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Cancer

Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium

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Abstract

Background: Increasing incidence of head and neck cancer (HNC) in young adults has been reported. We aimed to compare the role of major risk factors and family history of cancer in HNC in young adults and older patients.

Methods: We pooled data from 25 case-control studies and conducted separate analyses for adults ≤45 years old ('young adults', 2010 cases and 4042 controls) and >45 years old ('older adults', 17 700 cases and 22 704 controls). Using logistic regression with studies treated as random effects, we estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The young group of cases had a higher proportion of oral tongue cancer (16.0% in women; 11.0% in men) and unspecified oral cavity / oropharynx cancer (16.2%; 11.1%) and a lower proportion of larynx cancer (12.1%; 16.6%) than older adult cases. The proportions of never smokers or never drinkers among female cases were higher than among male cases in both age groups. Positive associations with HNC and duration or pack-years of smoking and drinking were similar across age groups. However, the attributable fractions (AFs) for smoking and drinking were lower in young when compared with older adults (AFs for smoking in young women, older women, young men and older men, respectively, = 19.9% (95% CI = 9.8%, 27.9%), 48.9% (46.6%, 50.8%), 46.2% (38.5%, 52.5%), 64.3% (62.2%, 66.4%); AFs for drinking = 5.3% (−11.2%, 18.0%), 20.0% (14.5%, 25.0%), 21.5% (5.0%, 34.9%) and 50.4% (46.1%, 54.3%). A family history of early-onset cancer was associated with HNC risk in the young [OR = 2.27 (95% CI = 1.26, 4.10)], but not in the older adults [OR = 1.10 (0.91, 1.31)]. The attributable fraction for family history of early-onset cancer was 23.2% (8.60% to 31.4%) in young compared with 2.20% (−2.41%, 5.80%) in older adults.

Conclusions: Differences in HNC aetiology according to age group may exist. The lower AF of cigarette smoking and alcohol drinking in young adults may be due to the reduced length of exposure due to the lower age. Other characteristics, such as those that are inherited, may play a more important role in HNC in young adults compared with older adults.

Key words: Head and neck neoplasms, adult, smoking, alcohol drinking, diet

Key Messages

- Positive associations of cigarette smoking and alcohol drinking with the risk of HNC were consistently lower in the people aged 45 years or younger when compared with those over 45 years old.
- The attributable fractions of cigarette smoking and alcohol drinking for HNC in the people aged 45 years or less were lower than in those over 45 years old, indicating roles of other risk factors in the HNC in young adults.
- The protective effect of a diet rich in fruits and vegetables on HNC was consistent across young and older people.
- Family history of cancer in young relatives was associated with an increased risk of HNC in young adults, but not in the older group.

Introduction

Approximately 550 000 new cases of head and neck cancer (HNC) are diagnosed worldwide annually.[1] Furthermore, an increasing incidence of head and neck neoplasms among young adults (YA) has been reported;[2] in particular, reports indicate an increase in tumours affecting the tongue and oropharynx among YA in India,[3] Europe,[4] the USA[5] and China.[6]

The aetiology of HNC in YA is still unclear. Some authors proposed that HNC in YA might be a distinct subset more related to genetic predisposition, or HPV infection, than HNC in older adults[7] because younger adults would have a reduced length of exposure to major carcinogenic factors,[8] mainly tobacco and alcohol consumption and a poor diet. Conversely, association studies specifically assessing YA have found non-negligible associations between these risk factors and HNC.[9,10] As these studies generally did not assess associations for older adults, it has not been possible to know whether the risks of HNC associated with its major risk factors are consistent across age groups.

Because YA represent a minority of HNC, studies that examined risk factors in this group comprised limited samples, which leads to imprecise results and does not allow for stratification by cancer subsites or sex. In addition, studies on HNC defined YA according to different age-group criteria, i.e. arbitrary age cut-off points ranging from 30[11] to 50 years,[10] thus leading to limited comparability of results.

The use of pooled data from a large number of case-control studies would provide increased statistical power for the analysis of lifestyle characteristics and family history of cancer associated with HNC in YA, thus allowing a rigorous assessment of the hypothesis that HNC in YA constitutes an aetiologically distinct subset. The International Head and Neck Cancer Epidemiology (INHANCE) Consortium [http://inhance.iarc.fr/] database provides a unique opportunity to investigate the aetiology of HNC in YA.

Methods

Study population characteristics

The INHANCE consortium was established in 2004 to elucidate the aetiology of HNC by providing opportunities for pooled analyses of risk factors on a large number of participants. This consortium pools epidemiological studies, mainly of case-control design, from many countries and regions (Europe, North and South America, Asia and Africa)—including studies from high-, medium- and low-income countries.[12] Version 1.3 of the INHANCE Consortium pooled dataset comprised 26 case-control studies from Europe, America and Asia.[13-38] The Germany-Saarland study from Europe did not include any cases aged 45 years or younger and was thus excluded. Subjects with missing data on age, sex and cancer subsite were excluded (40 cases and 3 controls aged 45 years or younger; and 156 cases and 23 controls older than 45 years). The YA group comprised 1910 cases and 4042 controls aged 45 or younger. Results for cases (n = 16 694) and controls (n = 22 772) older than 45 years of age (>45 years) were used for comparison.

Details of the 25 studies included in the analyses are shown in Supplementary Table 1 (available as Supplementary data at *IJE* online). Most of these were hospital-based case-control studies, and in the majority of these studies, the control subjects were matched to cases with regard to age, sex and additional characteristics (such as study centre, hospital and race/ethnicity).

