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Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium

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Background Sexual contact may be the means by which head and neck cancer patients are exposed to human papillomavirus (HPV).

Methods We undertook a pooled analysis of four population-based and four hospital-based case–control studies from the International

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Head and Neck Cancer Epidemiology (INHANCE) consortium, with participants from Argentina, Australia, Brazil, Canada, Cuba, India, Italy, Spain, Poland, Puerto Rico, Russia and the USA. The study included 5642 head and neck cancer cases and 6069 controls. We calculated odds ratios (ORs) of associations between cancer and specific sexual behaviours, including practice of oral sex, number of lifetime sexual partners and oral sex partners, age at sexual debut, a history of same-sex contact and a history of oral–anal contact. Findings were stratified by sex and disease subsite.

Results Cancer of the oropharynx was associated with having a history of six or more lifetime sexual partners [OR = 1.25, 95% confidence interval (CI) 1.01, 1.54] and four or more lifetime oral sex partners (OR = 2.25, 95% CI 1.42, 3.58). Cancer of the tonsil was associated with four or more lifetime oral sex partners (OR = 3.36, 95 % CI 1.32, 8.53), and, among men, with ever having oral sex (OR = 1.59, 95% CI 1.09, 2.33) and with an earlier age at sexual debut (OR = 2.36, 95% CI 1.37, 5.05). Cancer of the base of the tongue was associated with ever having oral sex among women (OR = 4.32, 95% CI 1.06, 17.6), having two sexual partners in comparison with only one (OR = 2.02, 95% CI 1.19, 3.46) and, among men, with a history of same-sex sexual contact (OR = 8.89, 95% CI 2.14, 36.8).

Conclusions Sexual behaviours are associated with cancer risk at the head and neck cancer subsites that have previously been associated with HPV infection.

Keywords Sexual practices, head and neck cancer, oropharyngeal neoplasms, homosexual, gay men, risk factors, pooled analyses

Introduction

Cancers of the head and neck are the fifth most common cancer worldwide, with more than 600 000 cases diagnosed each year.[1] These malignancies, the majority of which are squamous cell carcinomas, are made up of several anatomic subsites: the oral cavity, oropharynx, hypopharynx and larynx. Tobacco and alcohol consumption are established risk factors for these cancers.[2,3]

Recent research has highlighted the risk conferred by human papillomavirus (HPV) infection on head and neck cancer. The 2007 International Agency for Research on Cancer (IARC) monograph on HPV found sufficient evidence for HPV carcinogenicity of the oral cavity and oropharynx, and limited evidence for HPV carcinogenicity of the larynx.[4] In a review of 60 studies on HPV prevalence, HPV DNA was found in 26% of head and neck tumours, with a greater prevalence at the oropharynx, where 36% of lesions had HPV DNA.[5] The incidence of some head and neck cancers has increased in recent years, particularly among younger age groups, which may be at least partially attributed to HPV infection.[6,7]

We hypothesize that oral HPV infection is sexually acquired, although we cannot rule out the possibility of transmission via mouth-to-mouth contact or other means. There is increasing evidence that sexual behaviours are the means by which individuals with HPV-positive head and neck tumours are exposed to the virus.[8–16] Some studies of sexual practices and oral and pharyngeal cancer risk have found no associations among some of the behaviours examined, perhaps due to varying data collection methods, the inclusion of HPV-negative cases in the sample or to insufficient sample sizes for examining results by disease subsite.[10–12] The purpose of this study was to examine the risk of head and neck cancer associated with sexual practices.

Methods

International Head and Neck Cancer Epidemiology consortium

The current study used pooled data collected by the International Head and Neck Cancer Epidemiology (INHANCE) consortium.[17] The majority of INHANCE studies were hospital-based investigations. In-person

interviews were conducted in all studies with the exception of the Iowa study, in which participants completed self-administered questionnaires. Written informed consent was obtained from all study participants, and investigations were approved by the institutional review board at each study centre.

Participants

Participants for the current investigation were selected from the eight INHANCE studies that included questions on sexual practices (Table 1).[8,9,14,18–22] Subjects were included in this analysis if their tumour had been classified by the original study as an invasive tumour of the oral cavity, oropharynx, hypopharynx or larynx according to the International Classification of Diseases (ICDs)–Oncology, Version 2 (ICD-O-2)[23] or the ICD 9[24] or ICD 10.[25] The ICD-O-2 codes used to classify each tumour site were: (i) oral cavity (includes base of the tongue, lip, tongue, gum, floor of the mouth and hard palate): codes C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8 and C06.9; (ii) oropharynx (includes lingual tonsil, soft palate, uvula, tonsil and oropharynx): codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8 and C10.9; (iii) hypopharynx (includes pyriform sinus and hypopharynx): codes C12.9, C13.0–C13.2, C13.8 and C13.9; and (iv) larynx (includes glottis, supraglottis and subglottis): codes C32.0–C32.3 and C32.8–C32.9. As HPV has been isolated from cancers of the tonsils and the base of the tongue, we additionally examined the odds for these subsites separately.[15,26–29] Tonsil cancers were identified as C09.0, C09.1, C09.8 and C09.9. Base of the tongue cancers were identified as C01.9.

