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ORIGINAL PAPER

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 women and 1,516 men), 2,297 oropharynx (564 women and 1,733 men), 508 hypopharynx (96 women and 412 men), and 1,740 larynx (237 women and 1,503 men) cases from the INHANCE consortium of 15 head and neck cancer case–control studies. Controls numbered from 7,604 to 13,829

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subjects, depending on analysis. Analyses fitted linear-exponential excess ORs models.

Results ORs were increased in underweight (<18.5 BMI) relative to normal weight (18.5–24.9) and reduced in overweight and obese categories (≥25 BMI) for all sites and were homogeneous by sex. ORs by smoking and drinking in women compared with men 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

Introduction

Incidence and mortality rates for head and neck cancers (HNC), including cancers of the oral cavity, oropharynx, hypopharynx, and larynx, are higher in men than women [1–3]. Male-to-female ratios vary widely, with ratios of 4–20 in Southern, Central and Eastern Europe, 2–10 in Northern Europe and North America, and 1.5–2.5 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 men and women. 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 women [5–7] and one reported similar ORs by sex [8], while among cohort studies two reported ORs greater in women [9, 10] and one reported ORs greater in men [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 women but included only 49 female cases and no never-smokers [9]. For all HNC, a cohort study found greater smoking relative risks in men but included only 13 female cases who smoked [12]. Results for alcohol consumption are limited to one cohort study, showing greater relative risks in women [13] for HNC, and two case–control studies, one suggesting slightly greater ORs in men for oral cavity/pharynx [8] and another showing comparable ORs [6]. Two case–control studies reported ORs at lower BMIs greater for laryngeal

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cancer in women [14] and greater for oral cavity/pharyngeal cancer in men [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.

Materials 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, and International Multi-Center) ascertained BMI 2–5 years prior. In four studies (New York, Boston, Latin America, and International Multi-Center) with both measures, the Pearson correlation was 0.88 and ORs were similar. We therefore minimized missing data using BMI at enrollment or 2–5 years prior if values were missing.

For analyses of never and current cigarette-only smokers, there were 1,872 oral cavity (620 women and 1,252 men), 1,828 oropharynx (473 women and 1,355 men), 449 hypopharynx (84 women and 365 men), and 1,356 larynx (201 women and 1,155 men) cases (Table 1). Controls numbered 9,502 (3,621 women and 5,881 men). For analyses of BMI and of never and ≤10 DPD drinkers, there were 2,441 oral cavity (925 women and 1,516 men), 2,297 oropharynx (564 women and 1,733 men), 508 hypopharynx (96 women and 412 men), and 1,740 larynx (237 women, 1,503 men) cases. Controls numbered 13,829 (4,415 women and 9,414 men). Not all studies enrolled laryngeal cancer cases, resulting in fewer controls; with controls numbering 7,604 (2,815 women and 4,789 men) for the smoking analysis and 10,982 for the drinking analysis (3,420 women and 7,562 men). 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

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Table 1 Numbers of cases and controls by body mass index (BMI), smoking, and drinking variables by cancer site

	Oral cavity		Oropharynx		Hypopharynx		Larynx		Controls	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
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]										
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

Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium

[a] Includes ≤10 DPD drinkers

[b] Subjects with 30+ BMI

[c] Includes never and current cigarette-only smokers

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

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

where β represented the strength of association, i.e., the excess OR (EOR) per pack-year at $g(n) = 1$, and $g(\cdot)$ defined its variation with exposure delivery. Consistent with previous analyses, we set $g(n) = \exp\{\varphi_1 \ln(n) + \varphi_2 \ln(n)^2\}$. We compared the fit of model (1) with ORs for a cross-classification of pack-years and CPD relative to never-smokers. Within each $i = 1,\ldots,$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

$$\mathrm{OR}(d,n,s) = 1 + \sum_s \beta_s d_s g_s(n_s) \quad (2)$$

where sex-specific β_s parameters and $g_s(\cdot)$ functions replaced β and $g(\cdot)$ and where d_s equaled d and n_s equaled n within level s and zero otherwise. We used likelihood

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) by body mass index (BMI), smoking and drinking variables by cancer site

	Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Women		Men		Women		Men		Women		Men		Women		Men	
	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	
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	

Table 2 continued

	Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Women		Men		Women		Men		Women		Men		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
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	

Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium

[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 men and women

[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

ratio tests to assess whether sex-specific differences resulted from total exposure (different β's) or exposure rate (different $g(\cdot)$ 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 $g(\cdot)$ 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 between sex and one factor (e.g., pack-years) while minimizing the influence of the interaction between sex and its closely related correlate (e.g., CPD).