Cases were included in this analysis if the tumours had been classified in the original study as invasive HNC according to the International Classification of Diseases (ICD) Oncology, Version 2[39] (ICD-O-2), the ICD-9[40] or the ICD-10.[41] ICD-10 codes were used to classify each tumour into anatomical subsite categories: oral cavity (C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.8, C05.9, C06.0-C06.2, C06.8, C06.9), oropharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0-C10.4, C10.8, C10.9), hypopharynx (C12.9, C13.0-C13.2, C13.8 C13.9), oral-oropharynx-hypopharynx not otherwise specified (C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, C14.8) and larynx (C32.0-C32.3, C32.8, C32.9). Cancers of the salivary gland were excluded from our analysis because their aetiological pattern differs from that of other head and neck tumours.[42]

Our analysis included all histological types included in the ICD codes considered in the study. For the Milan and Aviano Italian multicentre studies and four centres in the International Multicentre study (Bangalore, Madras, Sudan and Trivandrum), no information on case histology was available. Of the 1570 young head and neck cancer cases for whom histological information was available, 88.2% of the female cases and 94.5% of the male cases were squamous cell carcinoma, whereas among the older cases, these proportions were 94.0% and 97.1%, respectively.

Data collection and pooling

For all studies, interviews were conducted face to face by trained interviewers. Written informed consent was obtained from the study subjects, and the investigations were approved by the institutional review boards at each of the institutions involved. Questionnaires were collected from all of the individual studies to assess data comparability and the wording of interview questions. The data from individual studies were received with the personal identifiers removed, and each data item was checked for illogical or missing values. Queries were sent to investigators, and inconsistencies were resolved.

The definition of ever or never cigarette smokers and ever or never drinkers used in this study has been previously described in detail.[42] Although questions regarding history of cigarette smoking varied across studies, never users of cigarettes, pipes and cigars did not exceed either 1 year of cigarette smoking or 100 cigarettes in a lifetime or ever smoked 'regularly'. Pack-years of cigarette smoking were calculated by multiplying the number of packs (defined as 20 cigarettes) per day by the number of years of smoking.

Subjects were asked about the duration, frequency and type of alcoholic beverages consumed (beer, wine, hard liquors and aperitifs). The definition of never drinkers also varied throughout the studies, from 0 drinks in a lifetime to <4 drinks per month. To address the different volume specifications for each type of alcoholic beverage by study, the number of drinks per day was calculated as the frequency of consumption of each alcoholic beverage type weighted by the relevant duration.

The assessment of diet has been described in detail previously.[43] The data were collected using food frequency questionnaires that obtained information about diet before sick (Milan, Aviano, France, IARC multicentre studies), 10 years prior to interview (Seattle study), 5 years prior to interview (Boston study), 2 years prior to interview (Italy multicentre and Switzerland studies), 1 year prior to interview (North Carolina, Rome, US multicentre and Western Europe studies), within the 3 years before the interview (Puerto Rico study), before having cancer (Los Angeles and MSKCC studies), between 1980 and 1990 (Heidelberg study) and the diet in the diagnosis (Central Europe study). Briefly, four major food categories were examined: vegetables, fruits, animal products and others (cereals and grains). Several food items and sub-food categories were identified within each major food category. Centre-specific quartiles were used among the controls for food groups. Of the 25 studies included, 21 collected data on diet. In the Boston and Seattle study, data on diet were available only for a subset of the subjects and those with no data were not included in the analysis.

The definition of 'family member with cancer' was described previously.[44] Four categories of cancers in the family were considered: (i) head and neck cancers, including only cancers with the previously described topography; (ii) other tobacco-related cancers [i.e. lung (C34), nasopharynx (C11), nasal cavity (C30), paranasal sinuses (C31), oesophagus (C15), stomach (C16), pancreas (C25), liver (C22), kidney (body and pelvis, C64), urinary bladder (C67), uterine cervix (C53) and bone marrow (myeloid leukaemia, C92)]; (iii) any cancer in relatives of any age; (iv) any cancer in young relatives.

Statistical analysis

The associations between cigarette smoking, alcohol consumption, diet, cancer in family members and HNC were assessed by estimating the odds ratios (ORs) and 95% confidence intervals (95% CIs) using mixed effects logistic regression models, with study centres as random intercepts. Respective ORs were calculated for each age group [$\leq$45 years old (yo) and >45 yo] and sex with adjustments for age, study, education, cigarette smoking (pack-years) and alcohol consumption (drinks/day). Multivariate adjusted models were further stratified according to cancer site (oral cavity, oropharynx and larynx) and smoking status (never smokers and ever smokers). The limited number of hypopharynx cancer cases (n = 108) in YA $\leq$45 yo did not allow stratification for that subsite. Linear trends in frequency, duration and cumulative use of tobacco or alcohol and frequency of food intake were assessed by *p*-values obtained from modelling the continuous forms of these variables.

To test for differences in results according to age group, we fitted models including subjects in both age groups with adjustment for age, study, education, cigarette smoking (pack-years) and alcohol consumption (drinks/day), plus an interaction term between age group and each variable of interest. *p*-Values for the interaction term were calculated using likelihood ratio tests and used as suggestive of differences or similarities in results according to age group

The fraction (AF) of cases with HNC attributable to cigarette smoking, alcohol drinking and family history of cancer was estimated using the formula $AF = p(ec) \times (OR - 1)/OR$, where p(ec) is the proportion exposed among the case subjects.[45]

An influence analysis was performed by testing for variation in estimates according to the strata defined by data collection period and geographical region of study. We also performed analyses to determine whether any individual study's data unduly influenced the results. Influence analyses were performed using STATA SE11 using xtmelogit command.

We tested for between-study and between–study centre heterogeneity by conducting a likelihood ratio test comparing a multivariate logistic model, not mixedeffects models, including the interaction terms between each study (other than the reference study) with the variable of interest and a model without the product terms, for the risk of HNC.

Results

Among cases, 10.7% were $\leq$45 yo. Compared with the >45 yo group, YA with HNC had a higher proportion of oral tongue cancer (16.0% in women and 11.0% in men) and unspecified oral cavity/oropharynx cancer (16.2% in women and 11.1% in men) and a lower proportion of larynx cancer (12.1% in women and 16.6% in men). With the exception of young female controls, higher proportions of never smokers and never drinkers were observed in young individuals as compared with the older subjects. A higher proportion of individuals with a higher education (Table 1) was found in YA cases and controls of both sexes when compared with the older group. Furthermore, across all of the age groups, the proportions of cases with oral tongue cancer, never smokers or never drinkers were higher among women than among men.