In most studies, controls were frequency matched to cases on the basis of age, sex and neighbourhood of residence, with some studies frequency matching on additional factors (study centre, hospital or race/ethnicity). In the hospital-based studies, controls were recruited from persons being seen in the same hospital as the cases, under the following conditions: persons presenting for annual or screening visits (Iowa); persons with a defined list of diseases unrelated to tobacco and alcohol (Central Europe, International Multicentre). In the population-based studies, eligibility included residence in the geographic area of the study, and recruitment occurred via random digit dial (Seattle, US Multicentre) or via random selection from residential lists (Boston, Puerto Rico). At all sites, exclusion criteria included no prior diagnosis of head and neck cancer.

Across the eight INHANCE studies, the questions on sexual practices were not asked to all participants in all centres. Within the International Multicentre Study, an extensive supplementary sexual history questionnaire was conducted at seven of the study sites (Barcelona, Granada, Havana, Montreal, Seville, Sydney and Warsaw), whereas the remaining study sites were only asked a small number of questions. In the Boston study, the sexual history questions were only asked to a subsample of the participants, as the questions were added after the beginning of data collection. In the US Multicentre Study, questions on sexual history were only asked to the younger participants (<60 years of age).

In order to limit bias due to non-response, we excluded seven study centres from the analysis (Ireland, Bangalore and Sudan from the International Multicentre Study; Banska Bystrica, Bucharest, Budapest and Lodz from the Central Europe study), which had >40% of the sexual history data missing. Additional sensitivity analyses examined if estimates changed when other study sites that were missing differing proportions of data (>10, >20 and >30%) were excluded from the sample; these results showed little appreciable change in effect estimates. Participants were additionally excluded if they were missing information on sex, race or age ($n = 49$, 0.4%). The final sample included 5642 head and neck cancer cases and 6069 controls.

Exposures

We used 11 exposure variables: whether participants had ever practiced oral sex on a partner (never/ever); the age at sexual debut ($\leqslant 18$ or $\geqslant 19$ years); the frequency of practising oral sex (occasionally, often, most of the time); the lifetime numbers of all sexual partners (1, 2, 3, 4–5, 6 or more) and of oral sex partners (0–1, 2–3, 4 or more); ever diagnosed with an sexually transmitted disease (STD; yes/no); ever having genital warts or condyloma (yes/no); ever diagnosed with herpes (yes/no); and if participants had ever had a partner who had genital warts (yes/no). Men were asked if they had ever had sex with a prostitute (never/ever). Participants were asked if they ever had sexual contact with a person of the same sex (never/ever); due to the small number of women answering yes to this question, results are only reported among men. Men were asked if they had ever had oral–anal contact. Details on data pooling are available in the Supplementary data available at *IJE* online.

Statistical analyses

The associations between sexual behaviours and head and neck cancer were estimated by unconditional logistic regression, with adjustment for study centre, age, race, educational attainment, alcohol drinking (ml/day), tobacco smoking (pack-years), years of cigar smoking and years of pipe smoking. When participants were missing information on educational attainment, we imputed that variable according to a method described previously.[30] Odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

We conducted likelihood ratio tests for heterogeneity of results by study site[31] but observed little evidence

Table 1 Summary of individual studies with information on sexual behaviours in the INHANCE consortium

Study location[a]	Recruitment period	Case subjects				Control subjects[b]		
		Source	Participation rate, %	Age eligibility, years	Total	Source	Participation rate, %	Total
Europe								
Central Europe (Moscow)[21]	1998–2003	Hospital	96	⩾15	367	Hospital patients	97	383
North America								
Seattle, WA[8,9]	1985–95	Cancer registry	54, 63[d]	18–65	407	Random digit dialing	63, 61[d]	607
Iowa[14]	1993–2006	Hospital	87	>17	546	Hospital patients	92	759
US Multicenter (Los Angeles, New Jersey, Atlanta, San Francisco)[c, 22]	1984–85	Cancer registry	75	18–59[e]	435	Random digit dialing and health care financing administration rosters	76	522
Boston, MA[18]	1999–2003	Medical facilities	89	⩾18	153	Resident list	49	247
South/Central America								
Puerto Rico[19]	1992–95	Cancer registry	71	21–79	350	Residential records	83	521
Latin America (Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, Sao Paulo)[c] (NA)	2000–2003	Hospital	95	15–79	2191	Hospital patients	86	1706
International								
International (Sydney, Milan, Granada, Montreal, Havana, Madras, Udine, Trivandrum, Aviano, Barcelona, Sevilla, Warsaw)[c,20]	1992–97	Hospital	89	NA	1193	Hospital/community	87	1324
				Total	**5642**			**6069**

[a]Representative publication in which study methods are available.
[b]All studies frequency matched controls to cases, minimally on age and sex. The Latin America study additionally frequency matched by study centre, whereas the US Multicentre Study additionally frequency matched by ethnicity.
[c]Multicentre Study.
[d]This study was comprised of two different case–control investigations.
[e]The sexual history questions were asked only of subjects <60 years of age.
NA = not applicable.

for heterogeneity. Fixed effect estimates were therefore provided.