We applied a similar model for drink-years and DPD, except $g(n) = \exp\{\varphi_1 \ln(n)\}$, 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 men and women

ORs relative to normal BMI (18.5–24.9) were increased for underweight BMIs for all cancer sites and both sexes (Table 2, Fig. 1). ORs were below one for categories ≥25 BMI, resulting in fourfold and greater ratios across the full BMI range. Homogeneity of ORs by sex was rejected for oral cavity cancer ($p = 0.04$); however, Fig. 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 men and 18.7 (9.8–35.5) for women, a fourfold ratio. Due to this presumed distortion of case–control odds in never-smoking females, ORs for other pack-years categories for women 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 women, 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 men and

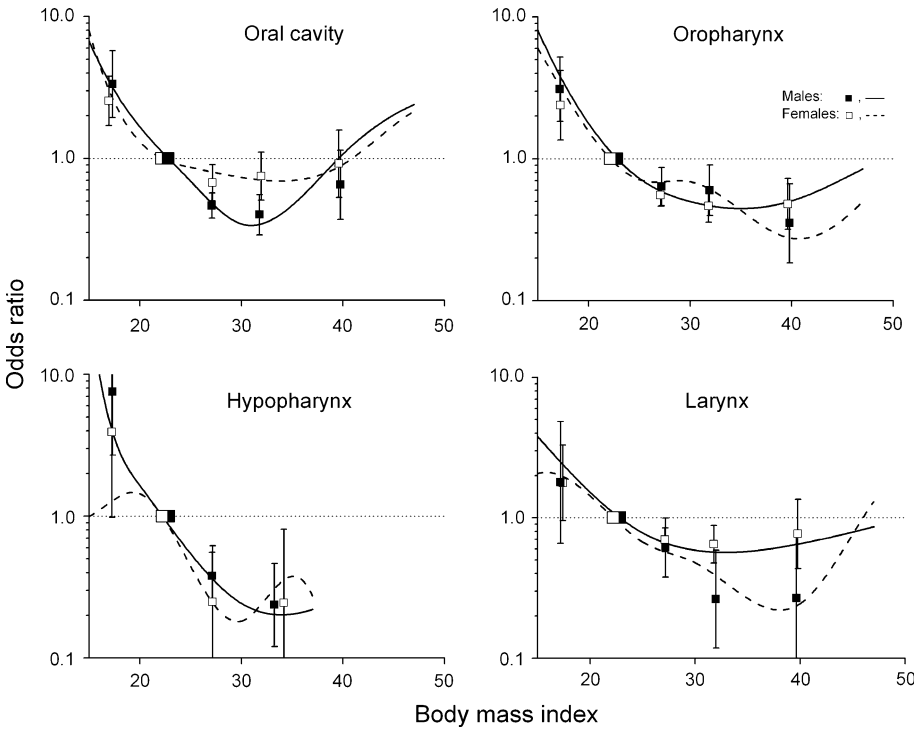

Fig. 1 Odds ratios for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers by categories of body mass index (BMI) for males (*solid symbol*) and females (*open symbol*) and fitted restricted cubic splines, with knots at 25, 30, and 40 BMI at all sites, except hypopharynx, with knots at 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

