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

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Key message Box

- 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 as low frequency of cigarettes smoking in the development of HNC.

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 (IPD) 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, 4 093 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 (OR=1.52, 95% 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 (HNC), low frequency cigarette smoking, risk factors, pooled analysis

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 $\leq$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 (1 241 upper aerodigestive tract (UADT) cancer cases and 2 835 controls) showed evidence for an increased risk of oral cavity and pharyngeal cancer beginning at 2 cigarettes per day, and an increased risk of laryngeal cancer beginning at 5 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 to never smokers, adjusted for alcohol consumption. McLaughlin et al (5) reported similar results in a 1 to 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 were 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 tumor 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 (Table1) 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, race and cases missing the subsite of HNC (110 cases and 127 controls). Then, to focus on the association with low cigarette smoking frequency and to avoid residual effects from other tobacco product, users of cigar, pipe, chew or snuff tobacco or straw cigarettes were excluded (3 206 cases and 2 913 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 9 110 controls). The final analysis dataset included 4 093 HNC cases and 13 416 controls from the 23 studies. Of the 3,260 HNC cases from studies with histological information, 3 067 (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 (1994-1997), Milan (1984-1989), Aviano, Italy multicenter, Switzerland, New York multicenter, Iowa, US multicenter, Seattle-Leo, Western Europe, North Carolina (2002-2006) studies) or a period specific frequency, usually by decades, changing habits or changing brand period (the Los Angeles, Seattle, Boston, Central Europe, International multicenter, Latin America, Sao Paulo, Germany-Heidelberg) 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 >20years).

Statistical analysis

The association of low frequency cigarette smoking with HNC was assessed by estimating odds ratios (OR) and 95% confidence intervals (CI) 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 years categories), sex, education (categorical), race/ethnicity, study/study center 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 center, 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 homogenous 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 (≤ 45, 46 – 50, 51 – 60, 61 – 70, and >70 years), sex, race/ethnicity, education level, source of control subjects (hospital-based versus population-based), and geographic 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.

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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 to 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 to 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 frequency of cigarette smoking for both hospital-based (n=15) and population-based (n=9) studies (the Western Europe study include 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, >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 table appendix).

We additionally adjusted, when the information was available, for BMI (all studies except for Rome, Seattle, International multicenter, Iowa, Central Europe, Sao Paulo, Germany-Heidelberg) and for family history of HNC (all studies except for Rome, Seattle, New York multicenter, Iowa, Western Europe and Seattle-Leo). The magnitudes of the associations were similar to those observed without the additional adjustments (see table appendix). Analysis of passive smoking was not conducted as this information was only available in 6 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 to 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 to 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 to 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 to 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 to 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 to 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 previously by Tuyns et al (4) and McLaughlin et al (5) and highlighted an approximately one and half-fold increased risk of HNC for smoking >0 to 3 cigarettes per day and a more than two-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 2 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 to make 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 straight forward for interpretation.

The higher increased risk of laryngeal cancer with cigarette smoking compared to 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 cigarette in a lifetime, smoked 1 cigarette/day for ≥1 year or 6 months, smoked 1 cigarette/week for ≥1 year or smoked ½ 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 to 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.

