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Smoking and Cancer

Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis

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Abstract

Background: Cigarette smoking is a major risk factor for head and neck cancer (HNC). To our knowledge, low cigarette smoking (<10 cigarettes per day) has not been extensively investigated in fine categories or among never alcohol drinkers.

Methods: We conducted a pooled analysis of individual participant data from 23 independent case-control studies including 19 660 HNC cases and 25 566 controls. After exclusion of subjects using other tobacco products including cigars, pipes, snuffed or chewed tobacco and straw cigarettes (tobacco product used in Brazil), as well as subjects smoking more than 10 cigarettes per day, 4093 HNC cases and 13 416 controls were included in the analysis. The lifetime average frequency of cigarette consumption was categorized as follows: never cigarette users, >0–3, >3–5, >5–10 cigarettes per day.

Results: Smoking >0–3 cigarettes per day was associated with a 50% increased risk of HNC in the study population [odds ratio (OR) = 1.52, 95% confidence interval (CI): (1.21, 1.90). Smoking >3–5 cigarettes per day was associated in each subgroup from OR = 2.01 (95% CI: 1.22, 3.31) among never alcohol drinkers to OR = 2.74 (95% CI: 2.01, 3.74) among women and in each cancer site, particularly laryngeal cancer (OR = 3.48, 95% CI: 2.40, 5.05). However, the observed increased risk of HNC for low smoking frequency was not found among smokers with smoking duration shorter than 20 years.

Conclusion: Our results suggest a public health message that low frequency of cigarette consumption contributes to the development of HNC. However, smoking duration seems to play at least an equal or a stronger role in the development of HNC.

Key words: Head and neck cancer, low frequency cigarette smoking, risk factors, pooled analysis

Key Messages

- There is no harmless level of cigarette consumption. Even smoking >0–3 cigarettes per day is associated with an increased HNC risk.
- This association between low frequency of cigarette consumption and HNC risk is consistent across subsites of head and neck cancer and among never alcohol drinkers.
- Smoking duration plays at least an equal or a stronger role compared with low frequency of cigarettes smoking in the development of HNC.

Introduction

Cigarette smoking is a well-established risk factor for head and neck cancer (HNC) with a well-defined dose-response relationship for duration and frequency of use.[1,2] Yet, in several epidemiological studies the lowest category of tobacco smoking has been defined as smoking ≤10 cigarettes per day. To our knowledge, only three studies have investigated the risk of HNC among participants smoking less than 10 cigarettes per day: Polesel *et al*.,[3] using cubic regression spline model among male current smokers only (1241 upper aerodigestive tract (UADT) cancer cases and 2 835 controls), showed evidence for an increased risk of oral cavity and pharyngeal cancer beginning at two cigarettes per day, and an increased risk of laryngeal cancer beginning at five cigarettes per day. Tuyns *et al*.[4] showed evidence for an increased risk of endolarynx (OR = 2.37, 95% CI: 1.3, 4.3) and of hypopharynx (OR = 4.18, 95% CI: 1.9, 9.3) associated with smoking 1 to 7 cigarettes per day compared with never smokers, adjusted for alcohol consumption. McLaughlin *et al*.[5] reported similar results in a 1–9 cigarettes per day category: OR = 5.2 (95% CI: 1.8, 15) for pharyngeal cancer. However, no analyses were conducted among finer cigarette smoking frequency categories or specific subgroups such as never alcohol drinkers.

Few studies have been able to address the risk of HNC among smokers of few cigarettes per day, due to the inadequate number of cases smoking less than 10 cigarettes per day. Consequently, either spline regression models needed to be utilized or broader categories of smoking frequency used.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium was established in 2004 to explore the potential head and neck risk factors that were difficult to evaluate in individual studies due to limited sample size. To participate in the INHANCE consortium, studies should provide individual participant data, with data available on demographic and tumour characteristics, alcohol consumption and tobacco use habits.[6,7]. Individual participant data allow re-analysis with new hypotheses formulated, various adjustments and specific subgroup analyses.

The purpose of this study is to assess the dose-response relationship between cigarette smoking and the risk of HNC among subjects smoking less than 10 cigarettes per day with better precision, while taking into account potential confounding and effect modifications. This analysis on low frequency of cigarette consumption was proposed to be performed within the INHANCE consortium database.

Methods

The version 1.4 of the INHANCE pooled dataset is an update of the version 1.0, previously described by Hashibe *et al*.[7] At the time of this analysis, the INHANCE V1.4 dataset included 29 case-control studies with 21 373 HNC cases and 29 548 controls.