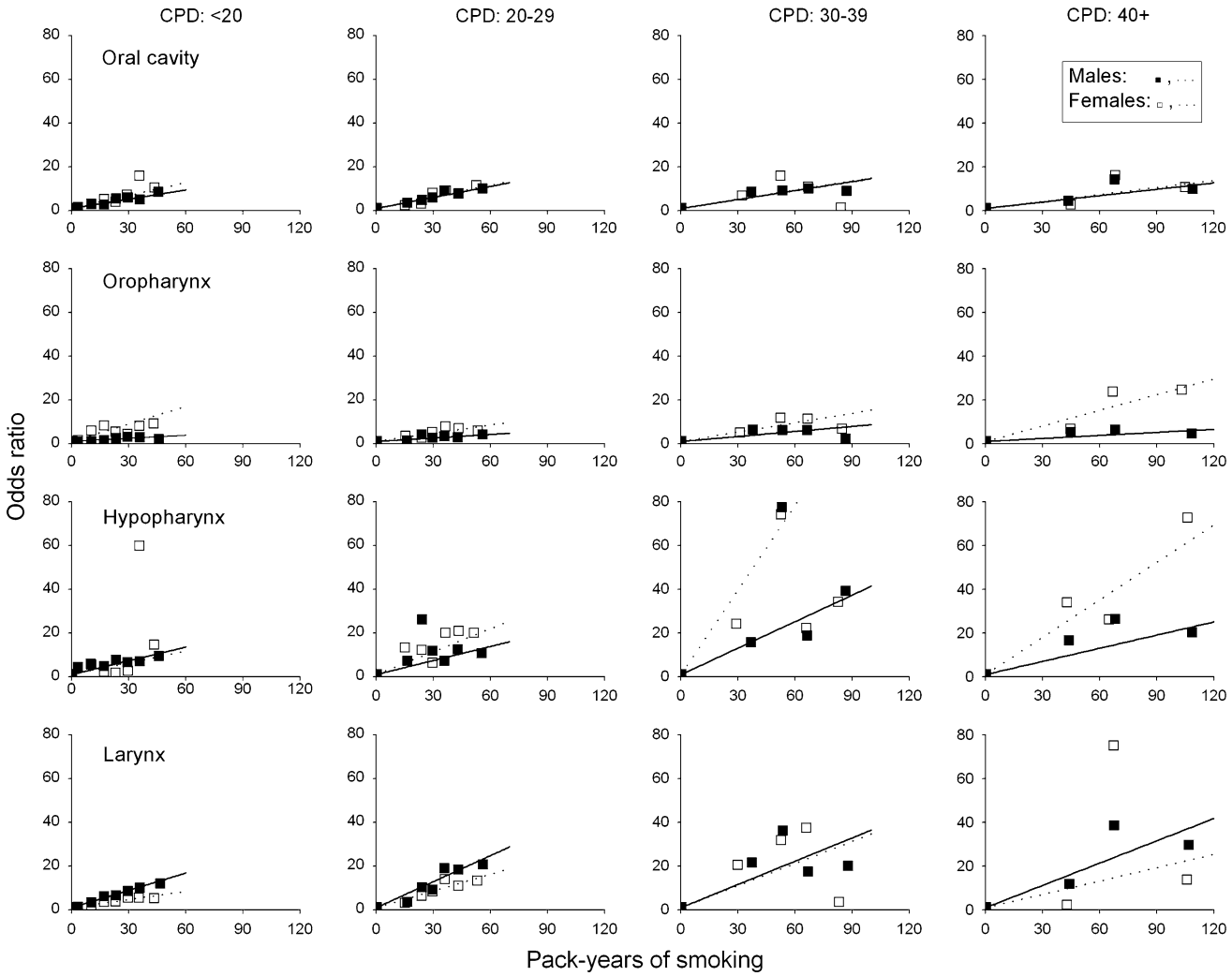

Fig. 2 Odds ratios for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancers by categories of pack-years and number of cigarettes smoked per day (CPD) for males (*solid symbol*) and females (*open symbol*), and a fitted model with linear odds ratios in pack-years. Bars represent 95% confidence interval. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers

women among smokers did not reject ($p = 0.97$). Adjusted for pack-years, ORs by CPD varied only for men ($p = 0.03$ 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 women ($p = 0.83$) (Table 2). Tests of homogeneity of ORs by drink-years and by DPD in men and women 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 (Fig. 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 men. Since the OR in women for never-smokers was 0.10, we fixed the referent parameter for female never-smokers to $\ln(0.10 \times 1.20) = -2.123$. ORs in women were consistently higher for oropharyngeal cancer and generally higher for hypopharyngeal cancer (Fig. 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