We conducted stratified analyses to determine if effect estimates of sexual behaviours varied between smokers and non-smokers. No evidence was seen for interaction between sexual behaviours and smoking (results not shown). Recent papers have highlighted a higher risk of HPV-positive tumours among younger persons.[7] Although the cross-sectional nature of data collection prohibited a true age–period–cohort analysis, we examined estimates by age and birth cohort, in order to determine if variation in sexual practices over time might influence the odds of head and neck cancer seen with sexual behaviours, little difference was seen (results not shown).

In order to distinguish the possible effects of having multiple sexual partners with the effect from ever having oral sex, we examined the potential confounding effects of each while controlling for the other. Results showed the additional control for these factors made little difference in effect estimates.

Results

Characteristics of the study population are shown in Table 2. Cases and controls differed significantly with respect to sex, race/ethnicity, educational attainment, cigarette smoking and alcohol drinking. There was considerable variation with regards to the numbers of sexual partners and the practice of oral sex by study location and demographics.

There was little evidence for increased odds of cancers of the oral cavity or larynx with any of the sexual behaviours examined, and no clear pattern could be ascertained with regards to sexual behaviours and cancer of the hypopharynx (Table 3). Having a history of six or more lifetime sexual partners and a history of four or more oral sex partners were associated with increased odds of oropharyngeal cancer.

Tonsil cancer was associated with ever having oral sex (among men), four or more oral sex partners (Table 4) and with a younger age at sexual debut (among men), although no trend could be seen with age (data not shown). Cancer of the base of the tongue was associated with a history of ever having oral sex (among women), and with having two sexual partners in comparison with only one. Among men, a history of same-sex contact was associated with base of the tongue cancer.

In general, the CIs between male and female participants overlapped, suggesting similar risks from sexual behaviours. Heterogeneity tests showed no significant differences between men and women when examining the outcomes of oral sex, the number of oral sex partners and the number of lifetime sexual partners. When examining the effect of age at sexual debut, significant differences were seen between men and women for both oral cavity cancers ($P = 0.004$) and tonsil cancers ($P = 0.004$).

Although the number of men reporting sex with prostitutes was small, no associations were seen between these behaviours and cancer (data not shown). Few participants reported ever having any STD, and fewer still reported specifically a history of herpes, genital warts or having had a partner with a history of genital warts. These conditions were not associated with disease status in multivariate analyses (data not shown). In addition, the frequency of having oral sex was not associated with disease status (data not shown).

Discussion

This is the largest study yet conducted on the association between sexual behaviours and head and neck cancers. Our analyses showed associations, albeit inconsistent, between certain sexual behaviours and cancers of the head and neck. Our results support previous findings of an increased risk of oropharyngeal cancers with HPV.[4] In addition, results support an increased risk for cancers of the tonsil and those of the base of the tongue, findings that are concordant with studies of HPV in head and neck tumours.[26,28] Associations were seen with a history of ever having oral sex, greater numbers of sexual partners and a history of same-sex contact. Similar to other studies, we found little evidence for any association of sexual behaviours with cancers of the oral cavity or of the larynx.[20]

The previous studies on this topic took place in the USA, India, Poland, Italy and Cuba, and all were case–control in design, including both hospital[10–16] and population based.[8,9] In contrast to the present study, most grouped together cancers of any head and neck subsite. Almost all observed elevated risks with some sexual behaviours but not others, with the most consistently elevated risk seen with a larger number of sexual partners,[8,9,11,13,16] with the exception of in Cuba, where a majority of cases and controls reported multiple sexual partners, likely limiting the power to find an association.[10] In the studies that stratified by gender, differential findings were observed between men and women, although no clear pattern was apparent as to whether men or women may be at greater risk.[9,13] In two studies, higher cancer risk was observed with a greater number of marriages, but not simultaneously with a greater number of sexual partners,[12,13] suggesting that subjects do modify responses based on social acceptability. Similar to that found here, no consistent elevated cancer risk was seen with STD history,[8–10,13,15] although higher effect estimates were observed in US-based studies, possibly due to more widespread STD screening. Studies with the most consistent, elevated effect estimates examined sexual behaviours among HPV-positive patients only.[14,16] Variations in