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Study Location (Reference†)	Recruitment period	Cases				Control‡		
		Source	Participation rate, %	Age eligibility, years	Total	Source	Participation rate, %	Total
Europe								
Milan, Italy	1984–1989	Hospital	95§	<80	416	Hospital (unhealthy)	95§	1,531
Aviano, Italy	1987–1992	Hospital	>95§	>18	482	Hospital (unhealthy)	95§	855
Italy (Aviano, Milan, Latina)‖	1990–1999	Hospital	>95	18–80	1,261	Hospital (unhealthy)	>95	2,716
Switzerland	1991–1997	Hospital	>95	<80	516	Hospital (unhealthy)	>95	883
Central Europe (Banska Bystrica, Bucharest, Budapest, Lodz, Moscow)‖	1998–2003	Hospital	96	≥15	762	Hospital (unhealthy)	97	907
Rome #	2002-2007	Hospital	98	>18	275	Hospital (unhealthy)	94	293
Western Europe #	2000-2005	Hospital	82	NA	1,701	Hospital (unhealthy)	68	1,993
Germany-Heidelberg #	1998-2000	Hospital	96	<80	246	Community	62.4	769
North America								
New York‖ #	1981-1990	Hospital	91	21-80	1,118	Hospital (unhealthy)	97	906
Seattle, WA	1985–1995	Cancer registry	54.4, 63.3¶	18–65	407	Random digit dialing	63.0, 60.9¶	607
Iowa	1993–2006	Hospital	87	>18	546	Hospital (unhealthy)	92	759
North Carolina	1994–1997	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	1,005
Houston, TX	2001-2006	Hospital	95	≥18	830	Hospital visitors	>80	865
Boston, MA #	1999-2003	Hospital	88.7	≥18	584	Resident list	48.7	659
US multicenter (New York, San Francisco, New Jersey, Atlanta) ‖#	1983-1984	Cancer registry	75	18-79	1,114	Random digit dialling, health care financing administration rosters	76	1,268
Seattle-Leo, WA #	1983-1987	Cancer registry	81	20-74	634	Random digit dialing	75	445
North Carolina pop-based #	2002-2006	Cancer registry	82	20-80	1,368	DMV files	61	1,396
Latin America								
Puerto Rico	1992–1995	Cancer registry	71	21–79	350	Residential records	83	521
Latin America (Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, São Paulo)‖ (NA)	2000–2003	Hospital	95	15–79	2,191	Hospital (unhealthy)	86	1,706
Sao Paulo‖ #	2002-2007	Hospital	>95	17–96	1,288	Hospital (unhealthy)	>95	1,076
International								
International (Italy, Spain, Ireland, Poland, Canada, Australia, Cuba, India, Sudan)‖	1992–1997	Hospital	88.7	NA	1,559	Hospital/ Community	87.3	1,676

*INHANCE = International Head and Neck Cancer Epidemiology; NA = not applicable/non available.
‡: All studies frequency matched control subjects to case subjects on age and sex. Additional frequency matching factors included study center (Italy, Central Europe, Latin America, and International multicenter studies), hospital (France and Sao Paulo study), ethnicity (Tampa and US multicenter studies), and neighborhood or city of residence (Los Angeles and Sao Paulo study).
§: Participation rate was not formally assessed, estimated response rate reported.
||: Multicenter study.
¶: Two response rates are reported because data were collected in two population-based case–control studies, the first from 1985–1989 among men and the second from 1990–1995 among men and women
Study added to the INHANCE 1.0 dataset
X information not available TO CHECK

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

Tables 2: Selected characteristics of the head and neck case subjects and controls subjects[§] from the INHANCE consortium

	Case		Controls	
	n	**%**	**n**	**%**
Total	4 093		13 416	
Age Categories				
<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*		<0.0001		
Sex				
Women	1678	41.0	5875	43.8
Men	2415	59.0	7541	56.2
p*		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‡	921	22.5	1881	14.0
p*		<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 graduate	596	15.5	2284	17.6
Missing#	246		454	
p*		<0.0001		
Subsite				
Oral cavity	1327	32.4		
Oropharynx	1179	28.8		
Hypopharynx	230	5.6		
Oral cavity/Pharynx NOS	488	11.9		
Larynx	797	19.5		
Head and neck overlap	72	1.8		

* Chi-square two-sided test

Rome does not have information on education

[§] Missing for age, sex, race and subsite as well as users of pipe or cigar or chewed tobacco or snuffed tobacco or straw cigarettes were excluded

‡ only cases and controls from Sao Paulo and Latin America study.