Table 3 Estimates of the excess odds ratio (OR) per pack-year within categories of cigarettes smoked per day[a] and sex

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

Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers

[a] Estimates of γ_j based on $\mathrm{OR}(d) = 1 + \sum \gamma_j \, \mathrm{d}_j$ 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

linearity, four tests were rejected at the 0.05-level (for oropharynx in the men 30–39 and 40+ CPD categories and in the women <20 CPD category, and for hypopharynx in the men 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 for CPD categories (Fig. 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 $g(\cdot)$ functions, while for hypopharynx, the models suggested similar β estimates ($p = 0.12$) and different $g(\cdot)$ 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 ($=1 + 34.5 \times 63.58 \times \exp\{-3.792 \times \ln(19.8) + 0.597 \times \ln(19.8)^2\}$) for women and 3.0 for men, while for hypopharyngeal cancer, fitted ORs were 15.0 for women and 10.4 for men 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 (Fig. 4). Among thirty-two tests of no departure from linearity, three tests were rejected (for oral cavity in the women <1.0 DPD category, for oropharynx in the women 3.0–4.9 category, and for hypopharynx in the men 5.0–10.0 category). ORs for oropharyngeal and hypopharyngeal cancers were larger in women, 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 women for oropharynx ($p < 0.01$) and hypopharynx ($p = 0.06$) and similar by sex for oral cavity ($p = 0.64$) and larynx ($p = 0.72$) (Fig. 5, 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 between sex and DPD ($p = 0.72$), but degraded significantly with the omission of the interaction between sex and drink-years ($p < 0.01$) (Supplemental Table S2). Thus, the increased ORs in