Table 2 Characteristics of the study population

	Cases		Controls		Sexual behaviours among controls					
					Percentage of those who had oral sex		Mean number of sexual partners		Median number of sexual partners	
	n	%	*n*	%	Men	Women	Men	Women	Men	Women
Studies and locations										
International Multicentre										
Australia (Sydney)	36	<1	59	1	42	50	5	1	1	1
Canada (Montreal)	32	<1	42	<1	70	64	17	3	7	2
Cuba (Havana)	144	3	199	3	69	41	25	2	15	1
India (Madras, Trivandrum)	379	7	382	6	9	[a]	1	1	1	1
Italy (Aviano, Milan, Udine)	131	2	148	2	57	[a]	4	1	3	1
Spain (Barcelona, Granada, Seville)	351	6	370	6	21	13	13	1	3	1
Poland (Warsaw)	120	2	124	2	52	21	12	1	8	1
Central Europe										
Russia (Moscow)	367	7	383	6	16	[a]	15	5	8	1
USA (Boston)	153	3	247	4	78	66	17	4	5	2
USA (Iowa)	546	10	759	13	51	44	15	4	5	2
USA (Seattle)	407	7	607	10	68	66	10	5	9	3
USA (Atlanta, Los Angeles, New Jersey, San Francisco)[b]	435	8	522	9						
Puerto Rico	350	6	521	9	26	18	11	3	5	2
Latin America										
Argentina (Buenos Aires)	348	6	207	3	42	12	30	2	15	1
Cuba (Havana)	196	3	176	3	59	41	36	3	35	2
Brazil (Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, Sao Paulo)	1647	29	1323	22	25	12	22	4	10	1
P-value[c]			<0.01		<0.01	<0.01	<0.01	0.03	<0.01	<0.01
Sex										
Female	1241	22	1658	27		34		3		1
Male	4401	78	4411	73	38		16		8	
P-value			<0.01			0.03		<0.01		<0.01
Race/ethnicity[d]										
White	2720	48	3497	58	44	43	13	3	5	2
Black	198	4	243	4	56	48	15	5	9	3
Hispanic Americans	33	<1	67	1	75	[e]	13	4	6	3
Asian or Pacific Islander	385	7	392	6	11	[e]	1	1	1	1
Other	115	2	164	3	25	30	12	3	6	2
Latin American	2191	39	1706	28	31	14	25	4	15	1
P-value			<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Educational attainment										
No formal	207	4	123	2	16	7	11	1	2	1
Less than junior high school	2517	47	2159	37	26	15	19	3	8	1
Some high school	889	17	902	15	39	39	14	3	7	1
High-school graduate	536	10	668	11	45	39	18	3	6	2
Some college/technical school	761	14	1174	20	58	53	12	4	6	2

(continued)

Table 2 Continued

	Cases		Controls		Sexual behaviours among controls					
					Percentage of those who had oral sex		Mean number of sexual partners		Median number of sexual partners	
	n	%	*n*	%	Men	Women	Men	Women	Men	Women
College graduate or more	422	8	819	14	54	59	15	5	5	2
P-value			<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Age (years)										
<40	215	4	416	7	61	68	16	6	8	2
40 to 49	1012	18	1180	19	51	54	17	4	8	2
50 to 59	1934	34	1966	32	42	40	18	3	8	1
60 to 69	1576	28	1568	26	29	24	16	3	8	2
⩾70	905	16	939	15	21	12	15	2	8	1
P-value			<0.01		<0.01	<0.01	0.3	<0.01	<0.01	<0.01
Birth cohort										
<1930	1279	23	1379	23	23	15	13	2	4	1
1930–39	1762	31	1771	29	32	29	16	3	6	1
1940–49	1571	28	1617	27	44	41	18	3	8	1
1950–59	856	15	962	16	48	48	19	5	8	2
⩾1960	174	3	340	6	54	69	19	6	8	3
P-value			<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Smoking										
Non-smokers	764	14	2242	37	37	27	13	3	4	1
1–20 pack-years	975	17	1562	26	42	45	15	4	6	2
21–40 pack-years	1559	28	1139	19	38	48	18	4	8	3
⩾41 pack-years	2287	41	1074	18	34	31	22	6	8	2
P-value			<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Alcohol drinking										
Never drinkers	815	15	1654	28	26	22	12	2	3	1
>0–3 ml/day or ⩽1 drink/week	469	9	788	13	44	43	16	3	4	2
>3–8 ml/day or 2 drinks/week	265	7	308	9	42	47	12	5	6	2
>8–18 ml/day or 1 drink/day	383	10	552	13	42	57	13	5	5	2
>18–40 ml/day or 2 drinks/day	541	13	789	13	41	55	17	5	6	2
>40–75 ml/day or 3–4 drinks/day	700	12	777	8	42	46	19	8	8	2
>75 ml/day or ⩾5 drinks/day	1883	35	820	14	37	48	25	7	14	4
P-value			<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[a]Female participants were not asked the question.
[b]This study's questionnaire did not include these questions.
[c]*P*-values were computed by chi-square, analysis of variance and Wilcoxon rank sum test.
[d]Information on ethnicity was not collected in the Central Europe and Latin America studies. In the Central Europe study, all subjects were classified as White, since the large majority of these populations are expected to be White. In the Latin America study, we categorized all subjects as 'Latin American'.
[e]Few women in these groups answered this question.
Both the International Multicenter and the Latin America studies had study sites in Cuba. The studies were conducted during different years, so there was not overlap between subjects.

results are likely due to small sample sizes (less than 150 cases) and limited numbers of persons who had ever engaged in certain sexual practices,[8,12,15] inclusion of HPV-negative cases and differences in the prevalence of HPV in different regions.

