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An Examination of Male and Female Odds Ratios by BMI, Cigarette Smoking and Alcohol Consumption for Cancers of the Oral Cavity, Pharynx and Larynx in Pooled Data from 15 Case-Control Studies

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Abstract

Background—Greater tobacco smoking and alcohol consumption and lower body mass index (BMI) increase odds ratios (OR) for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers; however, there are no comprehensive sex-specific comparisons of ORs for these factors.

Methods—We analyzed 2,441 oral cavity (925 females and 1,516 males), 2,297 oropharynx (564 females and 1,733 males), 508 hypopharynx (96 females and 412 males) and 1,740 larynx (237 females and 1,503 males) cases from the INHANCE consortium of 15 head and neck cancer case-control studies. Controls numbered from 7,604 to 13,829 subjects, depending on analysis. Analyses fitted linear-exponential excess ORs models.

Results—ORs were increased in underweight (<18.5 BMI) relative to overweight and obese categories (≥25 BMI) for all sites and were homogeneous by sex. ORs by smoking and drinking in females compared to males were significantly greater for oropharyngeal cancer ($p<0.01$ for both factors), suggestive for hypopharyngeal cancer ($p=0.05$ and $p=0.06$, respectively), but homogeneous for oral cavity ($p=0.56$ and $p=0.64$) and laryngeal ($p=0.18$ and $p=0.72$) cancers.

Conclusions—The extent that OR modifications of smoking and drinking by sex for oropharyngeal and, possibly, hypopharyngeal cancers represent true associations, or derive from unmeasured confounders or unobserved sex-related disease subtypes (e.g., human papillomavirus positive oropharyngeal cancer) remains to be clarified.

Keywords

Alcohol consumption; cigarette smoking; interactions; odds ratio models

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Incidence and mortality rates for head and neck cancers (HNC), including cancers of the oral cavity, oropharynx, hypopharynx and larynx, are higher in males than females [1–3]. Male to female ratios vary widely, with ratios of 4 to 20 in Southern, Central and Eastern Europe, 2 to 10 in Northern Europe and North America and 1.5 to 2.5 in Asia [4]. With cigarette smoking (pack-years and cigarettes smoked per day [CPD]), alcohol consumption (drinks-years and drinks per day [DPD]) and lean body composition, as measured by body mass index (BMI, weight[kg]/height[m]^2) representing important risk factors, a key question is the extent that odds ratios (OR) per unit exposure for these factors differ in males and females. Identification of sex-specific differences in ORs may offer important clues into disease etiology.

Few studies have compared sex-specific ORs for these factors. For cigarette smoking and oral cavity/pharyngeal cancer, among case-control studies, three reported ORs greater in females [5–7] and one reported similar ORs by sex [8], while among cohort studies two reported ORs greater in females [9,10] and one reported ORs greater in males [11], although two of the cohorts had only 10 [11] and 3 [10] female cases who smoked. For laryngeal cancer, one cohort study reported greater effects in females but included only 49 female cases and no never-smokers [9]. For all HNC, a cohort study found greater smoking relative risks in males but included only 13 female cases who smoked [12]. Results for alcohol consumption are limited to one cohort study, showing greater relative risks in females [13] for HNC, and two case-control studies, one suggesting slightly greater ORs in males for oral cavity/pharynx [8] and another showing comparable ORs [6]. Two case-control studies reported ORs at lower BMIs greater for laryngeal cancer in females [14] and greater for oral

cavity/pharyngeal cancer in males [15]. Thus, no definitive conclusions have emerged. To date, there have been no comprehensive sex-specific comparisons of ORs for HNCs by BMI, smoking and alcohol consumption.

For this analysis, we pooled data from 15 case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Previous INHANCE analyses have shown that ORs increased with smoking and alcohol consumption [16–18] and with lower BMI [19], and that lower BMIs enhanced the strengths of association for smoking and for alcohol consumption for oral cavity and pharyngeal, but not laryngeal cancer [20]. We extend these analyses to examine whether sex modifies ORs for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers by BMI, smoking and drinking.

MATERIAL AND METHODS

Study data

The INHANCE consortium includes large molecular epidemiologic studies of head and neck cancer [16,19]. (See http://inhance.iarc.fr/.) We pooled 15 studies that were used previously to analyze BMI, smoking and alcohol consumption [19,20]. A detailed description of these studies can be found in Hashibe et al [16–18].

For analysis of BMI and smoking, we restricted data to never and current cigarette-only smokers to remove complications from former smokers and use of other tobacco products. We repeated analyses in never and 10+ CPD smokers, since previous analyses suggested that <10 CPD smokers could influence modeling through increased variability from a limited range of pack-years [18,20]. For analysis of BMI and alcohol consumption, we analyzed never and ≤10 DPD drinkers (95.4% of controls) and ≥5 DPD drinkers (84.8% of controls), since there were few heavy drinkers and their inclusion distorted models. We did not limit data based on drinking cessation, since five studies (Milan, Aviano, Central Europe, New York, U.S. Multi-Center) lacked such information. However, when we repeated analyses in never and current drinkers in the 10 studies with information on drinking status, inference on differences by sex was unchanged.

We calculated alcohol consumption in standardized drinks/day by converting drinks/day into ethanol/day based on country-specific ethanol content in standard portion sizes and dividing by 15.6 mL of ethanol/drink [16].

BMIs were self-reported. Most studies (Milan, Aviano, Italy Multi-Center, Switzerland, New York, Tampa, Los Angeles, Houston, Boston, U.S. Multi-Center, Puerto Rico, Latin America and International Multi-Center) ascertained BMI at enrollment, while others (Central Europe, New York, Seattle, Boston, Latin America, International Multi-Center) ascertained BMI two to five years prior. In four studies (New York, Boston, Latin America, International Multi-Center) with both measures, the Pearson correlation was 0.88, and ORs were similar. We therefore minimized missing data by using BMI at enrollment or two to five years prior if values were missing.