The association with ever-smoking in YA was lower than in older subjects (Table 2, Supplementary Table 2 available as Supplementary data at *IJE* online). This difference remained in the analysis stratified by cancer sub site (Table 3), which also revealed substantially higher associations for larynx cancer in all age groups when compared with estimates for other subsites. The attributable fraction for cigarette smoking on the risk of HNC was 19.9% (95% CI = 9.8%, 27.9%) in young women, 48.9% (46.6%, 50.8%) in older women, 46.2% (38.5%, 52.5%) in young men and 64.3% (62.2%, 66.4%) in older men. In all age groups and sexes, the risk of HNC was directly associated with increasing duration, frequency or cumulative exposure to cigarette smoking, with a dose-response effect observed in cumulative cigarette consumption. ORs for both duration and cumulative strata of smoking were similar across age groups among men. Among women, lower ORs were found for smoking frequency in YA compared with the older group. Across all age groups, higher Ors were found for men than for women (Table 2, Supplementary Table 2 available as Supplementary data at *IJE* online).

Table 1. Characteristics of cases and controls. International Head and Neck Cancer Epidemiology Consortium

Characteristics	Women, n (%)									Men, n (%)							
	Cases				Controls					Cases				Controls			
	≤45yo		>45yo		≤45yo		>45yo			≤45yo		>45yo		≤45yo		>45yo	
	N	%	N	%	N	%	N	%		N	%	N	%	N	%	N	%
Cancer subsite																	
Oral cavity																	
Oral tongue	81	16.0	362	10.3		–	–	–		166	11.0	781	5.9	–	–	–	–
Floor of mouth	23	4.6	301	8.5		–	–	–		157	10.4	1076	8.2	–	–	–	–
Other parts,	111	21.0	844	23.9		–	–	–		203	13.5	1487	11.3	–	–	–	–
Oral cavity NOS																	
Oropharynx	120	23.8	881	25.0	–	–	–	–		428	28.4	3451	26.2	–	–	–	–
Hypopharynx	15	3.0	173	4.9	–	–	–	–		103	6.8	1118	8.5	–	–	–	–
Oropharynx NOS	82	16.2	392	11.1	–	–	–	–		167	11.1	1033	7.9	–	–	–	–
Overlapping palate	12	2.4	54	1.5	–						1.5	163	1.2	–	–	–	–
Larynx	61	12.1	506	14.4	–						16.	4002	30.4	–	–	–	–
Overlapping OC, PH, LA	0	0 0	9	0.3	–	81	16.0	362	10.3	–	0.7	61	0.5	–	–	–	–
All head and neck	505	100	3522	100	–	23	4.6	301	8.5	–	100	13 172	100	–	–	–	–
p-Value (YA x older group)[a]				<0.001				111	21.0	844	23.9	–	<0.001				
Tobacco smoking																	
Never smoker	231	45.7	1144	32.5	848	59.1	4003	64.2		251	16.8	1101	8.4	950	36.6	4698	28.5
Ever smoker	274	57.3	2372	67.3	588	41.0	2229	35.8		1246	83.2	12 015	91.2	1644	63.4	11 785	71.5
p-Value (YA x older group)				<0.001				<0.001					<0.001				<0.001
Alcohol drinking																	
Never drinker	208	41.2	1242	35.3	675	47.8	3010	48.3		171	11.4	911	6.9	533	20.6	2845	17.3
Ever drinker	297	58.8	2263	64.2	736	52.2	3218	51.7		1326	88.6	12 188	92.5	2051	79.4	13 615	82.7
p-Value (YA x older group)				0.013				0.761					<0.001				<0.001
Education level																	
No education	59	11.7	372	10.7	58	4.1	401	6.4		42	2.8	525	4.0	40	1.6	596	3.6
≤Junior high school	105	20.8	1078	30.9	407	28.9	2348	37.7		530	35.3	5852	44.4	822	31.9	6525	39.6
Some high school	79	15.7	641	18.0	174	12.4	922	14.8		279	18.6	2250	17.1	417	16.2	2708	16.4
High school graduate	85	16.9	535	15.1	203	14.4	781	12.6		222	14.8	1644	12.5	360	14.0	1807	11.0
Technical school / college	98	19.4	620	17.4	304	21.6	1056	17.0		246	16.4	1699	12.9	534	20.7	2626	15.9
≥College graduate	78	15.5	275	7.9	263	18.7	714	11.5		181	12.1	1182	9.0	407	15.8	2208	13.4
p-Value (YA x older group)[a]				<0.001				<0.001					<0.001				<0.001

yo, years old; NOS, not otherwise specified; OC, oral cavity; PH, pharynx; LA, larynx.
[a]Chi-squared test.

Table 2. Tobacco smoking and the risk of head and neck cancer according to sex and age. International Head and Neck Cancer Epidemiology Consortium