There is a possibility that the protective associations seen at some subsites may be due to data collection methods. The timing of interviews for some of the INHANCE studies may have impacted self-reported sexual behaviours because, at some study sites,

Table 3 Multivariate analysis of the association between sexual behaviours and cancers of the head and neck, by tumour site and sex[a]

	Men				Women				Total			
	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI
Oral cavity												
Ever had oral sex[b]												
No	571	1851	1.00		148	536	1.00		719	2387	1.00	
Yes	251	1008	0.78	(0.64, 0.96)	69	227	0.97	(0.64, 1.46)	320	1235	0.80	(0.67, 0.95)
Missing	39	105			20	68			59	173		
Age in years at sexual debut[c]												
⩾19	186	629	1.00		119	295	1.00		305	924	1.00	
⩽18	213	566	0.98	(0.75, 1.27)	62	220	0.40	(0.25, 0.63)	275	786	0.77	(0.62, 0.95)
Missing	40	178			25	151			65	329		
No. of lifetime sexual partners[b]												
1	240	684	1.00		289	721	1.00		529	1405	1.00	
2	54	211	1.00	(0.69, 1.45)	42	156	0.86	(0.56, 1.31)	96	367	0.96	(0.73, 1.26)
3	148	487	1.07	(0.81, 1.41)	63	182	0.86	(0.59, 1.26)	211	669	1.00	(0.81, 1.24)
4 or 5	73	257	1.04	(0.73, 1.47)	22	83	0.85	(0.49, 1.50)	95	340	0.94	(0.70, 1.25)
⩾6	580	1961	0.93	(0.75, 1.17)	48	167	0.67	(0.43, 1.03)	628	2128	0.88	(0.73, 1.06)
Missing	88	239			23	85			111	324		
No. of oral sex partners[d]												
0–1	147	576	1.00		71	236	1.00		218	812	1.00	
2–3	26	123	0.75	(0.44, 1.28)	13	50	0.81	(0.38, 1.73)	39	173	0.75	(0.49, 1.15)
⩾4	28	113	0.70	(0.40, 1.22)	4	14	2.25	(0.54, 9.34)	32	127	0.93	(0.56, 1.55)
Missing	43	120			3	7			46	127		
Ever had oral–anal contact[e,f]												
No	96	394	1.00									
Yes	5	31	0.72	(0.26, 2.04)								
Missing	2	8										
Ever had same-sex contact[e,g]												
No	406	1254	1.00									
Yes	11	32	0.78	(0.31, 1.94)								
Missing	54	97										
Oropharynx[h]												
Ever had oral sex[b]												
No	541	2034	1.00		98	494	1.00		640	2548	1.00	
Yes	253	997	1.05	(0.86, 1.29)	47	205	1.03	(0.62, 1.70)	301	1202	1.05	(0.87, 1.26)
Missing	22	56			4	17			27	74		
Age in years at sexual debut[c]												
⩾19	133	629	1.00		60	295	1.00		193	924	1.00	
⩽18	189	566	1.23	(0.92, 1.64)	51	220	0.82	(0.49, 1.38)	240	786	1.10	(0.86, 1.40)
Missing	42	178			16	150			58	328		
No. of lifetime sexual partners[b]												
1	126	684	1.00		94	721	1.00		220	1405	1.00	
2	64	211	1.62	(1.11, 2.34)	38	156	1.90	(1.15, 3.12)	102	367	1.63	(1.22, 2.18)

(continued)

Table 3 Continued

	Men				Women				Total			
	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI
3	114	487	1.21	(0.88, 1.65)	40	182	1.16	(0.71, 1.90)	154	669	1.15	(0.89, 1.48)
4–5	76	257	1.36	(0.94, 1.96)	17	83	1.24	(0.62, 2.47)	93	340	1.29	(0.94, 1.76)
⩾6	574	1961	1.30	(1.00, 1.68)	51	167	1.39	(0.85, 2.28)	625	2128	1.25	(1.01, 1.54)
Missing	75	239			13	85			88	324		
No. of oral sex partners[d]												
0–1	145	576	1.00		61	236	1.00		206	812	1.00	
2–3	34	123	1.22	(0.73, 2.02)	9	50	0.48	(0.19, 1.26)	43	173	1.00	(0.65, 1.54)
⩾4	50	113	2.03	(1.22, 3.37)	7	14	3.06	(0.78,12.09)	57	127	2.25	(1.42, 3.58)
Missing	38	120			4	7			42	127		
Ever had oral–anal contact[e,f]												
No	72	394	1.00									
Yes	6	31	1.31	(0.49, 3.53)								
Missing	2	8										
Ever had same-sex contact[e,g]												
No	348	1254	1.00									
Yes	14	32	1.02	(0.43, 2.42)								
Missing	58	97										
Hypopharynx												
Ever had oral sex[b]												
No	182	1428	1.00		17	367	1.00		199	1815	1.00	
Yes	44	552	0.70	(0.47, 1.02)	3	65	0.65	(0.11, 3.74)	47	617	0.71	(0.49, 1.03)
Missing	5	44			0	9			5	54		
Age in years at sexual debut[c]												
⩾19	3	131	1.00		0	93	1.00		3	224	1.00	
⩽18	6	199	0.49	(0.09, 2.78)	2	100			8	299	0.88	(0.17, 4.42)
Missing	1	103			0	83			1	186		
No. of lifetime sexual partners[b]												
1	14	267	1.00		6	339	1.00		20	606	1.00	
2	20	171	1.93	(0.90, 4.18)	6	137	2.76	(0.66, 11.54)	26	308	2.05	(1.07, 3.93)
3	36	319	1.55	(0.78, 3.09)	5	113	0.35	(0.05, 2.65)	41	432	1.60	(0.88, 2.90)
4–5	22	216	1.43	(0.67, 3.04)	2	80	0.23	(0.02, 3.23)	24	296	1.50	(0.76, 2.94)
⩾6	150	1520	1.20	(0.65, 2.20)	3	110	0.35	(0.05, 2.36)	153	1630	1.23	(0.72, 2.11)
Missing	6	93			1	30			7	123		
No. of oral sex partners[d]												
0–1	43	364	1.00		6	111	1.00		49	475	1.00	
2–3	11	66	1.74	(0.73, 4.14)	0	13			11	79	1.60	(0.69, 3.71)
⩾4	1	48	0.43	(0.04, 4.20)	1	7	161.90	(0, ∞)	2	55	0.80	(0.14, 4.45)
Missing	1	29			0	6			1	35		
Ever had oral–anal contact[e,f]												
No	10	386	1.00									
Yes	0	29										
Missing	0	8										

