NOS	306	2.7		

[1] We excluded the Sudan (100 cases and 102 controls) and India (576 cases and 582 controls) centers of the International Multicenter study because the Asia and Africa regions are not well represented for estimation of population attributable risks.

[2] Information on ethnicity was not collected in the Central Europe and Latin America studies. In the Central Europe study, all subjects were classified as non-Hispanic White, since the large majority of these populations are expected to be White. In the Latin American study, we categorized subjects as Latin American.

Table 2

Tobacco and alcohol multiplicative interaction parameters and attributable risks for head and neck cancer and subsites

	Cases		Controls		OR[1]	95%CI	PAR[2]	95%CI	
	N	%	N	%					
Head and neck cancer overall									
Alcohol alone	831	7.4	1587	9.8	1.06	(0.88, 1.28)	4.0	1.5	5.3
Tobacco alone	673	6.0	3653	22.6	2.37	(1.66, 3.39)	33.0	42.6	25.9
Tobacco and alcohol	9146	81.6	8574	53.1	5.73	(3.62, 9.06)	34.9	17.2	48.0
TOTAL	11211		16152		Ψ=2.15	(1.53, 3.04)	**72.0**	**61.2**	**79.1**
By subsite									
Oral cavity									
Alcohol alone	221	7.4	1587	9.8	0.79	(0.60, 1.04)	−1.1	−11.4	3.7
Tobacco alone	191	6.4	3653	22.6	1.74	(1.10, 2.76)	24.8	19.6	31.1
Tobacco and alcohol	2354	78.7	8574	53.1	4.78	(2.59, 8.81)	39.9	24.9	51.4
TOTAL	2992		16152		Ψ=3.09	(1.82, 5.23)	**63.7**	**44.7**	**74.7**
Pharynx									
Alcohol alone	247	6.1	1587	9.8	1.28	(0.91, 1.80)	5.6	1.9	7.3
Tobacco alone	289	7.2	3653	22.6	1.91	(1.39, 2.62)	24.3	30.7	19.2
Tobacco and alcohol	3321	82.2	8574	53.1	5.42	(3.21, 9.16)	41.6	25.0	53.7
TOTAL	4038		16152		Ψ=1.90	(1.41, 2.56)	**71.5**	**57.6**	**80.2**
Larynx									
Alcohol alone	284	9.6	1308	10.0	1.21	(0.77, 1.92)	2.9	−0.3	4.4
Tobacco alone	89	3.0	3041	23.2	6.76	(4.58, 9.96)	52.2	77.8	36.0
Tobacco and alcohol	2541	85.9	6850	52.2	14.22	(8.26,24.46)	33.4	4.5	52.1
TOTAL	2959		13130		Ψ=1.62	(0.85, 3.09)	**88.5**	**82.1**	**92.4**
By sex									
Head and neck cancer, women									
Alcohol alone	389	17.3	608	13.4	0.93	(0.73, 1.19)	1.6	−4.4	5.1
Tobacco alone	247	11.0	1348	29.6	2.83	(1.97, 4.06)	31.5	29.0	33.6
Tobacco and alcohol	1247	55.4	1181	25.9	6.66	(3.89,11.41)	24.3	16.4	31.2
TOTAL	2252		4553		Ψ=2.05	(1.35, 3.11)	**57.4**	**45.6**	**65.3**
Head and neck cancer, Men									

