

Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology 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,^{13,15} Sergio Koifman,¹⁶ Carlo La Vecchia,¹⁷ Philip Lazarus,¹⁸ Fabio Levi,¹⁹ Juan J. Lence,⁹ Dana Mates,²⁰ Elena Matos,²¹ Ana Menezes,²² Michael D. McClean,¹⁴ Joshua Muscat,¹⁸ 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,¹¹ Oxana Shangina,²⁸ Agnieszka Pilarska,²⁹ Zuo-Feng Zhang,³⁰ Gilles Ferro,¹ Julien Berthiller,¹ and Paolo Boffetta¹

¹IARC, Lyon, France; ²Institute of Hygiene, Università Cattolica del Sacro Cuore, Rome, Italy; ³Institut Català d'Oncologia, Barcelona, Spain; ⁴Fred Hutchinson Cancer Research Center, Seattle, Washington; ⁵Hospital Araujo Jorge, Goiania, Brazil; ⁶Aviano Cancer Centre, Aviano, Italy; ⁷Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; ⁸Specialized State Health Institute, Banská Bystrica, Slovakia; ⁹National Institute of Oncology and Radiobiology, Havana, Cuba; ¹⁰Universidade de Sao Paulo, Sao Paulo, Brazil; ¹¹National Cancer Institute, Bethesda, Maryland; ¹²Instituto de Investigación Epidemiológica, San José, Costa Rica; ¹³Harvard School of Public Health; ¹⁴Boston University School of Public Health, Boston, Massachusetts; ¹⁵Brown University, Providence, Rhode Island; ¹⁶Escola Nacional de Saude Publica, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; ¹⁷Istituto di Ricerche Farmacologiche Mario Negri, and University of Milan, Milan, Italy; ¹⁸Penn State College of Medicine, Hershey, Pennsylvania; ¹⁹Institut de médecine sociale et préventive, Université de Lausanne, Lausanne, Switzerland; ²⁰Institute of Public Health, Bucharest, Romania; ²¹Institute of Oncology Angel H. Roffo, University of Buenos Aires, Buenos Aires, Argentina; ²²Universidade Federal de Pelotas, Pelotas, Brazil; ²³University of North Carolina School of Public Health, Chapel Hill, North Carolina; ²⁴National Institute of Environmental Health, Budapest, Hungary; ²⁵College of Public Health, University of Iowa, Iowa City, Iowa; ²⁶University of Texas M. D. Anderson Cancer Center, Houston, Texas; ²⁷Institute of Occupational Medicine, Lodz, Poland; ²⁸Cancer Research Centre, Moscow, Russia; ²⁹2nd Maxillofacial Surgery Clinic, Medical Academy, Warsaw, Poland; and ³⁰University of California at Los Angeles School of Public Health, Los Angeles, California

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 because 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 Neck Cancer Epidemiology 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 ($\psi = 2.15$; 95% confidence interval, 1.53-3.04). The PAR for tobacco or alcohol was 72% (95% confidence interval, 61-79%) for head and

neck cancer, of which 4% was due to alcohol alone, 33% was due to 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 and for head and neck cancer among women and among young-onset cases. (Cancer Epidemiol Biomarkers Prev 2009;18(2):541-50)

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

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Requests for reprints: Mia Hashibe, Lifestyle, Environment and Cancer Group, Genetics and Epidemiology Cluster, IARC, 150 Cours Albert Thomas, 69008 Lyon, France. Phone: 33-4-72-73-80-32; Fax: 33-4-72-73-83-20. E-mail: hashibe@iarc.fr

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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, whereas 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 that 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 (a) to formally test the multiplicative model of interaction between alcohol and tobacco use with a very large sample size; (b) to assess the population attributable risk (PAR) due to the effects of alcohol alone, tobacco alone, and tobacco and alcohol combined; and (c) 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.

Materials and Methods

The INHANCE Consortium³¹ was established in 2004 based on the collaboration of research groups leading large epidemiology studies of head and neck cancer that are ongoing 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 with our previous publication (20), the current data set 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 PARs. Additionally in India, contrary to other countries, betel quid and areca nut chewing are major contributors to attributable fractions (AF) 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,

although 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.