(continued)

Table 3 Continued

	Men				Women				Total			
	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI
Ever had same-sex contact[e,g]												
No	29	412	1.00									
Yes	0	14										
Missing	9	12										
Larynx												
Ever had oral sex[b]												
No	586	1149	1.00		84	291	1.00		671	1460	1.00	
Yes	231	449	0.93	(0.76, 1.16)	13	47	0.84	(0.38, 1.87)	244	496	0.92	(0.75, 1.14)
Missing	17	38			7	6			25	45		
Age in years at sexual debut[c]												
⩾19	14	131	1.00		5	93	1.00		19	224	1.00	
⩽18	36	199	0.94	(0.44, 2.02)	12	100	2.13	(0.47, 9.58)	48	299	1.02	(0.53, 1.96)
Missing	6	103			1	83			7	186		
No. of lifetime sexual partners[b]												
1	76	257	1.00		56	331	1.00		132	588	1.00	
2	36	100	1.13	(0.68, 1.86)	25	102	1.40	(0.76, 2.58)	61	202	1.26	(0.86, 1.83)
3	105	282	0.85	(0.59, 1.24)	23	94	1.01	(0.52, 1.99)	128	376	0.93	(0.68, 1.28)
4–5	53	140	1.14	(0.72, 1.80)	12	65	0.93	(0.39, 2.21)	65	205	1.17	(0.79, 1.72)
⩾6	621	1349	0.89	(0.66, 1.22)	15	103	0.64	(0.31, 1.35)	636	1452	0.93	(0.71, 1.21)
Missing	25	68			9	16			34	84		
No. of oral sex partners[d]												
0–1	5	45	1.00		1	24	1.00		6	69	1.00	
2–3	2	15	35.82		2	7			4	22	4.07	(0.28, 58.46)
⩾4	5	37	20.73	(0.25, 1717)	0	6			5	43	20.74	(0.25, 1720)
Missing	5	22			3	3			8	25		
Ever had oral–anal contact[e,f]												
No	56	386	1.00									
Yes	2	29	0.59	(0.12, 2.94)								
Missing	8	8										
Ever had same-sex contact[e,g]												
No	14	97	1.00									
Yes	0	7										
Missing	3	9										

[a]ORs and 95% CIs control for age, race/ethnicity, educational attainment, study site, tobacco pack-years, alcohol ml/day and use of cigars and pipes. Analyses with men and women combined additionally control for sex.
[b]Data from International Multicentre, Central Europe, Boston, Iowa, Seattle, Puerto Rico and Latin American studies.
[c]Data from Seattle, Puerto Rico, Boston and International Multicentre.
[d]Data from Seattle, Puerto Rico and Boston.
[e]Asked of male subjects only.
[f]Data from Seattle and Iowa.
[g]Data from Seattle, Boston, the US Multicentre and the study sites in the International Multicentre study that completed the supplementary questionnaire.
[h]Includes the subsites of the tonsils and the base of the tongue.

Table 4 Multivariate analysis of sexual behaviours and cancers of the tonsil and of the base of the tongue, by sex[a]