For this analysis, we pooled data from 23 studies (Table 1) with available information on cigarette, cigar and pipe smoking status, duration and frequency, satisfying the criteria for the random-effect model used (each category of the low frequency of cigarette smoking variable should have at least one case or one control) including 19 660 cases and 25 566 controls. We then excluded subjects missing information for age, sex or race and cases missing the subsite of HNC (110 cases and 127 controls). Then, to focus on the association with low cigarette

Table 1. Summary of individual studies in INHANCE consortium pooled data version 1.4, by region and study period

Study location (reference[a])	Recruitment period	Cases				Control[b]		
		Source	Participation rate, %	Age eligibility, years	Total	Source	Participation rate, %	Total
Europe								
Milan, Italy	1984–89	Hospital	95[c]	<80	416	Hospital (unhealthy)	95[c]	1,531
Aviano, Italy	1987–92	Hospital	>95[c]	>18	482	Hospital (unhealthy)	95[c]	855
Italy (Aviano, Milan, Latina)[d]	1990–99	Hospital	>95	18–80	1261	Hospital (unhealthy)	>95	2,716
Switzerland	1991–97	Hospital	>95	<80	516	Hospital (unhealthy)	>95	883
Central Europe (Banska Bystrica, Bucharest, Budapest, Lodz, Moscow)[d]	1998–2003	Hospital	96	≥15	762	Hospital (unhealthy)	97	907
Rome[f]	2002–07	Hospital	98	>18	275	Hospital (unhealthy)	94	293
Western Europe[f]	2000–05	Hospital	82	NA	1701	Hospital (unhealthy)	68	1,993
Germany-Heidelberg[f]	1998–2000	Hospital	96	<80	246	Community	62.4	769
North America								
New York[d,f]	1981–90	Hospital	91	21-80	1118	Hospital (unhealthy)	97	906
Seattle, WA	1985–1995	Cancer registry	54.4, 63.3[e]	18–65	407	Random digit dialling	63.0, 60.9[e]	607
Iowa	1993–2006	Hospital	87	>18	546	Hospital (unhealthy)	92	759
North Carolina	1994–97	Hospital	88	>17	180	Hospital (unhealthy)	86	202
Tampa, FL	1994–2003	Hospital	98	≥18	207	Cancer screening clinic (healthy)	90	897
Los Angeles, CA	1999–2004	Cancer registry	49	18–65	417	Households Neighborhood	67.5	1005
Houston, TX	2001–06	Hospital	95	≥18	830	Hospital visitors	>80	865
Boston, MA[f]	1999–2003	Hospital	88.7	≥18	584	Resident list	48.7	659
US multicentre (New York, San Francisco, New Jersey, Atlanta)[d,f]	1983–84	Cancer registry	75	18-79	1114	Random digit dialling, health care financing administration rosters	76	1268
Seattle-Leo, WA[f]	1983–87	Cancer registry	81	20–74	634	Random digit dialling	75	445
North Carolina population-based[f]	2002–2006	Cancer registry	82	20–80	1368	DMV files[g]	61	1396
Latin America								
Puerto Rico	1992–95	Cancer registry	71	21–79	350	Residential records	83	521
Latin America (Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, São Paulo)[d] (NA)	2000–03	Hospital	95	15–79	2191	Hospital (unhealthy)	86	1706
Sao Paulo[d,f]	2002–07	Hospital	>95	17–96	1288	Hospital (unhealthy)	>95	1075
International								
International (Italy, Spain, Ireland, Poland, Canada, Australia, Cuba, India, Sudan)[d]	1992–97	Hospital	88.7	NA	1559	Hospital/ Community	87.3	1676

[a]INHANCE, International Head and Neck Cancer Epidemiology; NA, not applicable/non available.

[b]All studies frequency-matched control subjects to case subjects on age and sex. Additional frequency-matching factors included study centre (Italy, Central Europe, Latin America and International multicentre studies), hospital (France and Sao Paulo study), ethnicity (Tampa and US multicentre studies), and neighborhood or city of residence (Los Angeles and Sao Paulo study).

[c]Participation rate was not formally assessed, estimated response rate reported.

[d]Multicentre study.

[e]Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

[f]Study added to the INHANCE 1.0 dataset.