Table 1. Selected characteristics of head and neck cancer cases and controls

	Cases, n (%)	Controls, n (%)
Total	11,221	16,168
Study		
Milan	416 (3.7)	1,531 (9.5)
Aviano	482 (4.3)	855 (5.3)
Italy Multicenter	1,058 (9.4)	2,579 (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	1,118 (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)	1,005 (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	2,191 (19.5)	1,706 (10.6)
IARC Multicenter*	883 (7.9)	992 (6.1)
Age (y)		
<40	415 (3.7)	1,023 (6.3)
40-44	629 (5.6)	1,151 (7.1)
45-49	1,223 (10.9)	1,800 (11.1)
50-54	1,714 (15.3)	2,487 (15.4)
55-59	2,096 (18.7)	2,801 (17.3)
60-64	1,901 (16.9)	2,531 (15.7)
65-69	1,555 (13.9)	2,064 (12.8)
70-74	1,024 (9.1)	1,517 (9.4)
≥75	664 (5.9)	794 (4.9)
Sex		
Women	2,256 (20.1)	4,557 (28.2)
Men	8,965 (79.9)	11,611 (71.8)
Race/ethnicity		
White	8,272 (73.7)	13,358 (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)
Latin American	2,191 (19.5)	1,706 (10.6)
Education		
None	93 (0.8)	106 (0.7)
<Junior high school	4,347 (38.7)	6,169 (38.2)
Some high school	1,576 (14.0)	1,784 (11.0)
High school graduate	1,765 (15.7)	2,163 (13.4)
Vocational, some college	1,368 (12.2)	2,514 (15.5)
≥College	1,417 (12.6)	2,888 (17.9)
Missing	655 (5.8)	544 (3.4)
Subtype		
Oral	2,993 (26.7)	
Pharynx	4,040 (36.0)	
Oral/pharynx NOS	917 (8.2)	
Larynx	2,965 (26.4)	
Head and neck NOS	306 (2.7)	

NOTE: 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 because the large majority of these populations are expected to be White. In the Latin American study, we categorized subjects as Latin American.

Abbreviation: NOS, not otherwise specified.

*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 PARs.

³¹ <http://inhance.iarc.fr/>

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 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, larynx, or head and neck cancer unspecified. Subjects with cancers of the major salivary glands [parotid, submandibular, or sublingual glands; International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) codes C07-C08] or of the nasal cavity/ear/paranasal sinuses (ICD-O-2 codes C30-C31) were excluded 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% (8,034 of 9,265) of head and neck cancer cases were squamous cell carcinoma.

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 data set (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 to 20 cigarettes, 1 to 20 cigars, 1 to 20 pipes, 1 to 2 chewing products, or 1 to 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 the 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 (OR) and 95% confidence intervals (95% CI) using unconditional logistic regression models for each study. To assess interactions on the multiplicative scale, we estimated ORs 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 and 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; ref. 21). We estimated 95% CIs for each of these measures. The null values of RERI and AP are 0, whereas the null value for SI is 1.

The logistic regression models included age (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, or ≥ 75 y), 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 OR 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 because the large majority of these

Table 2. Tobacco and alcohol multiplicative interaction parameters and attributable risks for head and neck cancer and subsites