	Men				Women				Total			
	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI
Tonsil												
Ever had oral sex[b]												
No	97	1644	1.00		30	494	1.00		99	1539	1.00	
Yes	54	659	1.59	(1.09, 2.33)	13	205	1.05	(0.56, 1.97)	48	567	1.35	(0.91, 2.01)
Missing	4	35			0	17			2	35		
Age in years at sexual debut[c]												
⩾19	18	629	1.00		12	295	1.00		30	924	1.00	
⩽18	45	566	2.36	(1.37, 5.05)	9	220	0.49	(0.16, 1.46)	54	786	1.59	(0.93, 2.70)
Missing	2	178			2	150			4	328		
No. of lifetime sexual partners[b]												
1	32	684	1.00		21	710	1.00		53	1394	1.00	
2	14	211	1.30	(0.64, 2.62)	9	155	1.16	(0.44, 3.08)	23	366	1.26	(0.73, 2.18)
3	26	487	1.15	(0.63, 2.09)	15	176	1.35	(0.60, 3.06)	41	663	1.27	(0.80, 2.03)
4–5	18	257	1.06	(0.54, 2.06)	5	82	1.00	(0.31, 3.18)	23	339	1.05	(0.60, 1.83)
⩾6	154	1961	1.39	(0.87, 2.24)	18	165	1.73	(0.77, 3.88)	173	2125	1.43	(0.97, 2.11)
Missing	16	239			1	85			17	324		
No. of oral sex partners[d]												
0–1	48	576	1.00		20	236	1.00		68	812	1.00	
2–3	7	123	0.75	(0.30, 1.85)	3	50	0.75	(0.15, 3.75)	10	173	0.73	(0.34, 1.57)
⩾4	14	102	1.66	(0.58, 4.74)	3	14	63.61	(3.19, 1268)	17	116	3.36	(1.32, 8.53)
Missing	6	120			0	7			6	127		
Ever had oral–anal contact[e,f]												
No	33	394	1.00									
Yes	1	31	0.49	(0.06, 3.99)								
Missing	1	8										
Ever had same-sex contact[e,g]												
No	74	826	1.00									
Yes	4	24	1.28	(0.25, 6.64)								
Missing	12	13										
Base of the tongue												
Ever had oral sex[b]												
No	143	1900	1.00		13	437	1.00		156	2337	1.00	
Yes	55	787	1.19	(0.83, 1.72)	4	93	4.32	(1.06, 17.59)	59	802	1.25	(0.88, 1.79)
Missing	6	53			1	16			7	69		
Age in years at sexual debut[c]												
⩾19	10	274	1.00		2	186	1.00		12	460	1.00	
⩽18	31	402	1.62	(0.71, 3.70)	6	128	1.46	(0.19, 11.08)	37	530	1.69	(0.79, 3.60)
Missing	9	153			2	140			11	293		
No. of lifetime sexual partners[b]												
1	28	569	1.00		14	627	1.00		42	1196	1.00	
2	20	204	2.01	(1.03, 3.92)	10	153	2.16	(0.79, 5.91)	30	357	2.02	(1.19, 3.46)

(continued)

Table 4 Continued

	Men				Women				Total			
	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI
3	33	385	1.60	(0.87, 2.95)	3	120	0.58	(0.14, 2.47)	36	505	1.36	(0.81, 2.30)
4–5	24	242	1.67	(0.86, 3.23)	5	76	1.43	(0.36, 5.68)	29	318	1.59	(0.90, 2.81)
⩾6	142	1674	1.35	(0.80, 2.29)	6	106	1.88	(0.53, 6.69)	148	1780	1.26	(0.81, 1.97)
Missing	21	225			2	81			23	306		
No. of oral sex partners[d]												
0–1	25	319	1.00		5	87	1.00		30	406	1.00	
2–3	6	51	1.93	(0.65, 5.75)	0	6						
⩾4	3	11	2.73	(0.55,13.45)	0	1						
Missing	0	7			1	3						
Ever had oral–anal contact[e,f]												
No	26	386	1.00									
Yes	4	29	1.96	(0.57, 6.73)								
Missing	1	8										
Ever had same-sex contact[e,g]												
No	31	666	1.00									
Yes	3	13	8.89	(2.14, 36.8)								
Missing	2	11										

[a]ORs and 95% CIs control for age, race/ethnicity, educational attainment, study site, tobacco pack-years, alcohol ml/day and use of cigars and pipes. Analyses with men and women combined additionally control for sex.
[b]Data from International Multicentre, Central Europe, Boston, Iowa, Seattle, Puerto Rico and Latin American studies.
[c]Data from Seattle, Puerto Rico, Boston and International Multicentre.
[d]Data from Seattle, Puerto Rico and Boston.
[e]Asked of male subjects only.
[f]Data from Seattle and Iowa.
[g]Data from Seattle, Boston and the US Multicentre.

cases were interviewed at the time of their cancer diagnosis while still in the hospital: at the time of the interview they were more likely to have family members nearby, in comparison with the controls at their time of interview. In order to limit reporting bias, interviewers made efforts to speak to the cases alone. Nonetheless, given this potential reporting bias, we conclude that the results seen may be underestimates.

The tonsil and the base of the tongue form parts of Waldeyer's tonsillar ring, a group of lymphoid tissues that forms a ring around the opening of the throat. Of the subsites of the head and neck, Waldeyer's ring tumours exhibit among the highest prevalence of HPV.[26,32] Cancers in this area are more likely to have basaloid morphology, express the viral oncogenes E6 and E7 and are more likely to have wild type p53.[33–35] The differing morphological characteristics as well as improved survival among HPV-positive head and neck cancer patients have led researchers to suggest that these tumours should be treated as distinct entities.[36]

A high number of lifetime sexual partners is one of the leading risk factors for HPV acquisition.[37] This study found that having four or more lifetime oral sex partners was associated with a 3-fold increase in tonsil cancer risk. With cancer of the base of the tongue, elevated point estimates were seen with two lifetime sexual partners. An increased risk of oropharyngeal and base of the tongue cancers was seen with having two sexual partners, in comparison to having only one. Similar results have been previously reported.[38]

Nonetheless, no dose–response relationships were seen with an increasing number of sexual partners. Studies of sexual behaviour regularly find that men report more sexual partners than women; a perplexing discrepancy that has been attributed to male exaggeration and female underreporting.[39] If non-differential response biases influenced answers in the INHANCE studies, our ability to find a dose–response effect would have been impaired. A lack of a dose–response effect has been seen in other studies.[13]

In this study, age at sexual debut of ⩽18 years was associated with a 2-fold risk of tonsil cancer among men. Studies have previously associated earlier age at sexual debut with risky sexual behaviour, including higher numbers of partners and inconsistent condom use, as well as with greater use of tobacco and

alcohol.[40] Thus, it is possible that this factor represents a marker for riskier sexual behaviours, rather than a biologically relevant etiologic relationship.