Smoking	Women ≤45 yo				Women >45 yo				Men ≤45 yo				Men >45 yo			
	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)
Tobacco smoking[a]																
Never	231	848	1.00		1144	4003	1.00		251	950	1.00		1101	4698	1.00	
Ever	274	588	1.58	(1.22, 2.06)	2372	2229	3.63	(3.24, 4.06)	1246	1644	2.25	(1.86, 2.71)	12 015	11 785	3.36	(3.11, 3.64)
Missing	0	2	–	–	6	6	–	–	8	10	–	–	56	19	–	–
Duration (years)[a]																
Never smoker	231	848	1.00		1144	4003	1.00		950	251	1.00		1101	4698	1.00	
>0 to 10	38	171	0.83	(0.54, 1.28)	95	316	1.15	(0.88, 1.50)	299	99	1.22	(0.91, 1.64)	317	1116	1.08	(0.93, 1.26)
>10 to 20	79	220	1.37	(0.97, 1.94)	125	349	1.43	(1.13, 1.82)	616	247	1.52	(1.21, 1.92)	560	1658	1.30	(1.15, 1.48)
>20 to 30	133	172	2.93	(2.05, 4.18)	351	527	2.50	(2.10, 2.99)	626	740	3.96	(3.17, 4.94)	1678	2532	2.36	(2.13, 2.61)
>30 to 40	20	13	5.49	(2.40, 12.5)	850	589	4.92	(4.23, 5.73)	87	12	4.87	(3.39, 7.01)	4247	3370	4.20	(3.83, 4.60)
>40	0	0	–	–	927	429	6.66	(5.68, 7.81)	0	2	–	–	5099	3000	6.04	(5.50, 6.63)
Missing	4	14	–	–	30	25	–	–	14	26	–	–	170	128	–	–
p-trend				<0.001				<0.001				<0.001				<0.001
Frequency (cigarettes/day)[a]																
Never smoker	231	848	1.00		1144	4003	1.00		251	950	1.00		1101	4698	1.00	
>0 to 10	75	276	1.12	(0.80, 1.57)	566	948	2.34	(2.03, 2.71)	149	457	1.05	(0.81, 1.36)	1359	2720	1.80	(1.61, 1.98)
>10 to 20	119	216	1.84	(1.33, 2.55)	917	809	4.22	(3.67, 4.85)	562	689	2.76	(2.23, 3.42)	5031	5035	3.54	(3.25, 3.86)
>20 to 30	39	43	3.05	(1.78, 5.24)	422	220	6.07	(4.94, 7.45)	235	229	3.23	(2.46, 4.25)	2351	1720	4.49	(4.06, 4.98)
>30 to 40	24	36	2.07	(1.10, 3.89)	331	153	6.79	(5.34, 8.64)	198	184	3.05	(2.29, 4.08)	2027	1317	4.31	(4.24, 5.27)
>40	14	8	4.15	(1.50, 11.4)	114	79	4.56	(3.21, 6.47)	93	64	3.93	(2.62, 5.88)	1106	849	3.78	(3.33, 4.30)
Missing	3	11	–	–	28	26	–	–	17	31	–	–	197	163	–	–
p-trend				<0.001				<0.001				<0.001				<0.001
Pack-years[a]																
Never smoker	231	848	1.00		1144	4003	1.00		251	950	1.00		1101	698	1.00	
>0 to 10	80	321	1.00	(0.72, 1.39)	299	758	1.60	(1.35, 1.90)	175	581	1.19	(0.94, 1.52)	703	2170	1.26	(1.12, 1.41)
>10 to 20	69	143	1.85	(1.26, 2.72)	324	437	2.93	(2.44, 3.51)	253	433	2.09	(1.65, 2.66)	1018	1983	1.89	(1.69, 2.11)
>20 to 30	49	64	2.59	(1.60, 4.18)	357	335	3.91	(3.24, 4.71)	347	338	3.40	(2.66, 4.35)	1596	1871	3.14	(2.83, 3.48)
>30 to 40	35	24	5.21	(2.75, 9.90)	355	256	5.13	(4.19, 6.28)	185	115	5.29	(3.85, 7.26)	2176	1803	4.20	(3.79, 4.65)
>40 to 50	19	10	7.09	(2.89, 17.3)	334	165	6.75	(5.37, 8.47)	112	70	4.52	(3.11, 6.56)	1786	1290	4.81	(4.31, 5.36)
>50	17	10	6.50	(2.59, 16.3)	673	254	8.40	(6.93, 10.1)	163	82	5.41	(3.79, 7.71)	4549	2476	5.90	(5.37, 6.49)
Missing	5	18	–	–	36	30	–	–	19	35	–	–	243	211	–	–
p-trend				<0.001				<0.001				<0.001				<0.001

[a]ORs adjusted by sex, race, age, education level and drink day of alcohol (study centre as random intercept).

Table 3. Tobacco smoking and the risk of head and neck cancer by age group, separately according to cancer subsite. International Head and Neck Cancer Epidemiology Consortium

Subsite	≤45 yo				>45 yo			
	Cases	Controls	OR	(95% CI)	Cases	Controls	OR	(95% CI)
Oral cavity cancer								
Tobacco smoking[a]								
Never	220	1793	1.00		1009	8463	1.00	
Ever	519	2207	1.91	(1.53, 2.38)	3825	13 513	2.18	(1.99, 2.39)
Missing	2	12	–	–	17	25	–	–
Pack-years[a]								
Never smoker	220	1793	1.00		1009	8463	1.00	
>0 to 10	93	894	1.11	(0.83, 1.49)	293	277	0.92	(0.79, 1.08)
>10 to 20	117	569	1.87	(1.39, 2.51)	361	2312	1.39	(1.20, 1.61)
>20 to 30	129	397	2.80	(2.06, 3.81)	528	2136	2.22	(1.94, 2.54)
>30 to 40	71	136	4.09	(2.75, 6.07)	677	1998	2.82	(2.47, 3.21)
>40 to 50	39	78	3.73	(2.28, 6.11)	554	1413	3.25	(2.82, 3.74)
>50	64	92	4.99	(3.22, 7.73)	1360	2663	3.49	(3.10, 3.92)
Missing	8	53	–	–	69	241	–	–
p-trend				<0.001				<0.001
Oropharynx cancer								
Tobacco smoking[a]								
Never	133	1793	1.00		71	8463	1.00	
Ever	414	2207	1.86	(1.47, 2.37)	3755	13 513	2.77	(2.50, 3.08)
Missing	1	12	–	–	06	25	–	
Pack –years[a]								
Never smoker	133	1793	1.00		571	8463	1.00	
>0 to 10	66	894	1.01	(0.73, 1.40)	317	277	1.36	(1.16, 1.58)
>10 to 20	90	569	1.81	(1.31, 2.50)	371	2312	1.81	(1.56, 2.10)
>20 to 30	113	397	2.69	(1.94, 3.72)	503	2136	2.56	(2.22, 2.95)
>30 to 40	60	136	4.55	(3.02, 6.87)	641	1998	3.39	(2.95, 3.89)
>40 to 50	37	78	4.09	(2.48, 6.73)	481	1413	3.69	(3.17, 4.29)
>50	45	92	3.99	(2.46, 6.48)	1396	2663	4.96	(4.37, 5.62)
Missing	4	53	–	–	52	241	–	–
p-trend				<0.001				<0.001
Larynx cancer								
Tobacco smoking[a]								
Never	23	1371	1.00		243	7048	1.00	
Ever	285	184	6.34	(3.98, 10.1)	4237	11 448	8.31	(7.21, 9.58)
Missing	2	9	–	–	28	20	–	–
Pack-years[a]								
Never smoker	23	1371	1.00		243	7048	1.00	
>0 to 10	40	759	2.86	(1.65, 4.97)	229	2441	2.41	(1.98, 2.93)
>10 to 20	48	481	5.16	(2.99, 8.91)	359	2054	4.35	(3.63, 5.21)
>20 to 30	84	319	12.8	(7.51, 22.0)	581	1825	8.23	(6.94, 9.76)
>30 to 40	43	109	18.6	(10.1, 30.3)	784	1718	11.15	(9.44, 13.2)
>40 to 50	32	68	20.9	(10.8, 40.8)	684	1199	12.97	(10.9, 15.4)
>50	33	69	20.2	(10.4, 39.8)	1535	2010	18.03	(15.3, 21.1)
Missing	7	48	–	–	93	221	–	–
p-trend				<0.001				<0.001