	Cases, n (%)	Controls, n (%)	OR* (95% CI)	PAR [†] (95% CI)
Head and neck cancer overall				
Alcohol alone	831 (7.4)	1,587 (9.8)	1.06 (0.88-1.28)	4.0 (1.5-5.3)
Tobacco alone	673 (6.0)	3,653 (22.6)	2.37 (1.66-3.39)	33.0 (42.6-25.9)
Tobacco and alcohol	9,146 (81.6)	8,574 (53.1)	5.73 (3.62-9.06)	34.9 (17.2-48.0)
Total	11,211	16,152	$\psi = 2.15 (1.53-3.04)$	72.0 (61.2-79.1)
By subsite				
Oral cavity				
Alcohol alone	221 (7.4)	1,587 (9.8)	0.79 (0.60-1.04)	-1.1 (-11.4 to 3.7)
Tobacco alone	191 (6.4)	3,653 (22.6)	1.74 (1.10-2.76)	24.8 (19.6-31.1)
Tobacco and alcohol	2,354 (78.7)	8,574 (53.1)	4.78 (2.59-8.81)	39.9 (24.9-51.4)
Total	2,992	16,152	$\psi = 3.09 (1.82-5.23)$	63.7 (44.7-74.7)
Pharynx				
Alcohol alone	247 (6.1)	1,587 (9.8)	1.28 (0.91-1.80)	5.6 (1.9-7.3)
Tobacco alone	289 (7.2)	3,653 (22.6)	1.91 (1.39-2.62)	24.3 (30.7-19.2)
Tobacco and alcohol	3,321 (82.2)	8,574 (53.1)	5.42 (3.21-9.16)	41.6 (25.0-53.7)
Total	4,038	16,152	$\psi = 1.90 (1.41-2.56)$	71.5 (57.6-80.2)
Larynx				
Alcohol alone	284 (9.6)	1,308 (10.0)	1.21 (0.77-1.92)	2.9 (-0.3 to 4.4)
Tobacco alone	89 (3.0)	3,041 (23.2)	6.76 (4.58-9.96)	52.2 (77.8-36.0)
Tobacco and alcohol	2,541 (85.9)	6,850 (52.2)	14.22 (8.26-24.46)	33.4 (4.5-52.1)
Total	2,959	13,130	$\psi = 1.62 (0.85-3.09)$	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 to 5.1)
Tobacco alone	247 (11.0)	1,348 (29.6)	2.83 (1.97-4.06)	31.5 (29.0-33.6)
Tobacco and alcohol	1,247 (55.4)	1,181 (25.9)	6.66 (3.89-11.41)	24.3 (16.4-31.2)
Total	2,252	4,553	$\psi = 2.05 (1.35-3.11)$	57.4 (45.6-65.3)
Head and neck cancer, men				
Alcohol alone	442 (4.9)	979 (8.4)	1.07 (0.80-1.44)	0.9 (-3.7 to 3.2)
Tobacco alone	426 (4.8)	2,305 (19.9)	2.06 (1.34-3.18)	29.5 (21.2-41.9)
Tobacco and alcohol	7,899 (88.2)	7,393 (63.7)	5.19 (3.11-8.65)	43.6 (21.6-58.4)
Total	8,959	11,599	$\psi = 2.36 (1.66-3.36)$	74.0 (59.9-82.8)

(Continued on the following page)

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 with respect to unmeasured covariates; whether 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 y, 45-60 y, ≥60 y), 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 y before diagnosis (<18.5 kg/m², 18.5 to <25 kg/m², 25 to <30 kg/m², ≥30 kg/m²), and BMI at age 20 or 30 and after restriction to squamous cell carcinoma cases.

The PARs were estimated based on the formula $AF = p(ec) \times (OR - 1) / OR$, where $p(ec)$ is the proportion exposed among the cases (24). ORs adjusted for potential confounding factors were used in these equations. The CIs for the AFs were calculated from the lower and upper limit ORs. The PAR for tobacco and/or alcohol exposures (PAR_{total}) was 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 follows (25):

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

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

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

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

Table 2. Tobacco and alcohol multiplicative interaction parameters and attributable risks for head and neck cancer and subsites (Cont'd)