	Cases		Controls		OR[1]	95%CI	PAR[2]	95%CI	
	N	%	N	%					
Alcohol alone	442	4.9	979	8.4	1.07	(0.80, 1.44)	0.9	−3.7	3.2
Tobacco alone	426	4.8	2305	19.9	2.06	(1.34, 3.18)	29.5	21.2	41.9
Tobacco and alcohol	7899	88.2	7393	63.7	5.19	(3.11, 8.65)	43.6	21.6	58.4
TOTAL	8959		11599		Ψ=2.36	(1.66, 3.36)	**74.0**	**59.9**	**82.8**
By age									
Head and neck cancer, <45 years									
Alcohol alone	65	6.2	213	9.8	0.71	(0.46, 1.09)	−10.8	−34.8	1.8
Tobacco alone	130	12.5	547	25.2	1.01	(0.56, 1.82)	15.2	−0.2	20.8
Tobacco and alcohol	745	71.4	1036	47.7	2.17	(1.22, 3.86)	29.1	28.4	34.4
TOTAL	1043		2172		Ψ=2.93	(1.42, 6.02)	**33.5**	**−6.7**	**56.8**
Head and neck cancer, 45–60 years									
Alcohol alone	330	6.6	687	9.7	1.22	(0.88, 1.69)	2.5	−2.2	4.6
Tobacco alone	286	5.7	1650	23.3	2.7	(1.71, 4.25)	31.3	23.8	41.0
Tobacco and alcohol	4241	84.3	3818	53.9	6.65	(3.63,12.16)	43.0	24.1	56.4
TOTAL	5028		7079		Ψ=1.93	(1.40, 2.66)	**76.8**	**63.1**	**84.8**
Head and neck cancer, >60 years									
Alcohol alone	436	8.5	687	10.0	0.98	(0.75, 1.30)	3.2	0.0	5.0
Tobacco alone	257	5.0	1456	21.1	2.68	(1.94, 3.70)	35.1	26.1	48.5
Tobacco and alcohol	4160	80.9	3720	53.9	6.02	(3.94, 9.22)	34.4	14.3	48.4
TOTAL	5140		6901		Ψ=2.19	(1.46, 3.29)	**72.7**	**62.8**	**79.5**
By geographic region									
Head and neck cancer, Europe									
Alcohol alone	208	5.0	542	7.0	1.21	(0.75, 1.96)	4.6	−2.7	7.4
Tobacco alone	216	5.2	2101	27.2	3.72	(2.24, 6.18)	33.2	17.2	68.3
Tobacco and alcohol	3641	87.2	4225	54.6	11.72	(5.58,24.59)	46.5	7.1	65.8
TOTAL	4177		7736		Ψ=2.41	(1.35, 4.30)	**84.3**	**72.6**	**90.3**
Head and neck cancer, North America									
Alcohol alone	403	9.3	741	12.4	0.98	(0.74, 1.30)	4.3	−3.5	9.2
Tobacco alone	380	8.7	1162	19.4	1.48	(0.95, 2.30)	22.6	15.6	34.9
Tobacco and alcohol	3205	73.6	3026	50.5	2.84	(2.05, 3.94)	23.5	2.7	37.4

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2011 March 9.

	Cases		Controls		OR[1]	95%CI	PAR[2]	95%CI	
	N	%	N	%					
TOTAL	4352		5991		Ψ=1.98	(1.12, 3.49)	**50.5**	**34.2**	**62.2**
Head and neck cancer, Latin America									
Alcohol alone	220	8.2	304	12.5	1.07	(0.49, 2.36)	4.3	−0.2	5.6
Tobacco alone	77	2.9	390	16.1	3.35	(1.69, 6.65)	32.9	26.3	40.2
Tobacco and alcohol	2300	85.8	1323	54.6	9.78	(5.36,17.85)	45.7	30.1	57.7
TOTAL	2682		2425		Ψ=2.87	(1.16, 7.06)	**82.9**	**70.1**	**89.6**

Ψ = multiplicative interaction parameter.

[1] Odds ratios were adjusted for age, sex, education, race/ethnicity, and study center

$$PAR_{\text{alcohol alone}} = PAR_{\text{alcohol}} - PAR_{\text{tobacco and alcohol}}$$

$$PAR_{\text{tobacco alone}} = PAR_{\text{tobacco}} - PAR_{\text{tobacco and alcohol}}$$

$$PAR_{\text{tobacco and alcohol}} = PAR_{\text{tobacco}} + PAR_{\text{alcohol}} - PAR_{\text{total}}$$

[2] $$PAR_{\text{total}} = 1 - [((a_{11}/m)/OR_{11}) + ((a_{10}/m)/OR_{10}) + ((a_{01}/m)/OR_{01}) + ((a_{00}/m)/OR_{00})]$$ (31)

Where a=number of exposed cases, m=total number of cases.

First subscript refers to tobacco use (0=never tobacco user, 1=ever tobacco user), second subscript refers to alcohol use (0=never alcohol drinker, 1=ever alcohol drinker)

*Note that where PAR is negative, $PAR_{\text{alcohol}} < PAR_{\text{tobacco and alcohol}}$, suggesting the effect of alcohol was mainly with tobacco. The negative PAR does not suggest that alcohol prevented any cancers; the main effects for alcohol overall and among never tobacco users were not protective.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2011 March 9.

Table 3

Odds ratios and population attributable fractions for tobacco and alcohol frequency categories, for head and neck cancer and subsites