Tables 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

	Overall[1]				Never alcohol drinkers[2]				Overall without Oropharyngeal cases[3]			
Number of cigarettes smoked per day	Cases	Controls	OR#	95% CI	Cases	Controls	OR#	95% CI	Cases	Controls	OR#	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	

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

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

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

Random effect model used

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

	Oral cavity~				Hypopharynx*				Oropharynx||				Larynx#			
Daily number of cigarette smoked	Cases	Controls	OR&	95% CI	Cases	Controls	OR&	95% CI	Cases	Controls	OR&	95% CI	Cases	Controls	OR&	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, centers and drinks per day (categorical)

~ The Aviano, Boston, Los Angeles, Milan, North Carolina, Rome, Switzerland, Tampa, Seattle-LEO and Germany-Heidelberg studies were NOT included

* Only Aviano, Italy multicenter, New York, Latin America, US multicenter, Seattle-LEO, and Western Europe studies were included

|| The Milan, Central Europe, Seattle, North Carolina, Tampa, Boston,, and Germany-Heidelberg studies were NOT included

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

& Random effect models

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

Daily Number of cigarette smoked	Men[1]				Women[2]			
	Cases	Controls	OR#	95% CI	Cases	Controls	OR#	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, centers and drinks per day (categorical)
[1] The Boston, North Carolina, Tampa, Switzerland and Seattle-LEO studies were NOT included
[2] The Boston, Milan, Rome, Tampa and Germany-Heidelberg studies were NOT included
Random effect models

Tables 6: Adjusted OR (OR, 95% Confidence intervals) of HNC by lifetime average daily number of cigarettes smoked combined with duration of cigarette smoking in years, in the INHANCE consortium

	Cases	**Controls**	OR^	95% CI
Never smokers	1163	4329	1.00	Ref
>0-3 cig for <=10yrs	53	199	1.04	(0.75; 1.43)
>0-3 cig for >10-20yrs	27	77	1.39	(0.88, 2.20)
>0-3 cig for >20-30yrs	29	79	1.30	(0.83, 2.03)
>0-3 cig for >30yrs	76	104	2.64	(1.92, 3.63)
>3-5 cig for <=10yrs	30	98	1.04	(0.68, 1.59)
>3-5 cig for >10-20yrs	22	70	1.19	(0.72, 1.96)
>3-5 cig for >20-30yrs	37	55	2.35	(1.52, 3.65)
>3-5 cig for >30yrs	101	105	2.89	(2.13, 3.91)
>5-10 cig for <=10yrs	52	167	1.06	(0.76, 1.47)
>5-10 cig for >10-20yrs	55	220	0.94	(0.68, 1.29)
>5-10 cig for >20-30yrs	130	221	1.91	(1.49, 2.43)
>5-10 cig for >30yrs	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, centers and drinks per day (categorical)
[1] The Los Angeles, International Multicenter, US multicenter, Sao Paulo, Western Europe, North Carolina (pop based) studies were included
^Fixed effect model

Figure 1: Forest plot of the risk of HNC associated with lifetime consumption of 3 to 5 cigarettes per day compared to never smokers, in the INHANCE Consortium

Consumption of 3 to 5 cigarettes day	OR	95% CI
Random effects 314 / 710	2.14	1.729- 2.65
Study Cases / Controls		
Milan 6 / 45	2.47	0.92- 6.63
Aviano 15 / 23	7.61	2.42-23.90
Italy multicenter 16 / 109	1.48	0.82- 2.67
Switzerland 1 / 10	0.61	0.05- 7.10
Central Europe 8 / 17	4.80	1.75-13.17
New York Multicenter 14 / 22	1.91	0.89- 4.09
Seattle 5 / 9	2.22	0.63- 7.80
Iowa 6 / 7	2.85	0.87- 9.37
North Carolina Hosp 4 / 5	3.18	0.29-34.62
Tampa 1 / 25	0.25	0.02- 2.78
Los Angeles 7 / 33	0.67	0.28- 1.62
Houston 14 / 18	1.70	0.89- 3.25
Puerto Rico 4 / 14	3.36	0.83-13.55
Latin America 61 / 73	2.93	1.90- 4.52
International 23 / 44	2.44	1.33- 4.46
Boston 31 / 53	1.66	0.96- 2.87
Rome 5 / 8	2.49	0.56-11.07
US multicenter 17 / 31	1.78	0.88- 3.60
Sao Paulo 24 / 60	1.46	0.83- 2.57
Seattle Vaughan 4 / 6	3.10	0.69-13.87
Western Europe 29 / 46	2.63	1.56- 4.44
Germany Heidelberg 3 / 28	2.65	0.57-12.30
North Carolina Pop 16 / 24	2.14	1.00- 4.58