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Age at start of using tobacco on the risk of head and neck cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (INHANCE)

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*Abbreviations:*HNC, head and neck cancer

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ABSTRACT

Background: Tobacco use is a well-established risk factor for head and neck cancer (HNC). However, less is known about the potential impact of exposure to tobacco at an early age on HNC risk.
Methods: We analyzed individual-level data on ever tobacco smokers from 27 case-control studies (17,146 HNC cases and 17,449 controls) in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using random-effects logistic regression models.
Results: Without adjusting for tobacco packyears, we observed that younger age at starting tobacco use was associated with an increased HNC risk for ever smokers ($OR_{<10\ years\ vs.\ \geq 30\ years}$: 1.64, 95% CI: 1.35, 1.97). However, the observed association between age at starting tobacco use and HNC risk became null after adjusting for tobacco packyears ($OR_{<10\ years\ vs.\ \geq 30\ years}$: 0.97, 95% CI: 0.80, 1.19). In the stratified analyses on HNC subsites by tobacco packyears or years since quitting, no difference in the association between age at start and HNC risk was observed.
Conclusions: Results from this pooled analysis suggest that increased HNC risks observed with earlier age at starting tobacco smoking are largely due to longer duration and higher cumulative tobacco exposures.

1. Introduction

Head and neck cancer refers to a group of neoplasms originating from the upper aerodigestive tract, including the oral cavity, oropharynx, hypopharynx and larynx. According to the GLOBOCAN 2018 estimates, there were around 705,781 new head and neck cancer cases diagnosed and 358,144 deaths from head and neck cancer worldwide in 2018, consisting of 3.9% and 3.7% of all cancer sites for incidence and mortality, respectively [1]. The IARC Monographs on the evaluation of carcinogenic risks to humans have concluded that there is sufficient evidence that tobacco smoking is causally related to cancers of the oral cavity, pharynx, and larynx in humans [2]. In previous INHANCE analyses, we reported that the population attributable risk for head and neck cancer was 33% due to tobacco alone [3].

The risk of head and neck cancer increases with the duration and intensity of smoking tobacco [2,4]. Smokeless tobacco, such as chewing tobacco and snuff, also increases the risk of head and neck cancer [5–8]. However, whether teenagers are more vulnerable to the exposure of tobacco in terms of head and neck cancer risk, independent of the amount exposed, is less conclusive and is of special interest. Previous studies on the association between younger age at start of smoking and head and neck cancer reported inconsistent results. While several studies indicated elevated risks of head and neck cancer with earlier age at starting to smoke [9–16], others showed little evidence [17–21]. Even fewer studies have investigated the association of age at start of using smokeless tobacco products with head and neck cancer risk. Lewin et al. reported no association between age at start of using Swedish snuff and squamous cell carcinoma of the head and neck without adjustments for tobacco smoking duration or frequency [14]. In a cohort study in India, Jayalekshmi et al. reported no clear trend between age at start of chewing tobacco and oral cavity cancer without adjustments for tobacco smoking [22].

There are several limitations in the previous studies on the association of age at start of using tobacco with head and neck cancer risk. Some studies included people who have never used tobacco as the reference group [9–12,14,16,18,21,22] while others did not [13,15,17,19,20]. Second, individual studies might not have sufficient statistical power for the comparisons using fine age categories. The pooled data in the International Head and Neck Cancer Epidemiology (INHANCE) consortium [23] provides an opportunity to investigate the effect of age at start of using tobacco products on head and neck cancer with a very large sample size.

2. Material and methods

The current analysis included 27 individual case-control studies [12,18,24–47] comprising 19,416 head and neck cancer cases and 27,934 controls from the INHANCE pooled data version 1.4. After excluding subjects with missing data on age, sex, or race/ethnicity, and cases with missing information on the site of origin of their cancer (147 cases and 134 controls), the final data for analyses included 19,269 head and neck cancer cases and 27,800 controls. We further restricted the analyses to ever-tobacco users, which included 27 studies with 17,146 head and neck cancer cases and 17,449 controls (Table 1).

[1] These authors contributed equally to this work.

Table 1
Distribution of demographic characteristics among head and neck cancer cases and controls who have ever used tobacco products, in the INHANCE Consortium.