For analyses of never and current cigarette-only smokers, there were 1,872 oral cavity (620 females and 1,252 males), 1,828 oropharynx (473 females and 1,355 males), 449 hypopharynx (84 females and 365 males) and 1,356 larynx (201 females and 1,155 males) cases (Table 1). Controls numbered 9,502 (3,621 females and 5,881 males). For analyses of BMI and of never and ≤10 DPD drinkers, there were 2,441 oral cavity (925 females and 1,516 males), 2,297 oropharynx (564 females and 1,733 males), 508 hypopharynx (96 females and 412 males) and 1,740 larynx (237 females, 1,503 males) cases. Controls numbered 13,829 (4,415 females and 9,414 males). Not all studies enrolled laryngeal cancer

cases, resulting in fewer controls; with controls numbering 7,604 (2,815 females and 4,789 females) for the smoking analysis and 10,982 for the drinking analysis (3,420 females and 7,562 males). These numbers varied with analysis due to missing data and differed slightly from previous analysis due to updating of data.

Statistical models

We used logistic regression to estimate ORs for BMI categories and to fit cubic splines for continuous BMI [21].

As described previously, we fitted a linear-exponential excess OR model for total exposure (pack-years and drink-years) and exposure rate (CPD and DPD) [18,20]. This approach distinguished the disease and total exposure relationship from exposure delivery rate, i.e., the effect of increasing exposure rate and decreasing exposure duration for fixed total exposure. For continuous pack-years, d, and CPD, n, we fitted the model

$$\mathrm{OR}(d, n) = 1 + \beta\, d\, \mathrm{g}(n) \quad (1)$$

where β represented the strength of association, i.e., the excess OR (EOR) per pack-year at $g(n)=1$, and g(.) defined its variation with exposure delivery. Consistent with previous analyses, we set $g(n) = \exp\{\phi_1 \ln(n) + \phi_2 \ln(n)^2\}$. We compared the fit of model (1) with ORs for a cross-classification of pack-years and CPD relative to never-smokers. Within each i=1, …, I categories of CPD, ORs increased approximately linearly with pack-years, i.e., $\mathrm{OR}(d) = 1 + \gamma_i\, d$, where γ_i was the EOR/pack-year for category i. The fitted $\beta\, g(n)$ closely described the $\gamma_1, \ldots, \gamma_I$ estimates.

We extended model (1) to estimate sex-specific ORs as

$$\mathrm{OR}(d, n, s) = 1 + \sum\nolimits_s \beta_s\, d_s\, \mathrm{g}_s(n_s) \quad (2)$$

where sex-specific β_s parameters and $g_s(.)$ functions replaced β and g(.), and where d_s equaled d and n_s equaled n within level s and zero otherwise. We used likelihood ratio tests to assess whether sex-specific differences resulted from total exposure (different β's) or exposure rate (different g(.) parameters) or both. Since pack-years and CPD and drink-years and DPD were highly correlated, we evaluated interactions starting with model (2) then constraining the β's and/or g(.) functions to be equivalent across sex and examining the degradation in model fit. This approach, in contrast to starting with model (1) and enlarging the model, allowed for an evaluation of the interaction of sex and one factor (e.g., pack-years) while minimizing the influence of the interaction of sex and its closely related correlate (e.g., CPD).

We applied a similar model for drink-years and DPD, except $g(n) = \exp\{\phi_1 \ln(n)\}$, since the addition of $\ln(n)^2$ did not improve the model.

For BMI and smoking, we adjusted jointly for the cross-classification of study/center (39 levels), age (<40, 40–44, …,70–74, 70+) and drink-years (never drank and quartiles in drinkers) and individually for sex, education (none, did not complete high school, high school graduate, technical school or some college, college graduate and DPD (<1.0, 1.0–2.9, 3.0–4.9, 5.0+). For BMI and alcohol consumption, we adjusted jointly for the cross-classification of study/center, age and pack-years (never smoked and quartiles of pack-years), and individually for CPD (<20, 20–29, 30–39, 40+) and use of other tobacco products.

We used the Epicure program for analyses [22].

RESULTS

ORs by BMI, smoking and drinking for males and females

ORs relative to normal BMI (18.5–24.9) were increased for underweight BMIs for all cancer sites and both sexes (Table 2 and Figure 1). ORs were below one for categories ≥25 BMI, resulting in 4-fold and greater ratios across the full BMI range. Homogeneity of ORs by sex was rejected for oral cavity cancer (p=0.04); however, Figure 1 revealed no meaningful differences.

There were 25 never-smoking female laryngeal cancer cases, with nine cases in the Latin America Study and three cases or fewer in other studies, which markedly affected results. ORs with 95% confidence limits (CI) for 1–29 pack-years relative to never-smokers were 4.72 (3.3–6.7) for males and 18.7 (9.8–35.5) for females, a 4-fold ratio. Due to this presumed distortion of case control odds in never-smoking females, ORs for other pack-years categories for females were likewise affected. We therefore computed ORs relative to 1–29 pack-years (Table 2). ORs increased with pack-years for both sexes ($p<0.01$), except for hypopharynx, and were generally greater in females, with statistically significant differences only for oropharynx ($p<0.01$) and larynx ($p<0.01$). The result for laryngeal cancer was influenced by never-smokers, and the test of homogeneity of ORs by pack-years for males and females among smokers did not reject (p=0.97). Adjusted for pack-years, ORs by CPD varied only for males (p=0.03 for oropharynx and $p<0.01$ for larynx), while homogeneity of ORs by CPD across sex was not rejected for any site.

ORs increased significantly with drink-years for all sites. Adjusted for drink-years, ORs for DPD increased significantly for all sites and both sexes ($p<0.01$), except for laryngeal cancer in females (p=0.83) (Table 2). Tests of homogeneity of ORs by drink-years and by DPD in males and females did not reject.