[a]ORs adjusted on sex, age, study, education level and drink/day of alcohol (study centre as random intercept).

The association with ever drinking in YA was weaker than in the older group. However, risks according to strata of frequency, duration and cumulative consumption were similar across age groups, with the exception of the highest category of frequency of intake (≥5 drinks/day), which showed stronger associations in older than in young individuals (Table 4, Supplementary Table 3 available as Supplementary data at *IJE* online). Associations with alcohol

Table 4. Alcohol drinking and the risk of head and neck cancer according to sex and age subgroups. International Head and Neck Cancer Epidemiology Consortium

Alcohol drinking[a]	Women ≤45 yo				Women >45 yo				Men ≤45 yo				Men >45 yo			
	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)
Never	208	675	1.00		1242	3010	1.00		171	533	1.00		911	2845	1.00	
Ever	297	736	1.10	(0.84, 1.44)	2263	3218	1.45	(1.29, 1.63)	1326	2051	1.32	(1.06, 1.65)	12 188	13 615	2.18	(1.98, 2.40)
Missing	0	27	–	–	17	10	–	–	8	20	–	–	73	42	–	–
Duration (years)[a]																
Never drinker	207	663	1.00		1205	2913	1.00		16	529	1.00		897	2774	1.00	
>0 to 20	130	386	0.92	(0.67, 1.26)	282	434	1.41	(1.15, 1.73)	386	858	1.23	(0.96, 1.58)	660	1076	1.46	(1.27, 1.69)
>20 to 30	113	230	1.34	(0.93, 1.92)	388	521	1.67	(1.39, 2.02)	708	945	1.50	(1.17, 1.92)	1653	1921	2.10	(1.86, 2.37)
>30 to 40	9	24	0.67	(0.25, 1.78)	584	827	1.65	(1.40, 1.94)	12	105	1.65	(1.13, 2.42)	3789	3999	2.26	(2.03, 2.52)
>40 to 50	0	0	–	–	389	630	1.24	(1.03, 1.49)	0	2	–	–	3183	3264	2.31	(2.06, 2.58)
>50 to 60	0	0	–	–	160	248	1.26	(0.97, 1.64)	0	0	–	–	1284	1347	2.20	(1.92, 2.51)
>60	0	0	–	–	41	42	1.33	(0.80, 2.23)	0	0	–	–	221	202	2.07	(1.62, 2.65)
Missing	46	135	–	–	673	623	–	–	124	165	–	–	1485	1919	–	–
p-trend				0.353				<0.001				0.001				<0.001
Frequency (drinks/day)[a]																
Never	208	675	1.00		1242	3011	1.00		171	533	1.00		912	2850	1.00	
>0 to <1	149	468	0.90	(0.66, 1.22)	1034	1982	1.12	(0.98, 1.28)	251	687	0.93	(0.72, 1.21)	1893	4253	1.17	(1.05, 1.31)
1 to <3	62	17	1.29	(0.86, 1.96)	548	841	1.59	(1.35, 1.87)	298	554	1.34	(1.03, 1.75)	2630	4162	1.72	(1.54, 1.91)
3 to <5	31	34	2.43	(1.30, 4.54)	238	151	3.34	(2.55, 4.36)	157	297	1.31	(0.96, 1.79)	1891	2095	2.62	(2.33, 2.95)
≥5	36	30	2.48	(1.35, 4.55)	301	66	5.90	(4.32, 8.06)	559	437	2.68	(2.04, 3.53)	5159	2660	4.75	(4.26, 5.30)
Missing	19	74	–	–	159	187	–	–	69	96	–	–	687	482	–	–
p-trend				<0.001				<0.001				<0.001				<0.001
Drinks/day x years[a]																
Never drinker	208	650	1.00		1215	2925	1.00		166	522	1.00		869	2764	1.00	
>0 to 20	143	452	0.85	(0.62, 1.16)	675	1357	1.15	(0.99, 1.34)	29	700	1.03	(0.79, 1.33)	1073	218	1.20	(1.06, .36)
>20 to 30	19	46	1.62	(0.85, 3.08)	144	242	1.17	(0.90, 1.16)	62	162	0.99	(0.68, 1.46)	442	816	1.44	(1.23, 1.69)
>30 to 40	12	34	0.95	(0.42, 2.11)	99	182	1.23	(0.91, 1.66)	68	130	1.31	(0.89, 1.93)	392	751	1.43	(1.21, 1.68)
>40 to 50	10	32	1.25	(0.51, 3.03)	81	176	1.23	(0.89, 1.71)	45	106	1.14	(0.73, 1.77)	352	618	1.50	(1.26, 1.78)
>50 to 60	6	7	4.21	(1.23, 14.4)	81	126	1.39	(0.99, 1.96)	46	46	1.19	(0.76, 1.85)	339	548	1.61	(1.35, 1.93)
>60	56	48	2.78	(1.63, 4.74)	684	553	2.79	(2.34, 3.34)	696	663	2.31	(1.77, 3.03)	7824	6320	2.99	(2.70, 3.32)
Missing	55	169	–	–	543	677	–	–	163	223	–	–	1881	2167	–	–
p-trend				<0.001				<0.001				<0.001				<0.001

[a]ORs adjusted by sex, race, age, education level and pack-year of cigarette smoking (study centre as random intercept).

intake remained in the specific assessment of ever smokers, whereas in never smokers associations were observed only among older men (Supplementary Table 4, Supplementary Table 5, available as Supplementary data at *IJE* online). With respect to the duration of alcohol intake, differences by sex were observed: duration was not associated with HNC risk in young women, whereas direct associations were observed among young men, older women and older men (Table 4). The attributable fraction for alcohol drinking on the risk of HNC was 5.3% (95% CI = −11.2%, 18.0%) in young women, 20.0% (95%CI = 14.5%, 25.0%) in older women, 21.5% (5.0%, 34.9%) in young men and 50.4% (46.1%, 54.3%) in older men.