[g]Department of Motor Vehicles files.

smoking frequency and to avoid residual effects from other tobacco product, users of cigar, pipe, chew or snuff tobacco or straw cigarettes were excluded (3206 cases and 2913 controls). As the aim of the paper is to focus on low frequency of cigarette smoking, subjects smoking more than 10 cigarettes per day were excluded (12 251 cases and 9110 controls). The final analysis dataset included 4093 HNC cases and 13 416 controls from the 23 studies. Of the 3260 HNC cases from studies with histological information, 3067 (94.1%) were squamous cell carcinoma (SCC).

The number of cigarettes per day was defined differently among studies. It was either a lifetime average consumption (the Houston, Tampa, Puerto Rico, Rome, North Carolina (1994–97), Milan (1984–989), Aviano, Italy multicentre, Switzerland, New York multicentre, Iowa, US multicentre, Seattle-Leo, Western Europe, North Carolina (2002–06) studies) or a period-specific frequency, usually by decades, changing habits or changing brand period (the Los Angeles, Seattle, Boston, Central Europe, International multicentre, Latin America, Sao Paulo, Germany-Heidelberg studies). In the pooled analysis we used the lifetime average daily consumption by adding the information when it was directly available or calculating it by weighing each frequency of cigarette smoking by its specific duration of consumption. We also added a reference that provides more details (Hashibe *et al*. 2009).[8]

The frequency of cigarette smoking was defined in four categories (never cigarette users, >0–3 cigarettes per day, >3–5, >5–10) and analyses were conducted in the overall study population, among never alcohol users, for subsites of HNC (oral cavity, hypopharynx, oropharynx, oral cavity/pharynx not specified, and larynx, detailed in Hashibe *et al*. 2007),[7] by gender and among the different categories of duration of cigarette smoking and age at start of smoking cigarettes. One additional variable was created: combining low frequency of cigarette smoking categories and duration of cigarette smoking categories (<=10 years, 10–20 years and >20 years).

Statistical analysis

The association of low-frequency cigarette smoking with HNC was assessed by estimating odds ratios and 95% confidence intervals based on unconditional logistic regression models. To calculate summary estimates of associations, the study-specific estimates were included in a multivariate two-stage random-effects logistic regression model that included the DerSimonian and Laird estimator[9] which allows for unexplained sources of heterogeneity among studies. Pooled odds ratios were also estimated with a fixed-effects logistic regression model that adjusted for age (5-year categories), sex, education (categorical), race/ethnicity, study/study centre and number of alcoholic drinks per day (categorical). Number of drinks per day was set as a categorical variable to minimize the impact of the highest values. The Latin America and Sao Paulo studies did not assess race/ethnicity, thus we classified the subjects as a separate category 'Latin Americans-Brazilian'.

Since 246 cases and 454 controls were missing education level, we applied multiple imputations (five imputations) with the PROC MI procedure in SAS. We assumed that the education data were missing at random (i.e. whether education was missing or not did not depend on any other unobserved or missing values.[10] We used the logistic regression model[11] to predict education level with age, sex, race/ethnicity, study centre and case/control status within each region (Europe, North America, Latin America and Asia) separately. The logistic regression results to assess summary estimates for low cigarette smoking frequency for the five imputations were combined by the PROC MIANALYZE procedure.

We tested for heterogeneity across studies, using a likelihood ratio test derived from fitting a model with and a model without a product term between low cigarette smoking and the study indicator. Then, we compared twice the difference of the log likelihood ratio of these two models, with a chi square distribution. The degree of freedom of the test was the number of studies minus one. When heterogeneity between studies was detected ($P < 0.05$), the random-effect estimates were reported, otherwise the fixed-effects estimates were reported. We examined whether the results from the two-stage random-effects model and the fixed-effects logistic regression model were comparable in magnitude of effect. When random-effect estimates were estimated, individual studies missing cases or controls for any of the low cigarette consumption frequency categories were excluded, in order to have homogeneous contribution of studies across categories. We also conducted influence analysis, where each study was excluded one at a time to assure that the statistical significance and magnitude of the overall summary estimate was not dependent on any particular study. The trend test used for the analysis was a Cochrane–Armitage test.

A specific analysis was conducted after exclusion of oropharyngeal cancer cases. There is strong evidence that a large proportion of oropharyngeal cancers are caused by human papillomaviruses and are not related to tobacco smoking.[12,13] Analyses were then stratified by cancer site, age category (<40, 40–<45, 45–<50, 50–<55, 55–<60, 60–<65, 65–<70, 70–<75, >=75 years old), sex, race/ethnicity, education level, source of control subjects (hospital-based vs population-based), and geographical region (Europe, North America, South/ Central America, others).

We also repeated the analyses restricting the cases to SCC histology within the set of studies that had collected histology information.