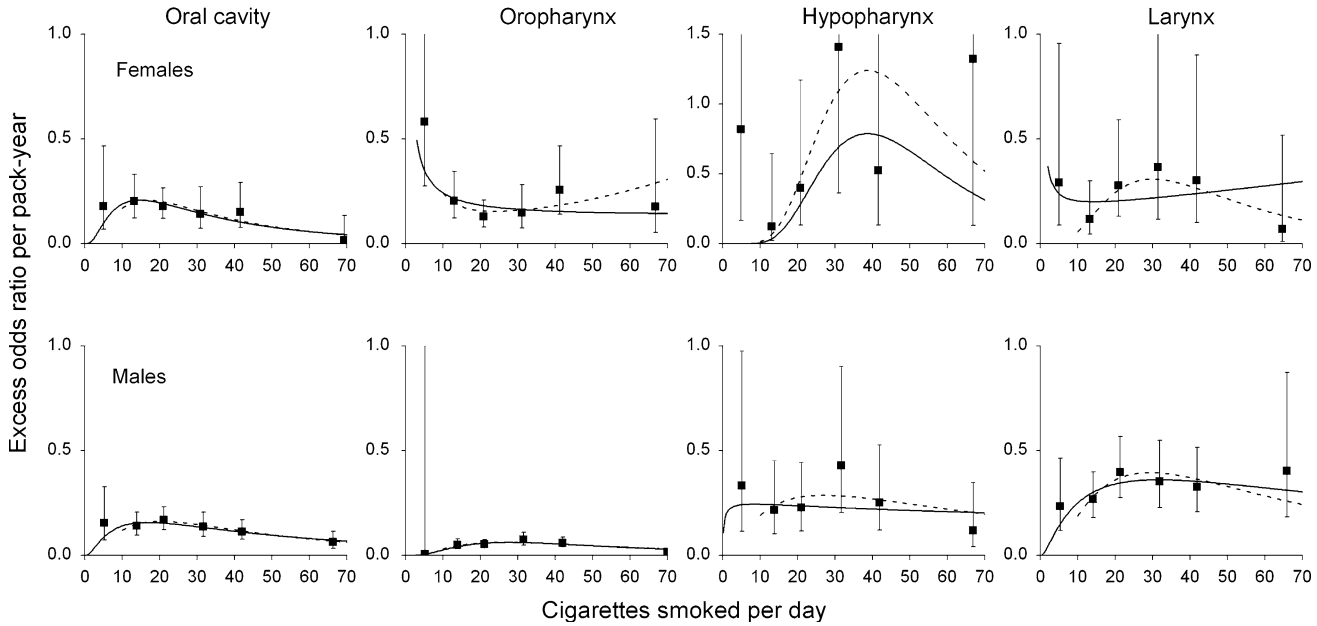

Fig. 3 Estimated excess odds ratios per pack-year for males and females for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers within categories of cigarettes per day (CPD) (*square symbol*) with 95% confidence interval, model (2) fitted to all data (*solid line*) and to never and 10+ CPD smokers (*dash line*). Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and current cigarette-only smokers

women derived primarily from effect modification of drink-years by sex (different β's), and not DPD by sex. Parameter estimates for this model were $\beta_{\text{female}} = 0.0341$, $\beta_{\text{male}} = 0.0073$, and $\varphi_1 = 0.339$. Among controls, drinkers, who consumed $\leq$10 DPD, averaged 77.3 drink-years and 2.2 DPD, resulting in fitted ORs for oropharyngeal cancer of 4.4 for women and 1.7 for men. For hypopharyngeal cancer, the fitted ORs using the parameter estimates $\beta_{\text{female}} = 0.0205$, $\beta_{\text{male}} = 0.0065$, and $\varphi_1 = 1.201$ were 5.1 for women and 2.3 for men. Fitted ORs were similar using the full model.

The enhancement of the alcohol association in women 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 men and women 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 men (1 of 15 parameters estimates smaller in women, $p < 0.01$), but no differential ORs for oropharynx (5 of 15 estimates were smaller in women, $p = 0.30$) hypopharynx (4 of 12 estimates were smaller in women, $p = 0.39$), or larynx (8 of 10 estimates were smaller in women, $p = 0.11$).

Study-specific results generally followed overall results in showing enhanced ORs by pack-years and drink-years in women for oropharyngeal and hypopharyngeal cancers. For smoking, 9 of 15 parameter estimates for pack-years were greater in women 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, women 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 women 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 ($p < 0.01$),