Joint ORs by pack-years and CPD with effect modification by sex

We computed ORs by categories of pack-years and CPD relative to never-smokers, and fitted a model with linear ORs in pack-years within CPD categories (Figure 2). For laryngeal cancer, we adjusted for female never-smokers by computing ORs relative to the lowest smoking category (>0 to <6.6 pack-years and <20 CPD, with means 3.4 pack-years and 4.5 CPD) and multiplying by 1.20, the OR for this category relative to never-smokers in males. Since the OR in females for never-smokers was 0.10, we fixed the referent parameter for female never-smokers to $\ln(0.10\times1.20) = -2.123$. ORs in females were consistently higher for oropharyngeal cancer and generally higher for hypopharyngeal cancer (Figure 2). The estimates of slope, EOR/pack-year, are shown in Table 3 for an expanded number of CPD categories. There were no consistent differences in ORs by sex for oral cavity and laryngeal cancers.

ORs by pack-years were generally linear within CPD categories. Among thirty-two tests of no departure from linearity, four tests were rejected at the 0.05-level (for oropharynx in the male 30–39 and 40+ CPD categories and in the female <20 CPD category, and for hypopharynx in the male 30–39 CPD category). However, after omitting one study [6], only one test was rejected. For each site, model (2), which included an offset for laryngeal cancer, closely fitted the EOR/pack-year estimates (Table 3) (square symbol) for CPD categories (Figure 3, solid line for all data and dash line for never and 10+ CPD smokers). At higher CPDs, the declining EOR/pack-year estimates indicated a diminishing strength of the pack-years association.

Sex modified the smoking association for oropharyngeal ($p<0.01$) and hypopharyngeal ($p=0.05$) cancers, but not for oral cavity ($p=0.56$) and laryngeal ($p=0.18$) cancers (Table 3). Hypothesis tests suggested that effect modification for oropharynx derived from both the interactions of pack-years with sex ($p<0.01$), i.e., different β's, and CPD with sex ($p<0.01$), i.e., different g(.) functions, while for hypopharynx the models suggested similar β estimates ($p=0.12$) and different g(.) functions ($p=0.04$) (Supplemental Material Table S1). We can obtain a rough characterization of the differences by computing fitted ORs from model (2) (parameter estimates from Table S1, restricted data). At 34.5 pack-years and 19.8 CPD, the means among smoking controls, fitted ORs for oropharyngeal cancer were 6.4 ($=1+34.5\ 63.58\ \exp\{-3.792\ \ln(19.8)+0.597\ \ln(19.8)^2\}$ for females and 3.0 for males, while for hypopharyngeal cancer, fitted ORs were 15.0 for females and 10.4 for males at the mean pack-years and CPD.

Joint ORs by drink-years and DPD with effect modification by sex

ORs by drink-years relative to never drinkers increased linearly within DPD categories (Figure 4). Among thirty-two tests of no departure from linearity, three tests were rejected (for oral cavity in the female <1.0 DPD category, for oropharynx in the female 3.0–4.9 category and for hypopharynx in the male 5.0–10.0 category). ORs for oropharyngeal and hypopharyngeal cancers were larger in females, while ORs for oral cavity and laryngeal cancers were similar by sex. Estimates of EOR/drink-year for an expanded number of DPD categories are shown in Table 4.

EOR/drink-year estimates by DPD categories (square symbol) generally increased with greater DPD, indicating a strengthening of the associations, and were greater in females for oropharynx ($p<0.01$) and hypopharynx ($p=0.06$) and similar by sex for oral cavity ($p=0.64$) and larynx ($p=0.72$) (Figure 5 and Table 4). For oropharyngeal cancer, the fit of model (2) with both interactions of sex and drink-years and of sex and DPD changed little with the omission of the interaction of sex and DPD ($p=0.72$), but degraded significantly with the omission of the interaction of sex and drink-years ($p<0.01$) (Supplemental Table S2). Thus, the increased ORs in females derived primarily from effect modification of drink-years by sex (different β's), and not DPD by sex. Parameter estimates for this model were $\beta_{female}=0.0341$, $\beta_{male}=0.0073$ and $\phi_1=0.339$. Among controls, drinkers who consumed ≤10 DPD, averaged 77.3 drink-years and 2.2 DPD, resulting in fitted ORs for oropharyngeal cancer of 4.4 for females and 1.7 for males. For hypopharyngeal cancer, the fitted ORs using the parameter estimates $\beta_{female}=0.0205$, $\beta_{male}=0.0065$ and $\phi_1=1.201$ were 5.1 for females and 2.3 for males. Fitted ORs were similar using the full model.

The enhancement of the alcohol association in females for oropharynx and hypopharynx, but not for oral cavity and larynx, may appear inconsistent with Table 2, in which homogeneity of ORs by sex was not rejected for any site. However, those were marginal rather than joint ORs. Repeating analyses in Table 2, tests of homogeneity of joint ORs by drink-years and DPD in males and females rejected for oropharyngeal cancer ($p<0.01$) and nearly rejected for hypopharyngeal cancers ($p=0.10$), as well as for oral cavity ($p=0.02$) but not for laryngeal cancer ($p=0.29$).

Study-specific results

We used a logistic model to examine sex-specific estimates for ln(BMI) by study and conducted sign tests of the null hypothesis of no preferential direction in trend to evaluate consistency of results across studies. Ten studies enrolled oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers and five studies enrolled oral cavity, oropharyngeal and hypopharyngeal cancers only. For ln(BMI), 98 of 104 parameter estimates (for each sex, 15 estimates for oral cancer and oropharynx, 12 for hypopharynx and 10 for larynx) were

negative ($p<0.01$), indicating increased ORs with lower BMIs. For oral cavity, there was a suggestion of enhanced ORs in males (1 of 15 parameters estimates smaller in females, $p<0.01$), but no differential ORs for oropharynx (5 of 15 estimates were smaller in females, $p=0.30$) hypopharynx (4 of 12 estimates were smaller in females, $p=0.39$) or larynx (8 of 10 estimates were smaller in females, $p=0.11$).