The analysis that included all HNC cases and controls indicated that the frequency of drinking, rather than the duration, played a more important role in HNC development. Considering this finding, we used stratified analyses to assess the role of drinking status (ever/never drinker) and the frequency of alcohol intake by cancer subsite (Table 5). Positive associations were comparable for alcohol consumption across age groups in all cancer subsites. In addition, Ors for alcohol consumption were higher for oropharynx than for cancers of other subsites.

The frequency of fruit and vegetable intake was inversely associated with HNC risk in both age groups (Table 6, Supplementary Table 6 available as Supplementary data at *IJE* online). This inverse association remained in the stratified analysis by sex, cancer subsite and smoking status (Supplementary Table 7, Supplementary Table 8, available as Supplementary data at *IJE* online). No association was observed between meat and cereal consumption and HNC risk in YA (Table 6). Conversely, positive associations were found for the highest quartile of intake of meat products in older men and the highest quartile of intake of cereals in women.

Family history of any cancer was directly associated with HNC only among the older group (Table 5, Supplementary Table 9 available as Supplementary data at *IJE* online). Borderline associations were found for family history of smoking-related cancers in the >45 age group, in which a family history of HNC was also positively associated with HNC risk. A family history of early-onset cancer was associated with HNC risk only in YA (Table 7). Among YA never smokers, a family history of any cancer was inversely associated with HNC whereas in YA ever smokers, a positive association was found. The attributable fraction for family history of early-onset cancer on the risk of HNC was 23.2% (95% CI = 8.6%, 31.4%) in young and 2.2% (−2.41%, 5.8%) in older adults.

Between-study heterogeneity was detected. ORs for tobacco, alcohol, diet and family history of cancer were similar in sensitivity analysis when excluding one study at time (results not shown) or according to the recruitment period of study (studies conducted before 2000 vs studies conducted after 2000). In addition, when cases with missing information on histology were excluded, the results did not significantly change (results not shown). As an exception, estimates for cigarette smoking (ever vs never smokers) in older women and men were higher in earlier studies when compared with later studies (results not shown). The geographical region of study also partially explained the effects of cigarette smoking and alcohol drinking. The risks for ever vs never cigarette smokers, as well as for ever vs never alcohol drinkers, were higher in Europe and Latin America in comparison with North America and Asia in both age groups and sexes (results not shown). Estimates for family history of cancer on HNC risk were higher in Latin America in comparison with North America and Europe. Conversely, inverse associations for family history of cancer and HNC risk were found among the young in Asia (results not shown).

Discussion

To our knowledge, this is the largest study evaluating the role of the major risk factors for HNC in YA (persons aged 45 years or less) as well as to compare risks in YA and older patients. The large sample size allowed us to elucidate any differences in the role of risk factors in HNC in YA according to age group, sex and cancer subsites. Our results supported the differences in the characteristics of cases aged 45 years or younger compared with those aged >45 years: YA comprised a lower proportion of drinkers and/or smokers and were more likely to have been diagnosed with oral and/or oropharynx cancer, as previously reported. Moreover, a higher proportion of oral tongue cancer was observed in YA compared with the older cases, as well as in women compared with men in all age groups. In addition, we found evidence that the importance of cigarette smoking in relation to HNC in YA may be limited by the lesser duration of exposure due to young age. We also found evidence that alcohol consumption is a risk factor for HNC in YA; however, a more intense association with heavy drinking was observed for the older group. Our results also indicate that the inverse association with fruit and vegetable intake is similar among young and older populations. Furthermore, aggregation of early malignancy diagnosis in the family was associated with HNC risk only among YA.

The characteristics of YA with HNC in terms of exposure to risk factors and cancer subsites are consistent with those described in previous studies performed in the USA,[46,47] the UK,[48] Italy,[9] Sri Lanka,[49] Brazil[50,51] and India.[52] All of these studies reported a higher percentage of women, never smokers, never drinkers and oral cavity

Table 5. Alcohol drinking and the risk of head and neck cancer by age group, separately according to cancer subsite. International Head and Neck Cancer Epidemiology Consortium