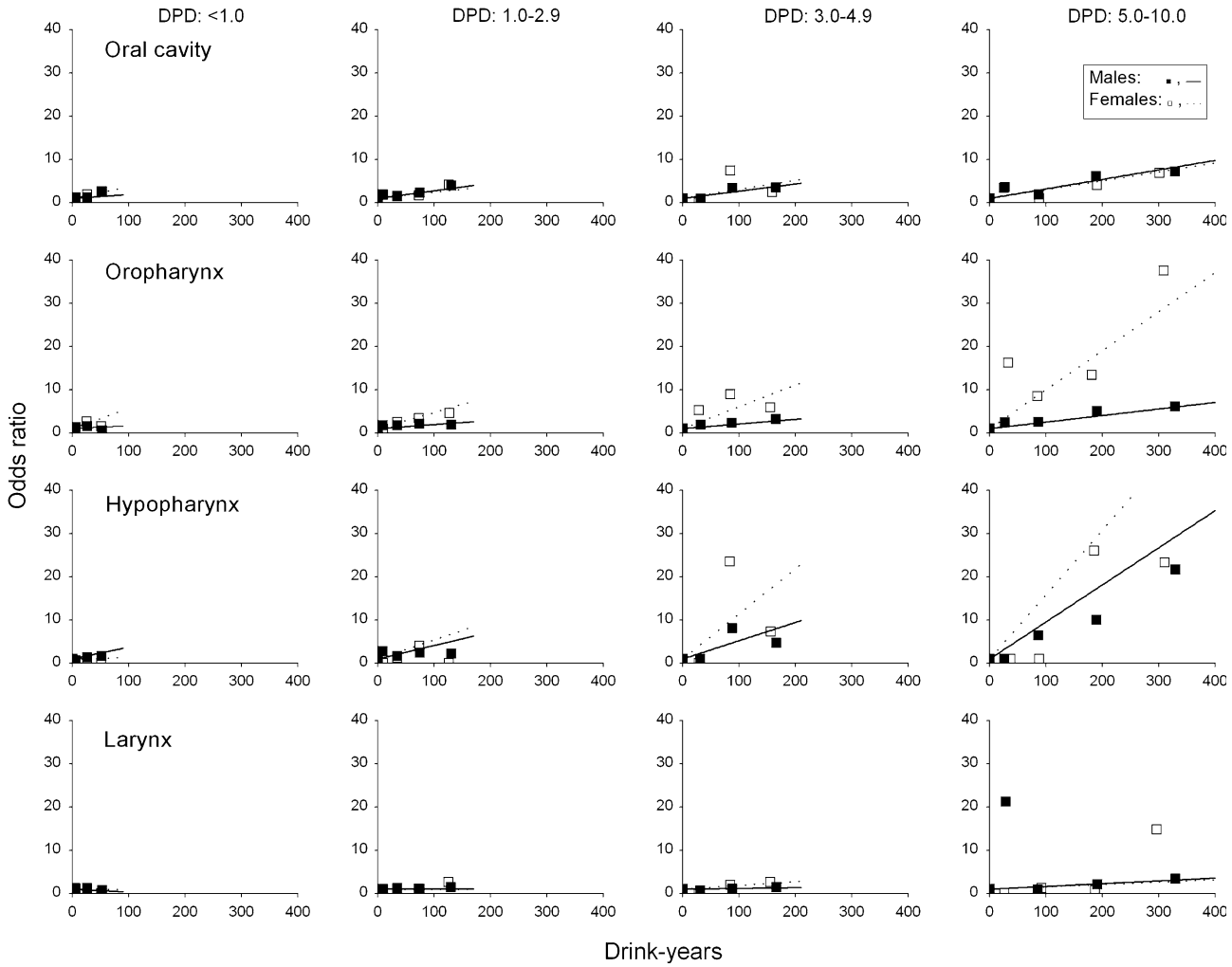

Fig. 4 Odds ratios for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers by categories of drink-years of alcohol consumption and number of drinks per day (DPD) for males (*solid symbol*) and females (*open symbol*), and a fitted model with linear odds ratios in drink-years. Bars represent 95% confidence interval. Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and ≤10 DPD drinkers

and 6 of 10 laryngeal cancer studies ($p = 0.75$), suggesting enhanced ORs for women 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 men and women. In addition, ORs by smoking and drinking were greater in women 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 women appeared to result from effect modification by drink-years, and not consumption rate (DPD). The enhanced ORs for smoking and drinking in women 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 1 year or more prior to diagnosis is weak [30], and not likely sufficient to induce our observed fourfold variation in ORs for BMI. Four INHANCE studies

Table 4 Estimates of the excess odds ratio (OR) per drink-year within categories of drinks per day a and sex

	Drinks per day							p^b
	<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	
Oral cavity cancers and controls								
Women	0.0039	0.0337	0.0220	0.0105	0.0202	0.0169	0.0274	0.64
Men	0.0050	0.0105	0.0135	0.0180	0.0163	0.0218	0.0213	
Oropharyngeal cancers and controls								
Women	0.0342	0.0514	0.0355	0.0377	0.0498	0.0725	0.1437	<0.01
Men	0.0050	0.0087	0.0159	0.0083	0.0109	0.0140	0.0166	
Hypopharyngeal cancers and controls								
Women	0.0050	0.0125	0.0419	0.0487	0.1112	0.1201	0.2072	0.06
Men	0.0050	0.0320	0.0301	0.0292	0.0406	0.0625	0.1080	
Laryngeal cancers and controls								
Women	0.0040	0.0029	0.0000	0.0002	0.0085	0.0000	0.0169	0.72
Men	0.0000	0.0050	0.0031	0.0006	0.0019	0.0051	0.0075	

Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for subjects consuming ≤10 drinks per day

[a] Estimates of γ_j based on $\mathrm{OR}(d) = 1 + \sum \gamma_j \mathrm{d}_j$ 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