Study-specific results generally followed overall results in showing enhanced ORs by pack-years and drink-years in females for oropharyngeal and hypopharyngeal cancers. For smoking, 9 of 15 parameter estimates for pack-years were greater in females for oral cavity cancer studies ($p=0.61$), 13 of 15 for oropharyngeal cancer studies ($p=0.01$), 8 of 11 for hypopharyngeal cancer studies ($p=0.23$) and 10 of 10 laryngeal ($p<0.01$) cancer studies. For laryngeal cancer, female estimates were greater for 7 of 10 studies ($p=0.34$) when we restricted data to smokers. Parameter estimates for drink-years were greater in females for 14 of 15 oral cavity cancer studies ($p=0.12$), for 13 of 15 oropharyngeal cancer studies ($p=0.01$), 12 of 13 hypopharyngeal studies ($p<0.01$) and 6 of 10 laryngeal cancer studies ($p=0.75$), suggesting enhanced ORs for females for oropharyngeal and hypopharyngeal cancers.

DISCUSSION

In previous INHANCE analyses, ORs were increased with lower BMIs and were larger for oral cavity/pharyngeal cancer compared with laryngeal cancer [16–20]. The current analysis demonstrated similar patterns and magnitudes in males and females. In addition, ORs by smoking and drinking were greater in females for oropharyngeal and, possibly, hypopharyngeal cancers, but similar by sex for oral cavity and laryngeal cancers. The enhanced association with alcohol consumption for oropharyngeal cancer in females appeared to result from effect modification by drink-years, and not consumption rate (DPD). The enhanced ORs for smoking and drinking in females for hypopharyngeal cancer should be interpreted cautiously since they were only 84 and 96 female case subjects, respectively.

Studies have consistently reported increased ORs for HNC with lower BMI [8,14,15,19,23–29], suggesting that our associations were unlikely due to misclassification, confounding or disease-related weight loss in the period prior to disease diagnosis, sometimes referred to as reverse causation [30]. For cancer outcomes, particularly those outside the gastrointestinal tract, evidence for substantial prodromal weight loss one year or more prior to diagnosis is weak [30], and not likely sufficient to induce our observed 4-fold variation in ORs for BMI. Four INHANCE studies ascertained BMI both at enrollment and 2 to 5 years prior. These BMI variables were highly correlated with a correlation coefficient of 0.88 and OR patterns were similar for each metric [19,20]. Thus, confounding from disease-related weight loss did not appear to strongly influence our results.

The increased ORs with lower BMI were similar in both sexes, indicating no effect modification, which was consistent with the few previous reports. Previously, one study found greater BMI effects for oral cavity/pharyngeal cancer in males [15], while another found greater effects for laryngeal cancer in females [14]. There was a slightly greater inverse association for BMI in males for oral leukoplakia, a frequent precursor condition [31], but no differential BMI association by sex for oral submucous fibrosis [32]. Thus, there is little current evidence of differential BMI associations for HNC by sex.

For all outcomes, the strength of the pack-years association diminished with increasing CPD, i.e., for fixed pack-years, higher CPD for shorter duration was less deleterious than lower CPD for longer duration, while the strength of the drink-years association increased with DPD through 10 DPD. While smoking was more strongly linked to laryngeal cancer

and drinking more strongly linked to oral cavity/pharyngeal cancer, we found significantly enhanced ORs for smoking and alcohol consumption in females for oropharyngeal and hypopharyngeal cancers, but similar ORs by sex for oral cavity and laryngeal cancers. For smoking, the female excess for pharyngeal cancer was consistent with several case-control [5–7] and cohort [9,10] studies but not all. A hospital-based case-control study reported similar smoking ORs by sex [8], while a cohort study found greater relative risks in males, but included only 10 female cases who smoked [11]. For laryngeal cancer, we found only one study, which reported greater effects in females, based on 49 female cases [33]. Published results for alcohol consumption by sex were limited to one cohort study showing greater relative risks in females [13] and two case-control studies, one suggesting slightly greater ORs for oral cavity/pharynx by drinking in males [8] and another showing similar ORs [6].

Sex-specific cancer susceptibility has been studied most intensively for smoking and lung cancer and has evoked considerable debate [34–39]. Analysis of two cohorts and a review of six others found comparable smoking associations by sex [38,39]. Moreover, U.S. lung cancer mortality rates in males and females have converged in recent birth cohorts, consistent with increasingly similar sex-specific smoking prevalence [40]. Thus, convincing epidemiologic evidence of increased susceptibility to cigarette smoke in either sex has not emerged.

There is no clear consensus for differential ORs by sex for other smoking-related cancers as well. While studies of bladder cancer and smoking have reported increased ORs in females [41,42], a pooled analysis of 8,000+ bladder cancer cases from 14 case-control studies identified a small increased association in males [43], and a recently published large case-control study found no difference in ORs by sex [44], suggesting that increased sex-related smoking susceptibility for bladder cancer remains unproven [45]. Similarly, a pooled analysis of 1,481 pancreatic cancer cases from eight studies in the Pancreatic Cancer Cohort Consortium observed no interaction of smoking by sex [46].

Misclassification of smoking, drinking and BMI or confounding from other risk factors, such as human papillomavirus (HPV), diet and occupation may have influenced results. In some populations, alcohol drinking may be less socially acceptable in women, leading to underreporting of consumption in women and overestimation of alcohol-related ORs. However, these influences were likely minimal, since associations were complex and differed by site, necessitating a very complex pattern of misclassification, reporting bias or confounding.

HPV infection has emerged as an important risk factor for oropharyngeal and, to a lesser extent, oral cavity cancers [1]; however, we do not think confounding appreciably influenced our results. We can estimate the possible impact of HPV status on our approximately 2-fold OR for oropharyngeal cancer in female compared to male smokers [47]. The U.S. National Health and Nutrition Survey (NHANES) 2003–2004 estimated HPV-16 seroprevalences for ages 50–59, the oldest category reported, of 7.0% in males and 13.9% in females [48]. While ORs have ranged widely, a meta-analysis reported OR=4.3 for the association of oropharyngeal cancer and HPV-16 seropositivity [49], resulting an adjusted OR for females of 1.7, minimally different from our 2-fold estimate. In NHANES III, conducted from 1991 to 1994, HPV-16 seropositive percentages for ages 50–59 were 10.2% in men and 11.0% in females, implying no HPV-16-related confounding [50]. This adjustment assumed multiplicative ORs, although ORs for smoking and HPV may be additive [51,52]. Using an adjustment procedure for additive models [53], the adjusted OR for females was unchanged at 2.0.