	Cases (N = 17,146)		Controls (N = 17,449)	
	n	%	n	%
Age, years				
< 40	467	2.7	936	5.4
40–44	868	5.1	1051	6.0
45–49	1787	10.4	1662	9.5
50–54	2658	15.5	2558	14.7
55–59	3207	18.7	3012	17.3
60–64	3032	17.7	2929	16.8
65–69	2513	14.7	2466	14.1
70–74	1710	10.0	1886	10.8
≥75	904	5.3	949	5.4
P[a]		< 0.001		
Sex				
Female	3123	18.2	3062	17.6
Male	14023	81.8	14387	82.5
P[a]		0.1061		
Race/ethnicity				
White	11071	64.6	12037	69.0
Black	1011	5.9	689	4.0
Hispanic	166	1.0	231	1.3
Asian/Pacific Islanders	953	5.6	2228	12.8
Brazilian	3786	22.1	2144	12.3
Others	159	0.9	120	0.7
P[a]		< 0.001		
Education level				
No formal education	574	3.7	218	1.5
Junior high school	6056	38.6	5030	33.7
Some high school	2711	17.3	2151	14.4
High school graduate	2505	16.0	2176	14.6
Technical school, some college	2473	15.7	3029	20.3
College graduate or higher	1390	8.9	2307	15.5
Missing	1437		2538	
P[a]		< 0.001		
Alcohol drinks per day				
Never drinkers	1711	10.5	2958	17.6
> 0–1	2806	17.3	4881	29.1
1–2	3305	20.3	4101	24.4
3–4	2213	13.6	2017	12.0
≥5	6211	38.2	2838	16.9
Missing	900		654	
P[a]		< 0.001		
Tobacco packyears				
> 0–10	1134	7.0	3633	21.7
11–20	1535	9.4	3021	18.0
21–30	2216	13.6	2682	16.0
31–40	2645	16.3	2352	14.0
41–50	2348	14.5	1639	9.8
> 50	6376	39.2	3438	20.5
Missing	892		684	
P[a]		< 0.001		
Years since quitting tobacco use				
Current users or quit < 1 year	12717	74.7	8423	48.7
1–9	1967	11.6	2402	13.9
10–19	1173	6.9	2699	15.5
≥20	1163	6.8	3767	21.8
Missing	126		158	
P[a]		< 0.001		
Cancer subsite				
Oral cavity	4668	27.2		
Oropharynx	4275	24.9		
Hypopharynx	1340	7.8		
Oral/pharynx NOS	1507	8.8		
Larynx	5079	29.6		
Unspecified	277	1.6		

[a] Chi-square test (two-sided).

Characteristics of individual studies included in the pooled data are provided in Supplementary Table 1. Among these 27 studies, 19 were hospital-based case-control studies, and in most studies, the control subjects were frequency matched to the case subjects on at least age, sex and additional factors (such as study center, hospital, and race/ethnicity). The Los Angeles study individually matched the controls to the cases on age decade, sex, and neighbourhood, although the matching was broken in the study analysis.

Questionnaire interviews in all studies were conducted face-to-face, except for the Iowa, Boston, and North Carolina (2002–2006) studies, in which study participants completed self-administered questionnaires. Written informed consent was obtained from every study subject, and the individual studies were approved by Institutional Review Boards at each of the institutes involved. Questionnaires were collected from all the individual studies, to assess the comparability of the data and wording of interview questions. Each data item was checked for illogical or missing values. Queries were sent to investigators and inconsistencies were resolved.

Cases included patients with invasive tumors of the oral cavity, oropharynx, hypopharynx, oral cavity/oropharynx/hypopharynx not otherwise specified (NOS), larynx, or head and neck cancer unspecified. Cancers of the salivary gland (ICD-O-2 C07-C08) were excluded from our analysis due to the different etiologic pattern from head and neck cancers [48]. The pooled data excluded lymphomas, minor salivary gland cancers, and sarcomas of the upper aerodigestive tract cases. Studies provided tumor site data using either the International Classification of Diseases-Oncology, Version 2 (ICD-O-2) or ICD 9 or 10. Among the 19,269 head and neck cancer cases, there were a total of 5452 oral cavity cancer cases, 4880 oropharyngeal cancer cases, 1417 hypopharyngeal cancer cases, 1852 oral cavity/pharynx not specified cases, 5347 laryngeal cancer cases and 321 unspecified head and neck cancer cases. Of the 14,878 head and neck cancer cases for which histological information was available, 14,355 were squamous cell carcinomas (96.5%).