Results

The distributions of cases and controls by selected characteristics are reported in Table 2. The proportion of cigarette smokers smoking a lifetime average ≤5 cigarettes per day was 72.8% among controls and 27.2% among cases. The highest proportion of smokers of ≤5 cigarettes per day were from the Boston study (63.5%) and the Los Angeles study (57.4%). Women were more likely than men to smoke a lifetime average of ≤5 cigarettes per day (43.0% vs 33.8%). Participants smoking ≤5 cigarettes per day were more likely to start smoking at a later age, for a shorter duration and to be former smokers (participants who stopped smoking for more than 1 year before answering the questionnaire) compared with participants smoking more than 5 cigarettes per day ($P < 0.01$ for each comparison).

HNC risk increased with greater smoking frequency in the overall study population, after exclusion of oropharyngeal cancer cases and among never alcohol drinkers (P for trend <0.01; Table 3). The OR for the category of >0–3 cigarettes/day was 1.52 (95% CI: 1.21, 1.90) for the overall study population and 1.35 (95% CI: 0.83, 2.18) among never alcohol drinkers. The association between smoking >3–5 cigarettes per day and the risk of HNC was observed among the overall study population (OR = 2.14, 95% CI: 1.73, 2.65) and among never alcohol drinkers (OR = 2.01, 95% CI: 1.22, 3.31).

Results by HNC subsite demonstrated the strongest dose-response relationship for hypopharyngeal and laryngeal cancer (P for trend <0.01; Table 4). For these subsites, the OR for smokers of >0–3 category cigarettes/day was 2.43 (95% CI: 1.23, 4.79) for hypopharynx and 2.68 (95% CI: 1.82, 3.95) for larynx.

Although the point estimates were slightly higher among women than men, the 95% CIs overlapped (Table 5). We observed that women smoking >0–3 cigarettes per day had an increased risk of HNC (OR = 1.77, 95% CI: 1.30, 2.40) compared with never smokers. For the combination of frequency and duration of smoking, we observed an association between HNC and each stratum of the low frequency of cigarette consumption with the highest stratum of smoking duration (Table 6). Figure 1 shows a forest plot of the study-specific estimates for the risk of HNC associated with smoking 3 to 5 cigarettes per day. All studies but Switzerland, Tampa and Los Angeles showed an increased risk of HNC for smoking 3 to 5 cigarettes per day. There was also an increased risk of smoking >0 to 3 cigarettes per day among current smokers (OR = 2.07, 95% CI: 1.53, 2.81) and among former smokers (OR = 1.32, 95% CI: 1.05, 1.66).

An analysis stratified by study design showed positive monotonic trends of increasing risks with increasing

Table 2. Selected characteristics of the head and neck case subjects and controls subjects[c] from the INHANCE consortium

	Cases		Controls	
	n	%	*n*	%
Total	4093		13416	
Age categories (years)				
<40	331	8.1	1149	8.6
40–<45	235	5.7	939	7.0
45–<50	369	9.0	1353	10.1
50–<55	521	12.7	1876	14.0
55–<60	628	15.3	2065	15.4
60–<65	597	14.6	1927	14.4
65–<70	519	12.7	1806	13.5
70–<75	476	11.6	1378	10.3
>=75	417	10.2	923	6.9
P[a]	<0.0001			
Sex				
Women	1678	41.0	5875	43.8
Men	2415	59.0	7541	56.2
P[a]	0.002			
Race				
White	2655	64.9	9968	74.3
Black	273	6.7	655	4.9
Hispanic	103	2.5	330	2.5
Asian	111	2.7	472	3.5
Other	30	0.7	110	0.8
Brazilian[d]	921	22.5	1881	14.0
P[a]	<0.0001			
Education				
None	129	3.4	272	2.1
Junior high school	1447	37.6	4533	35.0
Some high school	560	14.6	1856	14.3
High school graduate	513	13.3	1674	12.9
Vocational, some college	602	15.7	2343	18.1
Some graduation	596	15.5	2284	17.6
Missing[b]	246		454	
P[a]	<0.0001			
Subsite				
Oral cavity	1327	32.4		
Oropharynx	1179	28.8		
Hypopharynx	230	5.6		
Oral cavity/pharynx NOS[e]	488	11.9		
Larynx	797	19.5		
Head and neck overlap	72	1.8		

[a]Chi-square two-sided test.
[b]Rome does not have information on education.
[c]Missing for age, sex, race and subsite as well as users of pipe or cigar or chewed tobacco. Snuffed tobacco or straw cigarettes were excluded.
[d]Only cases and controls from Sao Paulo and Latin America study.
[e]Not Otherwise Specified.