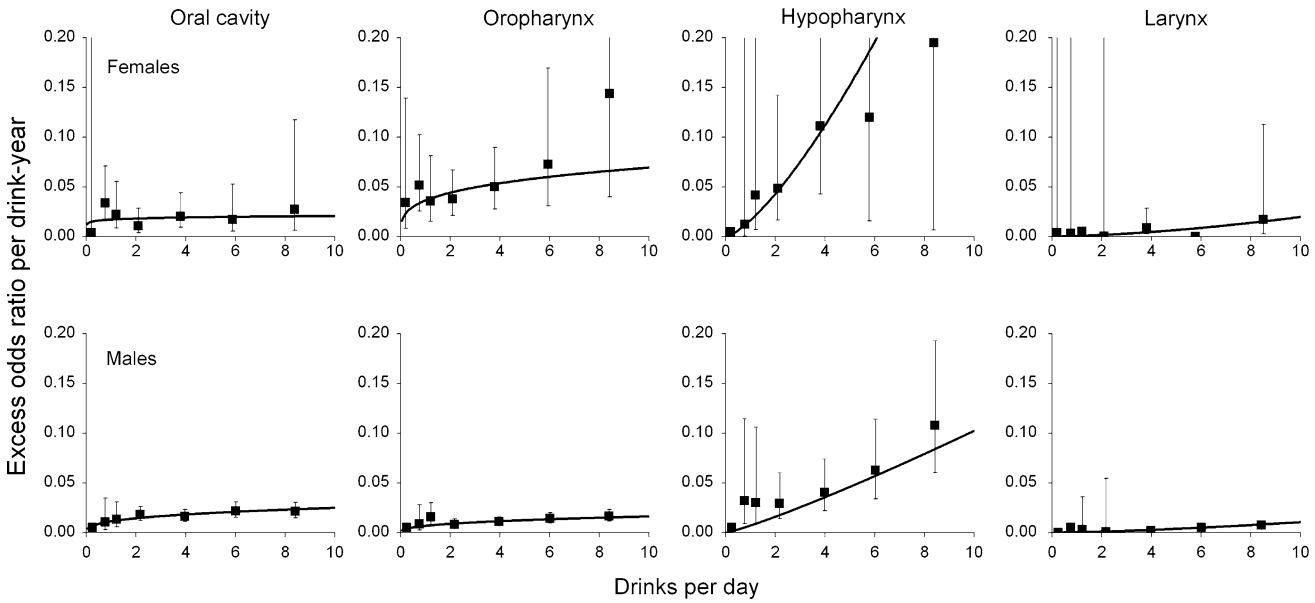

Fig. 5 Estimated excess odds ratios per drink-year for males and females for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers within categories of drinks per day (DPD) (*square symbol*) with 95% confidence interval, model (2) fitted to never and ≤10 DPD (*solid line*). Pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium for never and ≤10 DPD drinkers

ascertained BMI both at enrollment and 2–5 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 men [15], while another found greater effects for laryngeal cancer in women [14]. There was a slightly

greater inverse association for BMI in men for oral leukoplakia, a frequent precursor condition [31], but no differential BMI association by sex for oral submucous fibrosis [32]. Thus, there is a 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 women 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 men, but included only 10 female cases who smoked [11]. For laryngeal cancer, we found only one study, which reported greater effects in women, based on 49 female cases [33]. Published results for alcohol consumption by sex were limited to one cohort study showing greater relative risks in women [13] and two case–control studies, one suggesting slightly greater ORs for oral cavity/pharynx by drinking in men [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 men and women 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 women [41, 42], a pooled analysis of 8,000+ bladder cancer cases from 14 case–control studies identified a small increased association in men [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 twofold OR for oropharyngeal cancer in female compared with 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 men and 13.9% in women [48]. While ORs have ranged widely, a meta-analysis reported OR = 4.3 for the association of oropharyngeal cancer with HPV-16 seropositivity [49], resulting an adjusted OR for women of 1.7, minimally different from our twofold 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 women, 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 women 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 between 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 men [51, 55, 56], greater in women [57–60], or similar by sex [61, 62]. Thus, while enhanced ORs in women 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 men and women. We found no evidence for differential ORs for BMI by sex. We did find enhanced associations between cigarette smoking and alcohol consumption in women 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, remains to be clarified.

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