Subsite	≤45 years old				>45 years old			
	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)
Oral cavity cancer								
Alcohol drinking[a]								
Never	183	207	1.00		911	5830	1.00	
Ever	557	2758	1.24	(0.97, 1.57)	3919	16 119	1.61	(1.46, 1.79)
Missing	1	47			21			
Frequency (drinks/day)[a]								
Never drinker	183	1207	1.00		912	5836	1.00	
>0 to <1	131	1144	0.79	(0.59, 1.07)	900	6026	0.99	(0.88, 1.12)
1 to <3	126	705	1.39	(1.01, 1.90)	842	4745	1.34	(1.18, 1.52)
3 to <5	62	323	1.49	(1.01, 2.20)	524	2101	2.12	(1.83, 2.46)
≥5	196	464	2.77	(2.01, 3.83)	1380	2630	3.71	(3.25, 4.23)
Missing	43	169	–	–	293	663	–	–
p-trend				<0.001				<0.001
Oropharynx cancer								
Alcohol drinking[a]								
Never	83	207	1.00		447	5830	1.00	
Ever	464	2758	1.66	(1.25, 2.21)	3875	16 781	2.16	(1.92, 2.44)
Missing	1	47	–	–	10	52	–	–
Frequency (drinks/day)[a]								
Never drinker	83	207	1.00		447	5836	1.00	
>0 to <1	135	1144	1.24	(0.90, 1.72)	823	6026	1.28	(1.11, 1.47)
1 to <3	99	705	1.55	(1.09, 2.21)	819	4745	1.83	(1.59, 2.11)
3 to <5	43	323	1.40	(0.98, 2.41)	580	2101	3.13	(2.67, 3.66)
≥5	171	464	4.30	(2.98, 6.20)	1452	2630	5.68	(4.91, 6.55)
Missing	17	169	–	–	211	663	–	–
p-trend				<0.001				<0.001
Larynx cancer								
Alcohol drinking[a]								
Never	38	97	1.00		465	4698	1.00	
Ever	268	2270	1.25	(0.83, 1.87)	3999	13 781	1.90	(1.41, 1.80)
Missing	4	7	–	–	44	37	–	–
Frequency (drinks/day)[a]								
Never drinker	38	947	1.00		465	4704	1.00	
>0 to <1	5	889	0.89	(0.55, 1.44)	762	4726	1.03	(0.89, 1.19)
1 to <3	61	600	1.21	(0.75, 1.95)	961	4308	1.29	(1.12, 1.48)
3 to <5	40	296	1.33	(0.77, 2.27)	641	2016	1.76	(1.50, 2.06)
≥5	105	411	1.81	(1.13, 2.90)	1496	2372	2.82	(2.40, 3.25)
Missing	11	81	–	–	183	390	–	–
p-trend				<0.001				<0.001

[a]ORs adjusted on sex, age, study, education level and pack-years of cigarette smoking (study centre as random intercept).

cancer among YA with HNC compared with studies that included patients of all age groups. We also found a higher proportion of oral cavity cancer (especially oral tongue cancer) among the young cases and this proportion was higher among women. This finding agrees with those of previous studies which reported increasing rates for oral cavity tumours (especially oral tongue cancer) in individuals younger than 40 years of age in India,[3] Europe,[4] the USA[5,53] and China.[6]

Association studies on HNC risk factors among YA have been performed in several countries[9,10,49,50,54-68]. Most of the studies only included young patients with oral[49-51,57-61,63,64] and pharyngeal cancers,[9,65] whereas some other studies included only laryngeal cancer patients[68] and some included all HNC subsites.[10,54–56,62,66,67,69] The age cut-off for the 'young adult' group varied across the studies, including 30 years,[56,57] 35 years,[58] 40 years,[49–51,54,55,59,62,63,67–69] 45 years[9,60,61,64–66] and 50

Table 6. Diet and the risk of head and neck cancer according to sex and age subgroups. International Head and Neck Cancer Epidemiology Consortium

Diet	Women ≤45 yo				Women >45 yo				Men ≤45 yo				Men >45 yo			
	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)
Vegetables[a]																
1st quartile	114	233	1.00		741	1012	1.00		403	601	1.00		3602	3550	1.00	
2nd quartile	97	258	0.87	(0.59, 1.27)	624	1229	0.84	(0.71, 0.99)	294	514	0.86	(0.68, 1.07)	2407	3503	0.73	(0.68, 0.80)
3rd quartile	85	65	0.84	(0.57, 1.24)	606	1344	0.81	(0.69, 0.96)	188	473	0.60	(0.47, 0.76)	2046	3255	0.70	(0.64, 0.76)
4th quartile	78	303	0.67	(0.45, 0.99)	579	1565	0.72	(0.61, 0.84)	186	446	0.58	(0.45, 0.74)	1766	3753	0.59	(0.54, 0.64)
p-trend				0.052				<0.001				<0.001				<0.001
Fruit[a]																
1st quartile	156	292	1.00		834	919	1.00		471	640	1.00		3388	3821	1.00	
2nd quartile	75	250	0.78	(0.54, 1.14)	553	1131	0.68	(0.58, 0.81)	237	516	0.67	(0.53, 0.84)	3482	2375	0.72	(0.66, 0.78)
3rd quartile	69	21	0.72	(0.49, 1.06)	557	1501	0.64	(0.54, 0.75)	201	476	0.70	(0.55, 0.88)	3657	1956	0.65	(0.60, 0.71)
4th quartile	49	235	0.58	(0.38, 0.88)	488	1481	0.55	(0.47, 0.65)	146	378	0.57	(0.44, 0.74)	3433	1571	0.56	(0.51, 0.62)
p-trend				0.008				<0.001				<0.001				<0.001
Meat[a]																
1st quartile	83	258	1.00		687	1248	1.00		246	25	1.00		2287	3326	1.00	
2nd quartile	103	274	1.06	(0.70, 1.60)	647	1271	0.99	(0.84, 1.17)	221	484	0.76	(0.58, 0.99)	2221	3577	0.98	(0.89, 1.07)
3rd quartile	91	251	1.12	(0.74, 1.69)	587	1301	1.00	(0.85, 1.19)	232	531	0.79	(0.61, 1.03)	2364	3615	1.04	(0.95, 1.14)
4th quartile	88	249	1.12	(0.73, 1.71)	556	1157	1.05	(0.88, 1.24)	338	568	0.98	(0.76, 1.25)	2632	3277	1.17	(1.07, 1.28)
p-trend				0.556				0.609				0.857				<0.001
Cereals[a]																
1st quartile	99	303	1.00		683	1521	1.00		219	547	1.00		1997	2902	1.00	
2nd quartile	86	227	0.95	(0.62, 1.46)	513	1079	0.93	(0.78, 1.12)	180	365	1.03	(0.77, 1.38)	1591	2469	0.82	(0.73, 0.91)
3rd quartile	51	189	0.88	(0.55, 1.42)	465	948	1.21	(1.00, 1.45)	215	361	1.12	(0.84, 1.51)	1684	2778	0.91	(0.82, 1.02)
4th quartile	69	181	1.38	(0.88, 2.18)	400	736	1.37	(1.12, 1.67)	223	421	0.97	(0.72, 1.30)	1895	2766	0.98	(0.88, 1.10)
p-trend				0.261				<0.001				0.956				0.602

[a]ORs adjusted by sex, race, age, education level, pack-year of cigarette smoking and drink/day of alcohol (study centre as random intercept).