Head and neck cancers may consist of two etiologically distinct entities, with sexual behavior more strongly associated with HPV-16 positive tumors and with smoking, drinking and poor oral hygiene more strongly associated with HPV-16 negative tumors [51]. If HPV-16 tumor status were unrelated to sex, conditional on age, smoking and drinking, then the omission of tumor status would have reduced ORs in both sexes, due to outcome misclassification [54]. However, if females were predisposed to HPV-16 negative tumors, then the strength of smoking-related, and possibly drinking-related, associations would be enhanced relative to males, as we observed. Studies in case patients of the association of sex and tumor HPV status, either type 16 specifically or multiple high risk types, are mixed, with tumor prevalence rates for HPV infection greater in males [51,55,56], greater in females [57–60] or similar by sex [61,62]. Thus, while enhanced ORs in females for oropharyngeal and hypopharyngeal cancers for smoking and drinking may have derived from HPV infection, current studies are inconsistent in supporting that explanation. Analyses that incorporate tumor HPV status are needed.

In summary, while low BMI, greater smoking and alcohol consumption increased ORs for HNC, our pooled analysis of 15 case-control studies from the INHANCE consortium has provided the first comprehensive examination of differential susceptibility to these factors in males and females. We found no evidence for differential ORs for BMI by sex. We did find enhanced associations of cigarette smoking and alcohol consumption in females for oropharyngeal and, possibly, hypopharyngeal cancers, but not for oral cavity and laryngeal cancers. The extent that the effect modifications of ORs by sex derived from unmeasured confounders or resulted from sex-related factors linked to unobserved disease subtypes, e.g., HPV-positive oropharyngeal cancer, remain to be clarified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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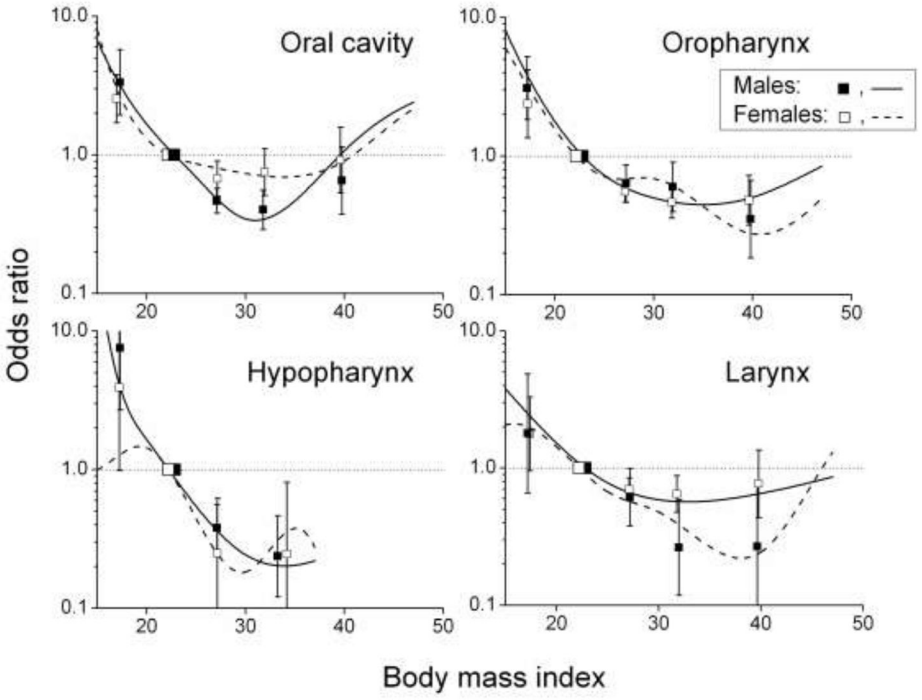

Figure 1.

Odds ratios for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers by categories of body mass index (BMI) for males (solid symbol) and females (open symbol) and fitted restricted cubic splines, with knots at 25, 30 and 40 BMI at all sites, except hypopharynx, with knots at 20 and 30 BMI. Abscissa values for ORs were located at the category means, with fitted splines adjusted to the mean BMI for the referent category. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and ≤10 DPD drinkers.

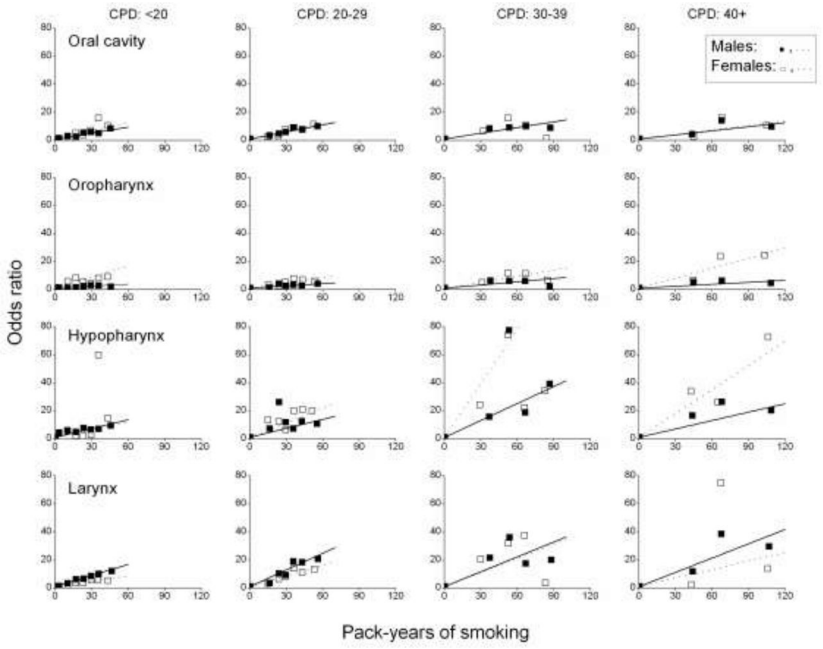

Figure 2.

Odds ratios for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers by categories of pack-years and number of cigarettes smoked per day (CPD) for males (solid symbol) and females (open symbol), and a fitted model with linear odds ratios in pack-years. Bars represent 95% confidence interval. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers.