Table 3. Lifetime average daily number of cigarettes smoked and the risk of HNC, among the overall population and among never alcohol drinkers, in the INHANCE consortium

Number of cigarettes smoked per day	Overall[a]				Never alcohol drinkers[b]				Overall without oropharyngeal cases[c]			
	Cases	Controls	OR[d]	95% CI	Cases	Controls	OR[d]	95% CI	Cases	Controls	OR[d]	95% CI
Never	1939	9239	1.00	Ref	724	2836	1.00	Ref	1635	8821	1.00	Ref
>0–3	250	793	1.52	(1.21, 1.90)	41	123	1.35	(0.83, 2.18)	212	779	1.56	(1.25, 1.93)
>3–5	314	710	2.14	(1.73, 2.65)	38	89	2.01	(1.22, 3.31)	278	680	2.30	(1.88, 2.81)
>5–10	1258	2215	2.60	(2.00, 3.40)	131	286	2.12	(1.48, 3.02)	1137	2125	2.98	(2.31, 3.82)
Missing	332	459			11	13			299	451		
P-value			<0.01				<0.01				<0.01	
P for heterogeneity across studies			<0.01				<0.01				<0.01	

[a]Adjusted on age (categorical), sex, race, education level, centres and drinks per day (categorical). The 23 studies were included.

[b]Adjusted on age (categorical), sex, race, education level and centres. The Switzerland, New York multicentre, Iowa, Los Angeles, Houston, Puerto Rico, Latin America, IARC multicentre, Sao Paulo, Western Europe and North Carolina population-based studies were included.

[c]Adjusted on age (categorical), sex, race, education level, centres and drinks per day. The 23 studies, except for the North Carolina and Tampa studies, were included.

[d]Random-effect model used.

Table 4. Lifetime average daily number of cigarettes smoked and the risk of HNC by subsite of cancer, in the INHANCE consortium

Daily number of cigarette smoked	Oral cavity[a]				Hypopharynx[b]				Oropharynx[c]				Larynx[d]			
	Cases	Controls	OR[e]	95% CI	Cases	Controls	OR[e]	95% CI	Cases	Controls	OR[e]	95% CI	Cases	Controls	OR[e]	95% CI
Never	653	6309	1.00		38	3521	1.00		520	7368	1.00		203	6010	1.00	
>0–3	62	548	1.48	(1.04, 2.09)	13	3443	2.43	(1.23, 4.79)	70	661	1.57	(1.10, 2.23)	58	581	2.68	(1.82, 3.95)
>3–5	79	474	2.23	(1.45, 3.42)	17	310	3.35	(1.78, 6.29)	64	528	2.17	(1.53, 3.06)	74	518	3.48	(2.40, 5.05)
>5–10	291	1501	2.18	(1.68, 2.83)	71	1032	4.38	(2.82, 6.82)	323	1724	2.85	(1.89, 4.08)	309	1543	5.21	(4.07, 6.68)
Missing	104	407			8	244			51	398			92	324		
P-value			<0.01				<0.01				<0.01				<0.01	
P for heterogeneity across studies			<0.01				<0.01				<0.01				<0.01	

Adjusted on age (categorical), race, education level, centres and drinks per day (categorical).

[a]The Aviano, Boston, Los Angeles, Milan, North Carolina, Rome, Switzerland, Tampa, Seattle-LEO and Germany-Heidelberg studies were not included.

[b]Only Aviano, Italy multicentre, New York, Latin America, US multicentre, Seattle-LEO and Western Europe studies were included.

[c]The Milan, Central Europe, Seattle, North Carolina, Tampa, Boston, and Germany-Heidelberg studies were not included.

[d]Only Milan, Central Europe, Italy Multicentre, New York, Iowa, Los Angeles, Latin America, Boston, Rome, Sao Paulo, Seattle-LEO, Western Europe, Germany-Heidelberg and North Carolina population-based studies were included.