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR* (95% CI)	PAR [†] (95% CI)
By age				
Head and neck cancer, <45 y				
Alcohol alone	65 (6.2)	213 (9.8)	0.71 (0.46-1.09)	-10.8 (-34.8 to 1.8)
Tobacco alone	130 (12.5)	547 (25.2)	1.01 (0.56-1.82)	15.2 (-0.2 to 20.8)
Tobacco and alcohol	745 (71.4)	1,036 (47.7)	2.17 (1.22-3.86)	29.1 (28.4-34.4)
Total	1,043	2,172	$\psi = 2.93$ (1.42-6.02)	33.5 (-6.7 to 56.8)
Head and neck cancer, 45-60 y				
Alcohol alone	330 (6.6)	687 (9.7)	1.22 (0.88-1.69)	2.5 (-2.2 to 4.6)
Tobacco alone	286 (5.7)	1,650 (23.3)	2.7 (1.71-4.25)	31.3 (23.8-41.0)
Tobacco and alcohol	4,241 (84.3)	3,818 (53.9)	6.65 (3.63-12.16)	43.0 (24.1-56.4)
Total	5,028	7,079	$\psi = 1.93$ (1.40-2.66)	76.8 (63.1-84.8)
Head and neck cancer, >60 y				
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)	1,456 (21.1)	2.68 (1.94-3.70)	35.1 (26.1-48.5)
Tobacco and alcohol	4,160 (80.9)	3,720 (53.9)	6.02 (3.94-9.22)	34.4 (14.3-48.4)
Total	5,140	6,901	$\psi = 2.19$ (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 to 7.4)
Tobacco alone	216 (5.2)	2,101 (27.2)	3.72 (2.24-6.18)	33.2 (17.2-68.3)
Tobacco and alcohol	3,641 (87.2)	4,225 (54.6)	11.72 (5.58-24.59)	46.5 (7.1-65.8)
Total	4,177	7,736	$\psi = 2.41$ (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 to 9.2)
Tobacco alone	380 (8.7)	1,162 (19.4)	1.48 (0.95-2.30)	22.6 (15.6-34.9)
Tobacco and alcohol	3,205 (73.6)	3,026 (50.5)	2.84 (2.05-3.94)	23.5 (2.7-37.4)
Total	4,352	5,991	$\psi = 1.98$ (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 to 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	2,300 (85.8)	1,323 (54.6)	9.78 (5.36-17.85)	45.7 (30.1-57.7)
Total	2,682	2,425	$\psi = 2.87$ (1.16-7.06)	82.9 (70.1-89.6)

NOTE: ψ = multiplicative interaction parameter. Note that where PAR is negative, $PAR_{\text{alcohol}} < PAR_{\text{tobacco and alcohol}}$, suggesting that 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.

*ORs were adjusted for age, sex, education, race/ethnicity, and study center.

[†] $PAR_{\text{alcohol alone}} = PAR_{\text{alcohol}} - PAR_{\text{tobacco and alcohol}}$; $PAR_{\text{tobacco alone}} = PAR_{\text{tobacco}} - PAR_{\text{tobacco and alcohol}}$; $PAR_{\text{tobacco and alcohol}} = PAR_{\text{tobacco}} + PAR_{\text{alcohol}} - PAR_{\text{total}}$; $PAR_{\text{total}} = 1 - [(a_{11}/m)/OR_{11}] + [(a_{10}/m)/OR_{10}] + [(a_{01}/m)/OR_{01}] + [(a_{00}/m)/OR_{00}]$ (25). 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), and second subscript refers to alcohol use (0 = never alcohol drinker, 1 = ever alcohol drinker).

higher proportion of men among cases compared with the controls. The majority of cases and controls were European in ethnic origin. Cases had completed lower levels of education than the controls.

The ORs 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 ($\psi = 2.15$; 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 [$5.73 / (2.37 * 1.06) = 2.28 \neq 2.15$], 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 [$5.04 / (2.17 * 0.98) = 2.37 \approx 2.38$].

By subsite, joint effects greater than multiplicative were observed for oral cavity cancer ($\psi = 3.09$; 95% CI, 1.82-5.23) and pharyngeal cancer ($\psi = 1.90$; 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 CI included the null value ($\psi = 1.62$; 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 ψ s are shown for head and neck cancer in Fig. 1 and for the subsites in Supplementary Figs. S1 to S3. Statistically significant differences were not observed in the ψ s 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 squamous cell carcinomas (8,034 cases) resulted in a ψ similar to the overall analysis ($\psi = 2.27$; 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 ORs.