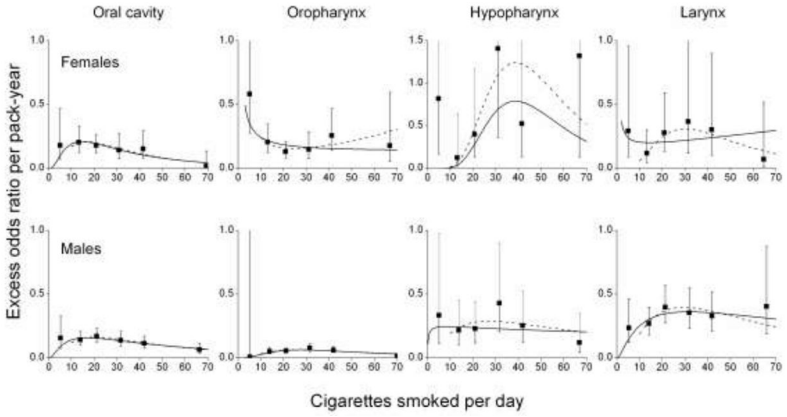

Figure 3.

Estimated excess odds ratios per pack-year for males and females for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers within categories of cigarettes per day (CPD) (square symbol) with 95% confidence interval, model (2) fitted to all data (solid line) and to never and 10+ CPD smokers (dash line). Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers.

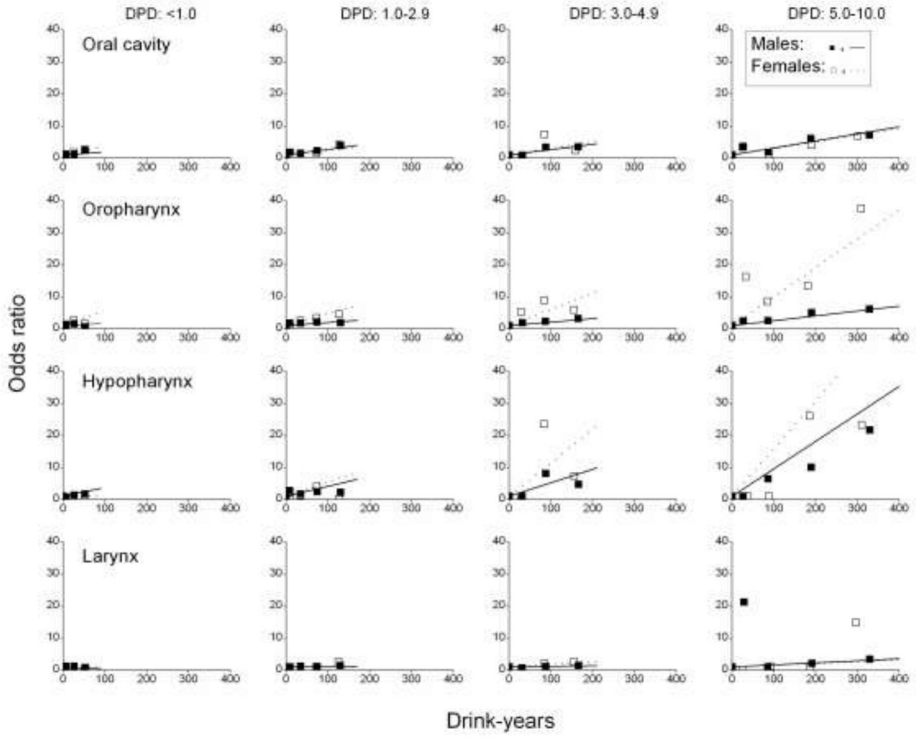

Figure 4.

Odds ratios for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers by categories of drink-years of alcohol consumption and number of drinks per day (DPD) for males (solid symbol) and females (open symbol), and a fitted model with linear odds ratios in drink-years. Bars represent 95% confidence interval. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and ≤10 DPD drinkers.

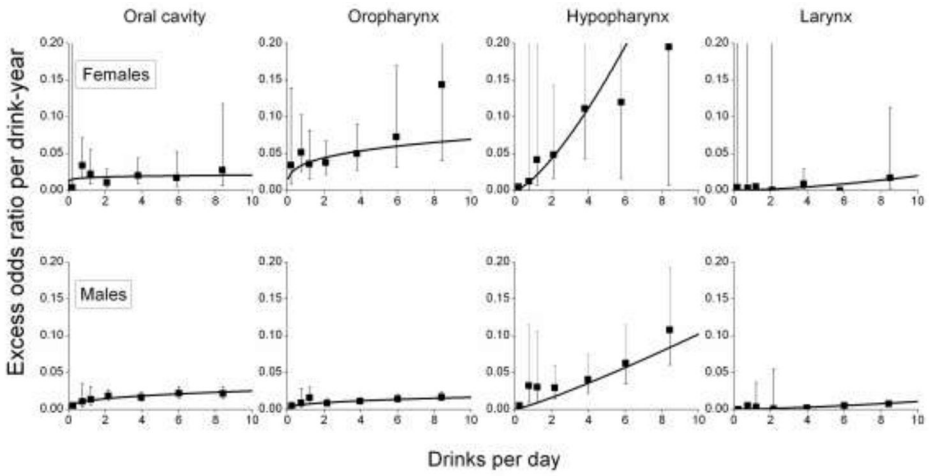

Figure 5.

Estimated excess odds ratios per drink-year for males and females for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers within categories of drinks per day (DPD) (square symbol) with 95% confidence interval, model (2) fitted to never and ≤10 DPD (solid line). Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and ≤10 DPD drinkers.

Table 1

Numbers of cases and controls by body mass index (BMI), smoking and drinking variables by cancer site. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.