Table 7. Family history of cancer and the risk of head and neck cancer according to age subgroups. International Head and Neck Cancer Epidemiology Consortium

History	≤45 yo				>45 yo			
	Case	Control	OR	(95% CI)	Case	Control	OR	(95% CI)
Family history of cancer (all sites)[a]								
No	1075	1075	1.00	1.00	7535	10 455	1.00	
Yes	308	308	1.15	(0.95, 1.39)	3387	5516	1.13	(1.05, 1.21)
Family history of smoking-related cancer[a]								
No	1041	1041	1.00		7743	10 342	1.00	
Yes	120	120	1.16	(0.87, 1.56)	1472	2093	1.80	(0.99, 1.18)
Family history of head and neck cancer[a]								
No	1149	2442	1.00		9068	12 937	1.00	
Yes	32	35	1.45	(0.81, 2.60)	476	323	1.63	(1.37, 1.93)
Family history of cancer in young relatives[a]								
No	72	196	1.00		1346	2800	1.00	
Yes	51	75	2.27	(1.26, 4.10)	439	642	1.10	(0.91, 1.31)

[a]ORs adjusted by sex, race, age, education level, pack-years of cigarette smoking and drink day of alcohol (study centre as random intercept).

years.[10] Most analyses of studies with an age cut-off of 45 or 50 yearsfound associations with diet, tobacco and alcohol.[9,10,61,64–66] Regarding studies with an age cut-off of 35 or 40 years, some of these studies reported that HNC in young cases was less strongly associated with drinking and smoking,[49–51,57,58,62,67,69] whereas others reported stronger associations.[59,69] The largest case group in studies that included persons only aged 45 years or younger comprised137 patients.[9]

The risk of HNC associated with the cumulative consumption of tobacco in YA found in the present study is in agreement with previous studies conducted in Europe.[2,9,10] No differences by age were observed with the strata of duration and cumulative consumption of cigarettes, thus supporting the hypothesis that the carcinogenic effect of cigarette smoking does not depend on age if the level of exposure is the same among young and older individuals. In addition, the weaker associations for ever smoking observed in YA as compared with the older group support the hypothesis that the relationship between cigarette smoking and head and neck carcinogenesis in YA may be limited by a reduced length of exposure due to young age.[8,64] Thus, this observation would indicate a more important role of other, unknown risk factors for HNC in YA.[8,57] Consistent with this hypothesis are also the lower attributable fractions found for tobacco in YA in comparison with the older group.

Frequent alcohol consumption was associated with HNC in young subjects and this finding has been reported by other investigators.[9,10,64] Kmietowicz[70] suggested that the increasing incidence of mouth cancer among young British subjects may be linked to a modified alcohol consumption pattern of higher frequency of alcohol consumption at very young ages. Although our data did not allow the assessment of 'binge' drinking, which is an alcohol intake pattern that has been associated with other lifestyle-associated cancers,[71] our findings regarding the frequency of alcohol intake suggest the impact of factors other than alcohol consumption on early head and neck carcinogenesis, as the associations with ever drinking were lower in YA than in the older group. Furthermore, drinking status in ever smokers presented a higher HNC risk in every age stratum, which supports the hypothesis that alcohol intake increases the carcinogenic effect of cigarette smoking in all age groups.[72]

Consistent with other studies, our results suggest that a high frequency of fruit and vegetable consumption is associated with a reduced risk of HNC in YA. Previous studies also found associations between a diet rich in fruits and vegetables and a reduced risk of HNC in all ages,[43] particularly in YA.[9,10,64,73] In contrast to the weaker relationship between tobacco or alcohol and HNC risk at young ages than older ages, the inverse association with fruit and vegetable consumption did not seem to be influenced by the length of exposure; the same observation was reported by Llewellyn *et al*.[64]

In our study, 20% of young cases had at least one family member with a history of any cancer. Although this proportion is similar to that observed in a previous study in Canada, which included only patients under 41 years of age,[62] other studies found higher proportions, such as 66% for cases under 46 years of age in England[48] and 55% for cases under 40 years of age[53] in the USA. Cancer aggregation seemed to play different roles in HNC carcinogenesis in YA compared with older adults in our study. Similarly to previous findings by Negri *et al.*[44] in a study including all age groups (that also used data from the INHANCE Consortium to assess the role of family history of cancer), family history of any cancer at any age was associated with HNC in individuals aged >45 years. However, no association was observed among individuals aged ≤45 years, which contrasts with the results of other studies that specifically assessed young patients.[50,54] Caution is needed when interpreting this result, as the probability of having a family member with cancer may be higher for older than for young people. Older people are more likely to have older relatives, and since cancer risk generally increases with age, the chances of having a relative with cancer would be higher for older persons. In contrast, direct associations with family history of cancer in YA were observed in ever smokers, whereas the association was inverse in never smokers. Further studies are needed to explain whether these results may be driven by a possible familial aggregation of risk factors or by some gene-environment interaction.

A novel finding of our study is the association between the aggregation of early-onset family history of cancer and HNC risk in YA. Similar results have been reported for lung cancer,[74,75] but the biological mechanisms that explain this association are still unclear. In addition, caution is needed in interpreting this result because only four studies were included and a very low percentage of patients (10%) from these studies had available relevant information. Thus, the possibility of information bias resulting from the higher proportion of missing information should be considered.

Our study has some limitations. Recall bias is a potential limitation that is difficult to overcome in case-control studies. Another limitation is that we were unable to examine HPV infection as a risk factor or adjust for it to determine whether the association between cigarette smoking and alcohol consumption in oropharyngeal cancer according to sex could be related to HPV infection status.

The major strength of our study was the large sample size of young HNC patients and controls, which allowed us to explore heterogeneity in risk by sex and cancer subsite in more detail than previously performed. We also used data from older patients as a basis for comparison and found evidence for differences in HNC aetiology according to major risk factors. Our results support the public health efforts to decrease the exposure to major risk factors for HNC in the population regardless of age. However, investigations of the role of other risk factors, such as HPV and inherited characteristics, in HNC in this age group are warranted.

Supplementary Data

Supplementary data are available at *IJE* online.

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