The 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), whereas the PAR for pharyngeal cancer was intermediate to those of oral cavity and laryngeal cancer. For women, the PAR for head and neck cancer seemed to be lower than for men. The overall PAR is probably closer to the PAR for men because 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 ψ s were fairly similar across age strata, but the PARs were substantially lower among subjects <45 years of age compared with 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 ORs 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

Table 3. ORs and population AFs for tobacco and alcohol frequency categories, for head and neck cancer and subsites

Tobacco	Alcohol	Cases (%)	Controls (%)	OR* (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 to 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)
<i>P</i> 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 to 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 to 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)
<i>P</i> 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)
Never	1-2 drinks/day	5.2	16.1	1.26 (0.92-1.73)	1.1 (-0.5 to 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)
<i>P</i> 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 to 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)
<i>P</i> for interaction					
0.63					

*ORs were adjusted on age, sex, education, race/ethnicity, and study center.

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

Head and neck cancer

Study name	cases	controls	ψ	Lower limit	Upper limit
Milan	416	1531	0.56	0.21	1.50
Aviano	482	855	1.93	0.32	11.63
Italy multicenter	1058	2577	2.93	1.34	6.40
Switzerland	516	883	4.39	1.80	10.70
Central Europe	760	907	2.63	0.74	9.36
New York	1117	906	2.87	1.68	4.89
Seattle	407	607	9.50	1.72	52.45
Iowa	545	759	5.02	2.66	9.47
North Carolina	180	202	0.77	0.16	3.65
Tampa	207	889	1.48	0.62	3.52
Los Angeles	415	1004	1.48	0.77	2.84
Texas	829	865	1.49	0.94	2.36
Puerto Rico	350	521	5.21	1.85	14.70
South America	2188	1705	2.68	1.69	4.25
Intl multicenter	882	988	1.60	0.93	2.74
Boston	584	659	0.63	0.30	1.35
Rome	275	294	3.75	1.44	9.74
Combined	11211	16152	2.15	1.53	3.04

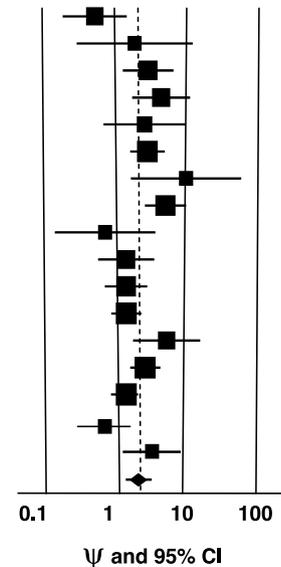


Figure 1. Multiplicative interaction parameters (ψ) for tobacco (cigarette, cigar, pipe, snuff, chewing tobacco) and alcohol by study and combined using INHANCE pooled data version 1.1. ORs used to calculate ψ were adjusted for age, sex, race/ethnicity, and education level.

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 was 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, whereas 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 data set), which reported PARs of 80% for men, 61% for women, and 74% overall (26). 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 seemed 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 ψ s 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 with 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 (27, 28), in contrast to a study including cases mostly from Europe (12).

Tobacco and alcohol seemed to be responsible for a smaller proportion of the head and neck cancer cases in individuals who were younger (< 45 years) compared with the older age groups. The number of cases and controls in subjects < 45 years was limited (although larger than any previous study), as reflected in the OR 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, HPV infection, or some nutritional factors, are more important risk factors in these groups, although further work is required to clarify this.

Although 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 was 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 CIs 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) because 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 (29). However, low fruit intake and low vegetable intake may increase risk by ~ 2 -fold (30), 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 (31), 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix A. 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 0.5 pack/week for ≥ 1 year (Iowa study), once a day for 1 year of time (New York); and 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 year of 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, and pan masala 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 as follows: "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); \geq once/month (Multicenter, Latin America studies); average ≥ 1 drink/week for ≥ 1 year (Iowa study); \geq once/week for ≥ 1 year (Tampa and Houston study); and ≥ 4 times/month of beer, wine, or liquor (North Carolina study).

Appendix B. Pooling Alcohol Variables

The volume specification for alcoholic beverages by type differed across studies. For example, a glass of wine was defined as 100 to 150 mL in the European studies, whereas the North American studies defined a wine glass as 3.6 to 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 (i.e., 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.

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