	Oral Cavity		Oropharynx		Hypopharynx		Larynx		Controls	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**
BMI[a]										
<18.5	189	110	63	91	9	31	20	55	178	140
18.5–24.9	463	825	317	817	65	243	124	765	2,048	3,547
25.0–29.9	172	441	116	603	14	116	64	515	1,373	4,293
30.0–34.9	65	113	53	171	8[b]	22[b]	19	131	573	1,163
35.0+	36	27	15	51			10	37	243	271
Pack-years[c]										
0	249	138	148	274	15	22	25	82	2,868	3,091
1–29	117	282	114	252	10	93	63	219	461	1,303
30–39	60	204	34	199	10	55	35	229	100	508
40–49	67	164	48	167	16	52	27	205	86	365
50–59	46	120	26	121	13	37	16	136	37	210
60+	81	344	103	342	20	106	35	284	69	404
Cigarettes per day (CPD)[c]										
1–19	112	297	112	279	12	98	72	341	404	1,260
20–29	150	415	90	358	23	108	64	422	236	950
30–39	46	142	45	179	16	57	17	148	57	267
40+	63	260	78	265	18	80	23	162	56	313
Drink-years[a]										
0	469	183	160	205	19	17	91	142	2,111	1,862
1–49	300	436	248	576	27	62	94	416	1,765	3,478
50–99	82	251	63	285	25	86	22	219	339	1,483
100–149	34	197	40	191	11	56	16	176	131	927
150–199	16	151	31	162	7	47	8	151	47	634
200+	24	298	22	314	7	144	6	399	22	1,030
Drinks per day (DPD)[a]										

	Oral Cavity		Oropharynx		Hypopharynx		Larynx		Controls	
	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males
0.01–0.9	245	309	189	398	22	45	85	287	1,447	2,583
1.0–2.9	132	399	110	446	24	99	32	368	686	2,354
3.0–4.9	45	250	55	290	20	84	21	247	133	1,327
5.0–10.0	34	375	50	394	11	167	8	459	38	1,288

[a] Includes ≤10 DPD drinkers.

[b] Subjects with 30+ BMI.

[c] Includes never and current cigarette-only smokers.

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) by body mass index (BMI), smoking and drinking variables by cancer site. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.

	Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Females		Males		Females		Males		Females		Males		Females		Males	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
BMI[a]																
<18.5	2.54	1.7–3.8	3.33	1.9–5.7	3.09	1.8–5.2	2.38	1.4–4.2	3.91	1.0–16.	7.54	2.7–21.	1.79	0.7–4.9	1.77	1.0–3.3
18.5–24.9	1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]	
25.0–29.9	0.67	0.5–0.9	0.46	0.4–0.6	0.63	0.5–0.9	0.55	0.5–0.7	0.25	0.1–0.6	0.38	0.3–0.6	0.61	0.4–1.0	0.70	0.6–0.8
30.0–34.9	0.75	0.5–1.1	0.40	0.3–0.6	0.60	0.4–0.9	0.46	0.4–0.6	0.24	0.1–0.8	0.24	0.1–0.5	0.26	0.1–0.6	0.65	0.5–0.9
35.0+	0.92	0.5–1.6	0.65	0.4–1.1	0.35	0.2–0.7	0.48	0.3–0.7					0.27	0.1–0.8	0.77	0.4–1.4
P-trend [c]	<0.01		<0.01		<0.01		<0.01		<0.01		0.10		<0.01		<0.01	
P-homogeneity[d]			0.04				0.61				0.75				0.14	
Pack-years[e]																
0	0.33	0.2–0.5	0.30	0.2–0.4	0.22	0.2–0.3	0.63	0.5–0.8	0.34	0.1–1.1	0.16	0.1–0.3	0.05	0.0–0.1	0.21	0.1–0.3
1–29	1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]	–
30–39	3.18	1.8–5.7	1.60	1.2–2.2	1.34	0.7–2.5	1.52	1.1–2.1	6.62	1.4–31.	0.74	0.4–1.3	2.22	1.1–4.5	2.06	1.5–2.8
40–49	3.30	1.7–6.3	1.97	1.3–2.9	1.80	0.9–3.6	1.67	1.1–2.5	6.37	1.5–27.	1.11	0.6–2.2	2.28	1.0–5.4	2.51	1.7–3.6
50–59	5.72	2.5–13.	1.62	1.0–2.6	2.11	0.8–5.2	1.66	1.0–2.7	9.81	1.6–62.	1.40	0.6–3.3	4.36	1.2–16.	3.35	2.1–5.4
60+	4.59	1.8–12.	2.79	1.7–4.7	3.57	1.4–9.2	1.78	1.0–3.0	1.62	0.2–12.	0.75	0.3–2.0	3.98	0.9–18.	3.24	1.9–5.6
P-trend	<0.01		<0.01		0.01		0.01		0.06		0.27		<0.01		<0.01	
P-homogeneity			0.12				<0.01				0.10				<0.01	
Cigarettes per day (CPD)[f]																
1–19	1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]	–
20–29	0.87	0.5–1.5	0.84	1.0–1.9	0.80	0.5–1.4	1.25	0.9–1.7	1.09	0.3–4.1	1.70	1.0–2.9	2.07	1.1–4.1	1.47	1.1–2.0
30–39	0.69	0.3–1.6	0.86	0.7–2.0	0.75	0.3–1.9	1.95	1.2–3.2	9.36	1.4–64.	4.89	2.0–12.	2.44	0.6–9.4	1.47	0.9–2.5
40+	0.70	0.3–1.9	0.84	0.6–1.9	1.36	0.5–3.6	1.75	1.0–3.0	10.7	1.3–85.	4.03	1.4–11.	1.99	0.4–9.0	1.81	1.0–3.2
P-trend	0.38		0.25		0.94		0.03		0.07		0.16		0.91		<0.01	
P-homogeneity			0.48				0.15				0.51				0.74	

	Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Females		Males		Females		Males		Females		Males		Females		Males	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Drink-years [g]																
0	1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]	--
1–49	0.94	0.7–1.2	1.01	0.9–1.5	1.38	1.0–1.8	1.31	1.1–1.6	0.59	0.3–1.3	0.84	0.4–1.7	1.14	0.8–1.7	0.91	0.7–1.2
50–99	1.61	0.9–2.9	1.95	1.2–2.7	2.20	1.2–4.0	1.25	0.9–1.7	3.49	0.8–15.	1.63	0.6–4.2	2.68	1.0–7.1	0.78	0.5–1.2
100–149	1.44	0.6–3.3	1.58	1.7–4.1	1.73	0.8–3.7	1.30	0.9–1.9	1.40	0.2–8.4	1.46	0.5–4.2	3.18	1.0–11.	0.99	0.6–1.6
150–199	1.96	0.5–6.6	1.94	1.9–5.5	2.65	1.0–7.1	1.64	1.0–2.6	1.07	0.1–11.	1.22	0.4–3.8	3.84	0.8–19.	1.13	0.7–1.9
200+	1.82	0.6–6.5	1.93	2.2–6.6	1.98	0.6–7.0	1.98	1.2–3.2	1.25	0.1–18.	2.65	0.8–8.4	3.79	0.6–26.	1.51	0.9–2.7
P–trend	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01		0.01		<0.01	
P–homogeneity			0.66				0.60				0.50				0.31	
Drinks per day (DPD)[h]																
0.01–0.9	1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]		1.00 [b]	
1.0–2.9	1.23	0.8–1.9	1.25	0.9–1.6	1.60	1.1–2.4	1.46	1.2–1.8	1.35	0.4–4.3	1.62	0.8–3.3	0.45	0.2–1.0	1.20	0.9–1.6
3.0–4.9	1.81	0.8–4.0	1.20	0.8–1.8	3.21	1.6–6.4	1.91	1.3–2.7	5.95	1.1–30.	3.33	1.4–8.2	0.67	0.2–2.3	1.20	0.8–1.9
5.0–10.0	2.37	0.8–7.5	1.75	1.1–2.8	7.63	2.8–21.	2.82	1.8–4.3	19.6	1.8–217.	7.03	2.6–19.	0.52	0.1–2.7	1.89	1.1–3.1
P-trend	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01		0.88		<0.01	
P-homogeneity					0.78		0.29				0.68				0.27	

[a] Includes ≤10 DPD drinkers. ORs adjusted for study, age, sex, education, type of tobacco product used, pack-years, CPD, years since cessation of smoking, drink-years and DPD.

[b] Referent category for ORs.

[c] P-value for test of no trend in ORs.

[d] P-value for test of homogeneity of category-specific ORs in males and females.

[e] Includes never and current cigarette-only smokers. ORs adjusted for study, age, sex, education, BMI, drink-years, DPD and CPD.

[f] Includes never and current cigarette-only smokers. ORs adjusted for study, age, sex, education, BMI, drink-years, DPD and pack-years.

[g] Includes ≤10 DPD drinkers. ORs adjusted for study, age, sex, education, BMI, pack-years, CPD, years since smoking cessation, use of other tobacco products and DPD.

[h] Includes ≤10 DPD drinkers. ORs adjusted for study, age, sex, education, BMI, pack-years, CPD, years since smoking cessation, use of other tobacco products and drink-years.

Table 3

Estimates of the excess odds ratio (OR) per pack-year within categories of cigarettes smoked per day [a] and sex. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers.

	Cigarettes smoked per day							
	<10	**10–19**	**20–29**	**30–39**	**49–49**	**50+**	**P*b***	**P*b,c***
				Oral cavity cancers and controls				
Females	0.1790	0.2014	0.1783	0.1402	0.1501	0.0145	0.56	0.60
Males	0.1546	0.1407	0.1683	0.1373	0.1135	0.0621		
				Oropharyngeal cancers and controls				
Females	0.5800	0.2048	0.1279	0.1459	0.2561	0.1761	<0.01	<0.01
Males	0.0046	0.0501	0.0527	0.0747	0.0597	0.0147		
				Hypopharyngeal cancers and controls				
Females	0.8187	0.1224	0.3969	1.4060	0.5217	1.3210	0.05	0.01
Males	0.3330	0.2163	0.2278	0.4283	0.2513	0.1188		
				Laryngeal cancers and controls				
Females	0.2916	0.1167	0.2776	0.3652	0.3013	0.0698	0.18	0.44
Males	0.2346	0.2681	0.3960	0.3529	0.3266	0.4018		

[a] Estimates of γ_j based on $OR(d) = 1 + \Sigma\ \gamma_j\ d_j$ where d_j and γ_j are the pack-years and estimated excess OR per pack-year for cigarette/day category j, respectively.

[b] P-value for 3-degrees of freedom chi-square tests of homogeneity of model (2) for continuous pack-years and cigarette/day by sex. Additional test results given in Supplement Table S1.

[c] P-value for data restricted to never and 10+ CPD smokers.

Table 4

Estimates of the excess odds ratio (OR) per drink-year within categories of drinks per day[a] and sex. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for subjects consuming ≤ 10 drinks per day.

	Drinks per day							
	<0.5	**0.5–0.9**	**1.0–1.9**	**2.0–2.9**	**3.0–4.9**	**5.0–6.9**	**7.0–10.0**	**P[b]**
Females	0.0039	0.0337	0.0220	0.0105	0.0202	0.0169	0.0274	0.64
Males	0.0050	0.0105	0.0135	0.0180	0.0163	0.0218	0.0213	
Females	0.0342	0.0514	0.0355	0.0377	0.0498	0.0725	0.1437	<0.01
Males	0.0050	0.0087	0.0159	0.0083	0.0109	0.0140	0.0166	
Females	0.0050	0.0125	0.0419	0.0487	0.1112	0.1201	0.2072	0.06
Males	0.0050	0.0320	0.0301	0.0292	0.0406	0.0625	0.1080	
Females	0.0040	0.0029	0.0000	0.0002	0.0085	0.0000	0.0169	0.72
Males	0.0000	0.0050	0.0031	0.0006	0.0019	0.0051	0.0075	

[a] Estimates of γ_j based on $OR(d) = 1 + \Sigma\ \gamma_j\ d_j$ where d_j and γ_j are drink-years and estimated excess OR per drink-year for drinks/day category j, respectively.

[b] P-values for 2-degrees of freedom chi-square tests of homogeneity of model (2) for continuous pack-years and cigarette/day by sex. Additional test results given in Supplement Table S2.