[e]Random-effect models.

frequency of cigarette smoking for both hospital-based ($n = 15$) and population-based ($n = 9$) studies (the Western Europe study includes studies with both population-based and hospital-based controls), with a slightly weaker trend in population-based studies (OR = 1.64, 95% CI: 0.90, 3.00; OR = 1.93, 95% CI: 1.31, 2.85; OR = 2.51, 95% CI: 1.50, 4.18 for > 0–3, >3–5 and >5–10 cigarettes/day, respectively; *P* for trend <0.01). When the analysis by region was conducted, an apparent positive trend of increasing risks with increasing frequency of cigarette smoking was observed in each region. Such relationship was found to be strongest in Europe and Latin America. The risk of HNC for smoking >0 to 3 cigarette per day was OR = 1.82 (95% CI: 1.15, 2.86) in Europe and OR = 1.98 (95% CI: 1.15, 3.39) in Latin America. Analyses restricted to squamous cell carcinoma yielded similar results (see Appendix Table 1A, available as Supplementary data at *IJE* online).

We additionally adjusted, when the information was available, for body mass index (BMI) (all studies except for Rome, Seattle, International multicentre, Iowa, Central Europe, Sao Paulo, Germany-Heidelberg) and for family history of HNC (all studies except for Rome, Seattle, New York multicentre, Iowa, Western Europe and Seattle-Leo).

Table 5. Lifetime average daily number of cigarettes smoked and the risk of HNC by gender, in the INHANCE consortium

Daily number of cigarettes smoked	Men[a]				Women[b]			
	Cases	Controls	OR[c]	95% CI	Cases	Controls	OR[c]	95% CI
Never	853	4099	1.00		882	3763	1.00	
>0–3	141	480	1.39	(0.96, 2.01)	101	278	1.77	(1.30, 2.40)
>3–5	160	409	2.05	(1.39, 3.02)	118	200	2.74	(2.01, 3.74)
>5–10	854	1420	2.83	(2.01, 3.98)	330	556	2.67	(2.02, 3.53)
Missing	235	250			84	180		
P-value			<0.01				<0.01	
P for heterogeneity across studies			<0.01				<0.01	

Adjusted on age (categorical), race, education level, centres and drinks per day (categorical).
[a]The Boston, North Carolina, Tampa, Switzerland and Seattle-LEO studies were not included.
[b]The Boston, Milan, Rome, Tampa and Germany-Heidelberg studies were not included.
[c]Random-effect models.

Table 6. Adjusted OR (95% CI) of HNC by lifetime average daily number of cigarettes smoked combined with duration of cigarette smoking in years, in the INHANCE consortium

Cigarettes daily	Cases	Controls	OR[a,b]	95% CI
Never smokers	1163	4329	1.00	Ref
>0–3 cig for <=10 yrs	53	199	1.04	(0.75, 1.43)
>0–3 cig for >10–20 yrs	27	77	1.39	(0.88, 2.20)
>0–3 cig for >20–30 yrs	29	79	1.30	(0.83, 2.03)
>0–3 cig for >30 yrs	76	104	2.64	(1.92, 3.63)
>3–5 cig for <=10 yrs	30	98	1.04	(0.68, 1.59)
>3–5 cig for >10–20 yrs	22	70	1.19	(0.72, 1.96)
>3–5 cig for >20–30 yrs	37	55	2.35	(1.52, 3.65)
>3–5 cig for >30 yrs	101	105	2.89	(2.13, 3.91)
>5–10 cig for <=10 yrs	52	167	1.06	(0.76, 1.47)
>5–10 cig for >10–20 yrs	55	220	0.94	(0.68, 1.29)
>5–10 cig for >20–30 yrs	130	221	1.91	(1.49, 2.43)
>5–10 cig for >30 yrs	541	412	4.17	(3.54, 4.90)
Missing	229	164		
P for heterogeneity			0.05	
P for trend			<0.01	

Adjusted on age (categorical), race, education level, centres and drinks per day (categorical); yrs, years.
[a]The Los Angeles, International Multicentre, US multicentre, Sao Paulo, Western Europe, North Carolina (population-based) studies were included.
[b]Fixed-effect model.

The magnitudes of the associations were similar to those observed without the additional adjustments (see Appendix Table 1A, available as Supplementary data at *IJE* online). Analysis of passive smoking was not conducted as this information was only available in six studies (Central Europe, Latin America, Puerto Rico, Tampa, Los Angeles and Houston), and this would have resulted in a restricted number of cases and controls. However, based on our previous analysis on passive smoking,[14] the modest association with passive smoking was observed among never tobacco users. Thus, we suspect the dose-response relationship among smokers presented here would not be significantly biased.