In the tobacco section of the questionnaires, subjects were asked if they were users of each specific type of tobacco including cigarettes, cigars, pipes, chewing tobacco, snuff, cigarillos, and straw-cigarettes. Type of tobacco use varied across studies as follows: 1) cigarettes, cigars, pipes, chewing tobacco, or snuff in 13 studies including Houston, Iowa, Los Angeles, Memorial Sloan Kettering Cancer Center (MSKCC), New York Multicenter, North Carolina (1994–1997), North Carolina (2002–2006), Seattle (1985–1995), Seattle-Leo, Tampa, US Multicenter, Puerto Rico, and International Multicenter studies (Tampa study combined information on chewing tobacco and snuff); 2) cigarettes, cigars, pipes or cigarillos in France (1987–1992) and Germany-Heidelberg study (France study combined information on cigar and cigarillo); 3) cigarettes, cigars, pipes, or straw-cigarettes in Sao Paulo study; 4) cigarettes, cigars, pipes, or chewing tobacco in Boston study; 5) cigarettes, cigars, or pipes in 8 studies including Aviano, Central Europe, Italy Multicenter, Milan (1984–1989), Milan (2006–2009), Rome, Switzerland, and Latin America studies; and 6) cigarettes in Germany-Saarland and Japan (2001–2005) studies. We assumed that studies which did not collect information on a specific tobacco product had negligible prevalence of use in their population. Among ever tobacco users, age at start of using each specific tobacco product was asked. Houston and MSKCC studies collected information on the use of cigarettes, cigars, pipes, chewing tobacco, and snuff, but information on age at start of smoking was only available for cigarette smokers.

2.1. Statistical methods

We categorized age at start of using tobacco products into 5-year categories as < 10, 10–14, 15–19, 20–24, 25–29 and ≥30 years. We estimated odds ratios (OR) and 95% confidence intervals (95% CI) using random effect regression models (PROC GLIMMIX procedure) with study center as the random effect intercept. In one model, covariates included age (categories shown in Table 1), sex, education (categories shown), race/ethnicity (categories shown), alcohol drinks per day (continuous). In another model, covariates additionally included duration of using chewing tobacco (continuous), duration of using snuff (continuous), and years since quitting tobacco use

(continuous). Finally, covariates in the final model additionally included packyears of tobacco smoking (continuous) and the product term for interaction between alcohol drinks per day and packyears of tobacco smoking. Packyears of tobacco smoking was defined as the sum of 1) the number of packs of cigarettes smoked per day multiplied by the years of smoking cigarettes, 2) cigar-, 3) pipe-, 4) cigarillo-, and 5) straw-cigarettes-equivalent cigarette packyears. Tobacco contents were taken to be the equivalent of four cigarettes for one roll of cigar, 3.5 cigarettes for one roll of pipe, two cigarettes for one roll of cigarillo, and five cigarettes for one roll of straw-cigarette [49]. One tobacco packyear was equal to smoking 20 cigarettes (1 pack) per day for a year.

Age at the start, duration, time since quitting tobacco use, and age at diagnosis are four time-related variables when modeling tobacco history. To reduce multicollinearity, we used tobacco packyears to replace the use of intensity and duration as separate variables and used categorized ages instead of continuous variables [50].

For subjects missing education level (1658 cases and 3999 controls), we applied multiple imputation with the PROC MI procedure in the SAS statistical software. We assumed that the education data are missing at random (MAR), i.e. whether education is missing or not does not depend on any other unobserved or missing values [51]. We used the logistic regression model [52] to predict education level with age, sex, race/ethnicity, study, and case/control status as the covariates, for each of the geographic regions (Europe, South America, and North America) separately. The logistic regression results to assess summary estimates for the five imputations were combined by the PROC MIANALYZE procedure in SAS. We summarized estimates of associations in a random effect logistic regression model, which allowed for unexplained sources of heterogeneity between studies [53].