Cases and controls in this study differed in sexual behaviours, drinking and tobacco use. We observed associations between heavier smoking and alcohol use with risky sexual behaviours, both in the overall sample and when examining only the population-based studies, although the associations were not always consistent. Although there are conflicting findings, other studies suggest persons who drink more heavily are more likely to engage in risky sexual behaviours, such as having multiple sexual partners and less consistent condom use.[41] Tobacco use has similarly been associated with certain risky sexual behaviours.[42–44] Given these associations the possibility exists for residual confounding in our results. Despite efforts to select controls independent of tobacco use, controls in the Central Europe study had higher smoking rates than expected. Hospitalized patients frequently have higher smoking rates than the general population,[45] although the exclusion of persons with tobacco-related diseases, as done in that study, is a common strategy employed to reduce this bias. Nonetheless, given potential associations between alcohol and tobacco use with sexual behaviours, controls may have been overmatched to cases in the Central Europe study.

As there are few reports of cancer rates among men who have sex with men (MSM), the finding of a higher risk of base of the tongue cancers associated with same-sex contact was notable. These results should be taken with caution, because we were not able to adjust for the number of sexual partners in these analyses, as that information was not collected in all studies. Nonetheless, our findings support those of a study that examined cancer incidence among men in registered homosexual partnerships in Denmark, which reported a 5-fold increased risk of cancers of the tonsils and a 4-fold increased risk of cancers of the mouth.[46] However, other lifestyle factors may in part explain increased risks of these cancers seen in MSM. Compared with heterosexual men, MSM have greater tobacco use[43] and also may have higher passive smoke exposure.[47]

Differences in HPV prevalence by age have been observed and have been attributed to poorer immune response among older persons.[48] In many countries, cervical HPV is highest in adolescence and early adulthood, dropping in mid-life and then rising in older adulthood.[49] Variation in risk by age may be also due to cohort effects in risk behaviours. Studies in the USA, Australia, Russia and Brazil point to generational changes in sexual behaviour, with individuals who came of age in recent years having an earlier age at sexual debut, greater numbers of sexual partners and a higher likelihood of engaging in oral sex in comparison with those who came of age in earlier decades.[50–53] Birth cohort analyses of cervical cancer incidence find decreasing rates of cervical cancer from cohorts born in 1900 through those born in 1940, followed by increasing rates for later birth cohorts;[54] there have additionally been increases in anal and vulvar cancer incidence in the past 40 years.[55–57] However, studies in some countries, notably India and Italy, have not found evidence of generational differences in HPV prevalence or sexual behaviour.[49,58]

The variety of questions asked at the study centres allowed us to examine the potential effects of a number of behaviours. In combination with the stratification by head and neck subsite, this analysis included multiple tests ($n = 204$) and this limitation must be considered in interpreting results. We *a priori* hypothesized that elevated risks would be seen for oropharyngeal, tonsil and base of the tongue cancers. For the other analyses, after Bonferroni correction, no findings remained significant, with the exception of oral cavity cancer and age at sexual debut among women ($P = 0.02$).

A limitation of this study was the pooled design. The studies had different populations, protocols, sources of controls and methods of data collection, which may contribute to different findings across sites. Disparate cohorts may have differing behaviours and reside in areas with a different prevalence of HPV. We tried in part to account for these differences in the analysis by adjustment for study site. In addition, heterogeneity testing yielded little evidence of differences by study in effect estimates. We were unable to stratify by HPV status, as it was not collected in the studies; this may account for null results or the lack of dose–response findings. An additional limitation is that researchers have questioned the validity of self-reported sexual behaviours, with particular concerns for underreporting of stigmatized behaviours.[59] All but one of the studies was conducted by face-to-face interview, a method that has the advantage of limiting non-response as well as the possibility of the participant building rapport with the interviewer, but with the disadvantage of limiting privacy. There is also the possibility of recall bias between cases and controls. As all studies on this topic including the present study have been retrospective in nature, we are not able to gauge a possible effect from recall bias. However, one previous study compared risk between HPV-positive and HPV-negative cancer cases, and found strong associations between sexual behaviours among HPV-positive persons only,[16] suggesting effects may be observed independent of recall. The types of questions used in these studies are similar to those used on studies of sexual activities and cervical cancer, suggesting they should be sufficient to detect an association. In addition to the above study limitations, we have no information on other factors that may be relevant to HPV transmission, such as frequency of condom use,[15] and of other potential risk factors for head and neck cancer,

such as diet,[60] which was not available from all INHANCE studies.

The associations seen in this study add additional indirect evidence that HPV is a cause of oropharyngeal, tonsillar and base of the tongue cancers, and studies should be undertaken to determine whether HPV vaccines can prevent HPV infection and ultimately head and neck cancers.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- Sexual behaviours are hypothesized to be the method by which head and neck cancer patients are exposed to HPV.
- This study examines sexual behaviours in a large pooled analysis of case–control studies of head and neck cancers.
- We observed increased risks for certain sexual behaviours with cancers of the oropharynx, tonsil and base of the tongue.

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