Finally, we conducted sensitivity analyses to assess whether or not one or several studies had a strong influence on the observed associations. When we omitted each study from the analysis one at a time, the Aviano and the Tampa studies accounted for heterogeneity the most. When the Aviano study was not included, the summary estimate for smoking 3 to 5 cigarettes per day compared with never smokers was 2.04 (95% CI: 1.69, 2.46) and when the Tampa study was not included, the summary estimate was 2.18 (95% CI: 1.76, 2.69) as compared with the overall summary estimate of 2.14 (95% CI: 1.73, 2.65). When both studies were excluded from the summary estimate, the OR was 2.06 (95% CI: 1.71, 2.49).

The sensitivity analysis was also conducted for smoking >0 to 3 cigarettes per day. When we omitted each study from the analysis one at a time, the Seattle and the North Carolina (hospital-based) studies accounted for heterogeneity the most. When the Seattle study was not included, the summary estimate for smoking >0 to 3 cigarettes per day compared with never smokers was 1.55 (95% CI: 1.24, 1.95) and when the North Carolina study was not included, the summary estimate was 1.50 (95% CI: 1.19, 1.88) as compared with the overall summary estimate of 1.52 (95% CI: 1.21, 1.90). When both studies were excluded from the summary estimate, the OR was 1.54 (95% CI: 1.22, 1.93).

Discussion

The ability to pool individual data from studies allowed us to detect an increased risk of HNC with smoking less than 10 cigarettes more precisely than it has been reported

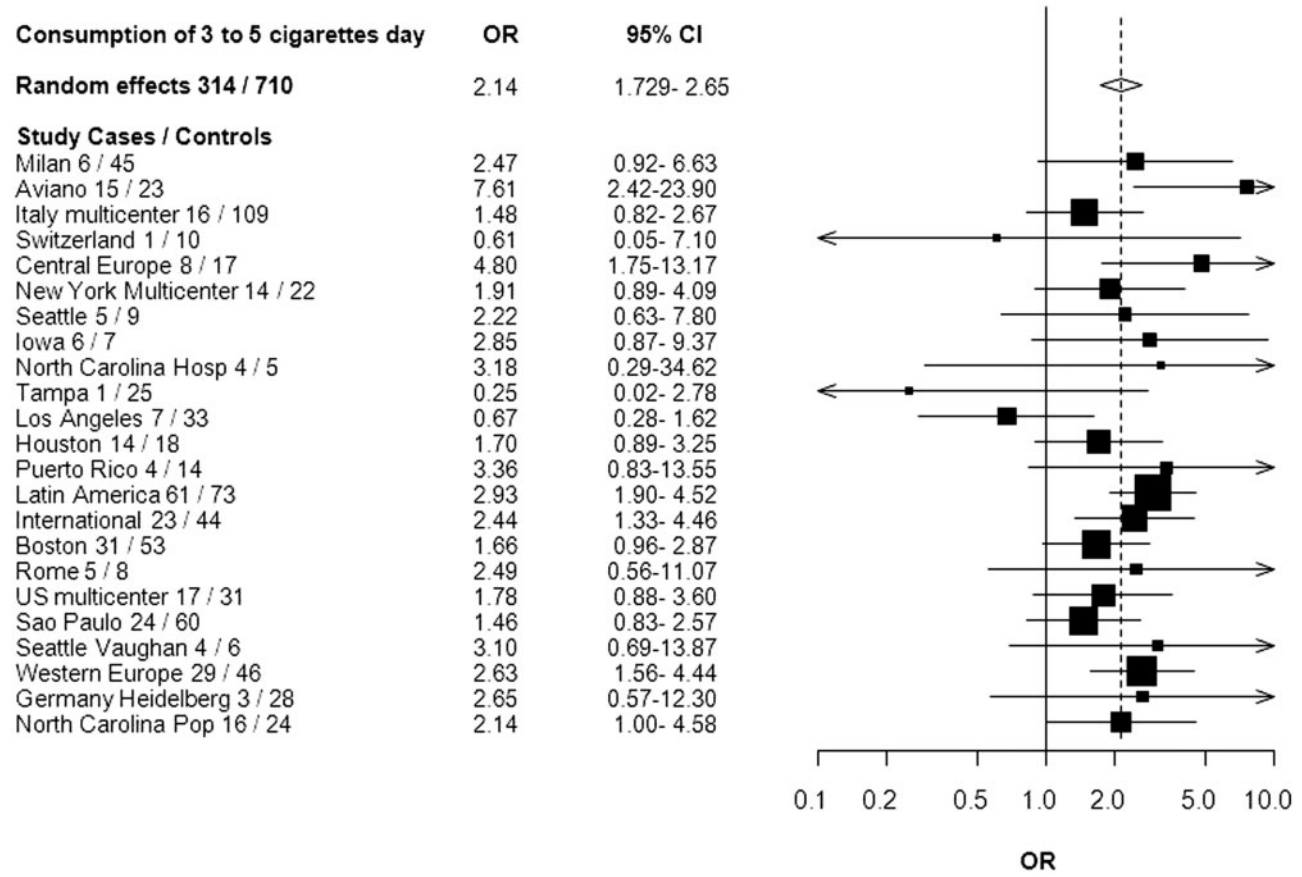

Figure 1. Forest plot of the risk of HNC associated with lifetime consumption of 3 to 5 cigarettes per day compared with never smokers, in the INHANCE Consortium. Pop, population-based; hosp, hospital.