Stratified analyses were conducted by cancer subsites (oral, oropharynx, hypopharynx, and larynx), years since quitting tobacco use (current, < 20 years, and ≥20 years), tobacco packyears (≤20 tobacco packyears and > 20 tobacco packyears), and duration of using tobacco (1–19 years, 20–39 years, and ≥40 years).

3. Results

The distributions of age, race/ethnicity, and education level were different between the case and control groups (Table 1). The controls had a higher proportion of younger subjects and more educated participants than the cases. Among the individuals who started using tobacco products before 10 year-old, more than half were from South or Central America, where straw cigarettes are used (data no shown).

Without adjusting for tobacco-related covariates, we observed that age at start of using tobacco was positively associated with head and neck cancer risk with a linear trend (P for trend < 0.01, OR of < 10 years vs. ≥ 30 years: 1.49, 95% CI: 1.25, 1.79, in the basic model; Table 2). However, after the adjustment on tobacco exposures, we observed no association and no dose-response relationship (P for trend = 0.21) between age at start of using tobacco and head and neck cancer risk. When we changed the reference group to ≥25 years for all the models we tested, the inference remained the same (Supplementary Table 2).

When stratified by head and neck cancer subsites, younger age at start of using tobacco products was associated with increased risks of oropharyngeal and laryngeal cancer in the model without adjusting for tobacco packyears. In the model adjusting for tobacco packyears, however, age at start of using tobacco products was not associated with oropharyngeal and laryngeal cancer risk (Table 3). When we changed the reference group to starting tobacco habits at ≥ 25 years old, the inference remained the same (Supplementary Table 3). For oral cavity cancer, younger age at start of using tobacco suggested an inverse dose-response with younger ages at starting tobacco being associated with lower ORs, although the CIs were wide (P for trend < 0.01).

In stratified analyses by time since quitting tobacco use (Table 4), younger age at start of using tobacco was associated with head and neck cancer risk (P for trend < 0.01) among current tobacco users. However, after adjustment for tobacco packyears, no associations were detected. Stratified analysis by tobacco packyears was performed to further examine how tobacco packyears modified the trend. No association was observed regardless of tobacco packyears strata (Table 5).

We did not adjust for duration of using tobacco because it was highly correlated with age at start of using tobacco products. The distribution of cases and controls showed that more people with younger age at start of using tobacco products were in the group with ≥40 years duration of using tobacco products (Table 6). Within the group with similar duration of using tobacco products, an association was observed between age at start of using tobacco products and head and neck cancer risk within those with duration of 20–39 years. However, such observations disappeared with adjustment for tobacco packyears. The results remained similar when we changed the reference group from ≥30 years to ≥25 years (Supplementary Tables 4–6).

4. Discussion

In this large data pooling project, we observed an association between younger age at start of using tobacco and the risk of head and neck cancer among people who ever used tobacco products. However, the association was no longer observed after adjusting for tobacco related factors. Stratified analyses by head and neck cancer subsites, years since quitting tobacco use, tobacco packyears, and duration of using tobacco products showed little evidence of the association between earlier age at start of using tobacco and head and neck cancer risk after adjustment by tobacco related factors.

Table 2
Age at start of using tobacco products and the risk of head and neck cancer, in the INHANCE Consortium.

	Cases (%)	Controls (%)	Basic Model		Model without tobacco packyears		Model adjusted for tobacco packyears	
			OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI
≥30	713 (4.3)	1079 (6.3)	1.00	Referent	1.00	Referent	1.00	Referent
25–29	841 (5.1)	1164 (6.8)	1.14	0.99, 1.32	1.28	1.10, 1.49	1.05	0.89, 1.23
20–24	3297 (19.9)	4512 (26.4)	1.31	1.16, 1.48	1.50	1.33, 1.71	1.13	0.98, 1.29
15–19	7432 (44.8)	7386 (43.2)	1.35	1.20, 1.51	1.59	1.41, 1.79	1.08	0.94, 1.23
10–14	3594 (21.7)	2573 (15.1)	1.43	1.26, 1.62	1.60	1.40, 1.82	0.99	0.85, 1.14
< 10	707 (4.3)	380 (2.2)	1.49	1.25, 1.79	1.64	1.35, 1.97	0.97	0.80, 1.19
Missing	562	355						
P_{trend}			< 0.01		< 0.01		0.21	

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Model was adjusted for age, sex, race/ethnicity, education levels, and alcohol drinks per day.