Tobacco	Alcohol	Cases	Controls	OR[1]	95%CI	PAR	95%CI
Head and neck cancer							
Never	Never	5.2	14.8	1.00			
1–20 cigs/day	Never	5.1	7.7	2.20	(1.57–3.09)	2.9	(1.9, 3.6)
>20 cigs/day	Never	2.5	2.4	4.15	(2.44–7.07)	2.0	(1.5, 2.2)
Never	1–2 drinks/day	4.4	16.1	1.03	(0.84–1.25)	0.1	(−0.9, 0.9)
1–20 cigs/day	1–2 drinks/day	18.4	21.5	3.09	(2.13–4.50)	12.8	(10.0, 14.7)
>20 cigs/day	1–2 drinks/day	10.6	8.2	4.81	(3.21–7.20)	8.7	(7.5, 9.4)
Never	>=3 drinks/day	1.5	6.2	1.91	(1.27–2.87)	0.7	(0.3, 1.0)
1–20 cigs/day	>=3 drinks/day	27.3	15.2	9.92	(6.36–15.46)	25.2	(23.6, 26.2)
>20 cigs/day	>=3 drinks/day	25.1	7.8	14.23	(8.30–24.40)	24.0	(22.7, 24.8)
Total		**10,851**	**15,751**			**76.3**	**(66.8, 82.8)**
P for interaction				<0.01			
Oral cavity cancer							
Never	Never	7.9	14.8	1.00			
1–20 cigs/day	Never	5.7	7.7	1.72	(1.17, 2.53)	2.4%	(0.8, 3.4)
>20 cigs/day	Never	2	2.4	3.13	(1.14, 8.59)	1.4%	(0.2, 1.8)
Never	1–2 drinks/day	5.1	16.1	0.88	(0.65, 1.20)	−0.7%	(−2.8, 0.9)
1–20 cigs/day	1–2 drinks/day	19.2	21.5	2.72	(1.47, 5.04)	12.2%	(6.1, 15.4)
>20 cigs/day	1–2 drinks/day	10.1	8.2	3.23	(1.84, 5.67)	7.0%	(4.6, 8.3)
Never	>=3 drinks/day	0.9	6.2	1.05	(0.62, 1.77)	0.0%	(−0.6, 0.4)
1–20 cigs/day	>=3 drinks/day	23.9	15.2	9.60	(5.04,18.28)	21.4%	(19.2, 22.6)
>20 cigs/day	>=3 drinks/day	25.1	7.8	15.49	(7.24,33.14)	23.5%	(21.6, 24.4)
Total		**2,875**	**15,751**			**67.1%**	**(49.3, 77.2)**
P for interaction				<0.01			
Pharyngeal cancer							
Never	Never	4.6	14.8	1.00			
1–20 cigs/day	Never	4.3	7.7	1.90	(1.34, 2.68)	2.0	(1.1, 2.7)
>20 cigs/day	Never	2.1	2.4	2.83	(1.66, 4.82)	1.3	(0.8, 1.6)

Tobacco	Alcohol	Cases	Controls	OR[1]	95%CI	PAR	95%CI
Never	1–2 drinks/day	5.2	16.1	1.26	(0.92, 1.73)	1.1	(−0.5, 2.2)
1–20 cigs/day	1–2 drinks/day	16.3	21.5	2.57	(1.72, 3.83)	10.0	(6.8, 12.1)
>20 cigs/day	1–2 drinks/day	10.2	8.2	4.10	(2.66, 6.32)	7.7	(6.4, 8.6)
Never	>=3 drinks/day	1.9	6.2	2.94	(1.73, 5.02)	1.3	(0.8, 1.5)
1–20 cigs/day	>=3 drinks/day	28.9	15.2	11.37	(6.50,19.89)	26.4	(24.5, 27.5)
>20 cigs/day	>=3 drinks/day	26.5	7.8	14.29	(7.26,28.15)	24.6	(22.8, 25.5)
Total		**3,899**	**15,751**			**74.3**	**(62.7, 81.7)**
P for interaction				<0.01			
Laryngeal cancer							
Never	Never	1.6	14.9	1.00			
1–20 cigs/day	Never	5.9	7.9	6.06	(4.03, 9.11)	4.9	(4.4, 5.2)
>20 cigs/day	Never	3.9	2.2	12.83	(7.95,20.71)	3.6	(3.4, 3.7)
Never	1–2 drinks/day	1.8	16.3	1.20	(0.72, 2.02)	0.3	(−0.7, 0.9)
1–20 cigs/day	1–2 drinks/day	20.8	21.3	8.33	(5.07,13.69)	18.3	(16.7, 19.3)
>20 cigs/day	1–2 drinks/day	12.7	7.3	16.91	(9.66,29.61)	11.9	(11.4, 12.3)
Never	>=3 drinks/day	1.2	6.6	3.16	(1.23, 8.16)	0.8	(0.2, 1.0)
1–20 cigs/day	>=3 drinks/day	28.8	16.5	18.94	(10.64,33.71)	27.3	(26.1, 27.9)
>20 cigs/day	>=3 drinks/day	23.4	7.1	36.87	(16.60,81.90)	22.8	(22.0, 23.2)
Total		**2,901**	**12,935**			**89.9**	**(83.5, 93.5)**
P for interaction				0.63			

[1]Odds ratios were adjusted on age, sex, education, race/ethnicity and study center.

[2]The total number of cases and controls are different from table 2 due to missing values for the tobacco and alcohol frequency categories.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2011 March 9.