previously by Tuyns *et al.*[4] and McLaughlin *et al.*[5] and highlighted an approximately 1.5-fold increased risk of HNC for smoking >0 to 3 cigarettes per day and a more than 2-fold increased risk of HNC for smoking >3 to 5 cigarettes per day. This also corroborates the results reported by Polesel *et al.*[3] that there is an increased risk regardless of the number of cigarettes smoked per day. Polesel showed evidence for an increased OR of UADT cancer for smoking two cigarettes per day. The present analysis provides additional details for the finer categories of smoking frequency with adequate sample size.

From a methodological point of view we decided to investigate the frequency of cigarette smoking as a categorical variable with fine categories instead of a continuous variable. Even though using a continuous variable might increase the precision of the estimates, it implies making some assumptions on the shape of the slope and might introduce mis-specification bias. There is no need for such assumptions when using a categorical variable. The large number of cases and controls provides for sufficient precision, and keeps the results straightforward for interpretation.

The higher increased risk of laryngeal cancer with cigarette smoking compared with the other head and neck subsites is consistent with the previous findings[12,13] and with the previous reports from INHANCE studies that active smoking is a stronger risk factor for laryngeal cancers than for oral cavity cancer among never alcohol drinkers.[7]

The analysis combining the smoking frequency with smoking duration is consistent with the previous observations that duration of smoking seems to play at least an equal or a stronger role in the development of HNC[4] even among never alcohol drinkers.

A potential limitation with regards to the data pooling was the variation of definition for 'ever cigarette smokers' (among whom the frequency of cigarette smoking was measured) used in the different studies: ever smoked, smoked ≥100 cigarettes in a lifetime, smoked 1 cigarette/day for ≥1 year or 6 months, smoked 1 cigarette/week for ≥1 year or smoked half a pack/week for ≥1 year. However, these different classifications are relatively minor and likely to be non-differential between cases and controls. Thus, this might lead to an underestimation of the assessment. In addition, some individuals with very minimal cigarette use may have been categorized as 'never cigarette users' in the analysis due to the definition or the wording of the questions. The studies with higher threshold

for the classification were the Tampa study (smoking cigarettes less than once a day for <1 year as never users of cigarettes) and Latin America study (<1 cigarette per day for 1 year as never cigarette smokers). However, the ORs for the lowest category of smokers (>0–3 per day) were not consistently lower or higher for these studies compared with the others included in our pooled analysis.

Recall bias may be another limitation for our pooled analysis because information about cigarette smoking and the other exposures was collected for cases after the diagnosis of HNC. However, we observed associations between low-frequency cigarette smoking in both hospital-based and population-based studies, which may be susceptible to recall bias in different degrees. In addition, there might be residual confounding by the other risk factors. However, our study sample size allowed us to investigate the association among never alcohol drinkers to eliminate the possible residual confounding by alcohol drinking. Additionally, further adjustment for body mass index and family history of HNC did not support that the observed association could be accounted for by these factors. Although heterogeneity across studies was important, in the >0–3 and 3 to 5 cigarettes per day, the sensitivity analyses showed that exclusion of studies contributing the most in the heterogeneity did not lead to major changes in the estimates for both categories.

Finally, as specified in the method section, analyses were conducted on data from studies participating in the INHANCE consortium. Some published and unpublished studies might not be included, but publication bias is not a concern for this type of analysis because we did not select studies from the literature. Additionally, the large sample size and the quality of the studies included allow our estimates to be accurate.

In summary, this pooling project provides evidence for a carcinogenic consequence of cigarette smoking at low frequency. The results of this study send a public health message to the community: there is no harmless level of cigarette consumption, even smoking >0–3 cigarettes per day is associated with an increased HNC risk. However, smoking duration seems to play at least an equal or a stronger role in the development of HNC in light smokers.

Supplementary Data

Supplementary data are available at *IJE* online.

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