[b] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

[c] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, tobacco packyears, interaction between alcohol drinks per day and tobacco packyears, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

Table 3
Age at start of using tobacco products and the risk of head and neck cancer, by subsite, in the INHANCE Consortium.

	Cases/ Controls	Model without tobacco packyears		Model adjusted for tobacco packyears	
		OR[a]	95% CI	OR[b]	95% CI
Oral cavity					
≥30	250/1043	1.00	Referent	1.00	Referent
25–29	260/1124	1.20	0.95, 1.52	1.00	0.78, 1.29
20–24	881/4402	1.29	1.06, 1.56	0.99	0.80, 1.23
15–19	1968/7049	1.33	1.10, 1.60	0.94	0.76, 1.16
10–14	890/2538	1.20	0.98, 1.47	0.77	0.62, 0.96
< 10	193/377	1.37	1.04, 1.81	0.84	0.62, 1.13
Missing	226/355				
P_{trend}		0.09		< 0.01	
Oropharynx					
≥30	157/1043	1.00	Referent	1.00	Referent
25–29	210/1124	1.31	1.02, 1.70	1.10	0.84, 1.44
20–24	797/4402	1.45	1.17, 1.80	1.13	0.91, 1.42
15–19	1972/7049	1.51	1.23, 1.86	1.08	0.87, 1.35
10–14	889/2538	1.46	1.17, 1.82	0.98	0.77, 1.24
< 10	159/377	1.51	1.12, 2.03	0.92	0.67, 1.27
Missing	105/355				
P_{trend}		< 0.01		0.16	
Hypopharynx					
≥30	54/941	1.00	Referent	1.00	Referent
25–29	65/1065	1.14	0.75, 1.73	0.88	0.57, 1.37
20–24	308/4137	1.63	1.16, 2.30	1.16	0.80, 1.68
15–19	547/6520	1.48	1.06, 2.07	0.92	0.64, 1.33
10–14	277/2313	1.44	1.00, 2.06	0.81	0.55, 1.20
< 10	64/349	1.51	0.95, 2.39	0.81	0.50, 1.33
Missing	25/260				
P_{trend}		0.12		0.04	
Larynx					
≥30	160/855	1.00	Referent	1.00	Referent
25–29	217/969	1.58	1.23, 2.04	1.13	0.87, 1.47
20–24	2218/5954	1.96	1.59, 2.42	1.25	1.00, 1.55
15–19	1142/2052	2.23	1.82, 2.73	1.23	0.99, 1.53
10–14	219/313	2.46	1.98, 3.06	1.20	0.95, 1.51
< 10	2218/5954	2.38	1.79, 3.16	1.16	0.86, 1.57
Missing	173/246				
P_{trend}		< 0.01		0.40	

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

[b] Model was additionally adjusted for tobacco packyears and interaction between alcohol drinks per day and tobacco packyears.

Table 4
Age at start of using tobacco products and the risk of head and neck cancer, by years since quitting tobacco use, in the INHANCE Consortium.

	Cases/ Controls	Model without tobacco packyears		Model adjusted for tobacco packyears	
		OR[a]	95% CI	OR[b]	95% CI
Current tobacco users					
≥30	529/659	1.00	Referent	1.00	Referent
25–29	616/575	1.49	1.23, 1.79	1.11	0.91, 1.36
20–24	2389/2147	1.79	1.53, 2.08	1.15	0.97, 1.37
15–19	5399/3282	1.83	1.58, 2.13	1.01	0.85, 1.19
10–14	2767/1307	1.86	1.58, 2.18	0.90	0.75, 1.08
< 10	543/203	1.88	1.49, 2.37	0.86	0.66, 1.10
Missing	474/250				
P_{trend}		< 0.01		< 0.01	
Quit tobacco use < 20 years					
≥30	132/268	1.00	Referent	1.00	Referent
25–29	158/345	0.93	0.68, 1.28	0.89	0.64, 1.22
20–24	651/1346	1.09	0.84, 1.42	0.99	0.75, 1.30
15–19	1414/2250	1.18	0.91, 1.51	1.04	0.80, 1.36
10–14	633/763	1.18	0.90, 1.55	1.02	0.76, 1.37
< 10	130/108	1.28	0.87, 1.89	1.10	0.73, 1.64
Missing	22/21				
P_{trend}		0.03		0.33	
Quit tobacco use ≥20 years					
≥30	41/124	1.00	Referent	1.00	Referent
25–29	54/230	0.78	0.47, 1.29	0.74	0.44, 1.23
20–24	237/997	0.83	0.55, 1.26	0.77	0.50, 1.19
15–19	600/1837	0.96	0.64, 1.44	0.86	0.57, 1.31
10–14	189/498	0.93	0.60, 1.43	0.78	0.49, 1.23
< 10	32/69	0.87	0.47, 1.62	0.76	0.40, 1.44
Missing	10/12				
P_{trend}		0.48		0.85	

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

[b] Model was additionally adjusted for tobacco packyears and interaction between alcohol drinks per day and tobacco packyears.

Previous studies [9–16] reported the potential association between younger age at start of using tobacco and increased risks of the head and neck cancer, which implied that early tobacco exposure is associated with a higher head and neck cancer risk later in life. In a study of former smokers with lung cancer, Wiencke et al. [54] reported higher DNA damage levels in lungs of patients who started to smoke at an earlier age, indicating that either early-age smoking may impair normal DNA repair function or young smokers may be more susceptible to DNA adduct formation. However, the reported association could simply reflect longer duration, which is a key aspect in the process of tobacco-related carcinogenesis. In our study, to elucidate the role of age at start of using tobacco, we carefully adjusted for other smoking-related factors in the indirect pathways and confounding factors, such as tobacco packyears, interaction between alcohol drinks per day and tobacco packyears, duration of chewing tobacco, duration of using snuff, and years since quitting tobacco use. We estimated the cancer risk in tobacco-users by including people who started using tobacco at ≥30-year-old as the reference group. The association between earlier age at starting tobacco and head and neck cancer risk was no longer present after adjusting for smoking-related factors, implying that the previously observed association of age at start of using tobacco with the risk of head and neck cancer may not be a direct effect but was mediated by smoking duration and frequency.

In this study, adjusting for human papillomavirus (HPV) infection was not feasible since the information was not available across all of the individual studies. HPV infection is primarily linked with oropharyngeal cancer [55]. Moreover, HPV-positive oropharyngeal cancer patients tend to be younger, male, and less likely to smoke [56]. This study restricted to ever-tobacco users with adjustment for age and sex in the analyses. If people with HPV infection tended to start smoking earlier in their life, then ORs of head and neck cancer may be biased away from the null without adjustment for HPV exposure. However, since the association between age at start and the risk of head and neck cancer was null after adjustment for tobacco packyears, HPV infection status is unlikely to influence our conclusion.

It is logically impossible to compare age at start while adjusting for duration of using tobacco products in the case-control study because age at start of using tobacco has less variation among those with similar age at diagnosis and duration, and it is difficult to assess their effects separately. We used tobacco packyears, which combined smoking duration and frequency to adjust for the effect of smoking and to minimize the multicollinearity issue. We conducted stratified analyses to alleviate the effect of years of using tobacco products on head and neck cancer risk. Null associations were observed after adjustment for tobacco related variables.

One possible limitation in our study is recall bias. Being aware of disease status and understanding that smoking is related to their disease,

Table 5
Age at start of using tobacco products and the risk of head and neck cancer, by tobacco packyears, in the INHANCE Consortium.

	Cases/ Controls	Model without tobacco packyears		Model adjusted for tobacco packyears	
		OR[a]	95% CI	OR[b]	95% CI
≤20 tobacco packyears					
≥30	306/705	1.00	Referent	1.00	Referent
25–29	223/609	0.94	0.74, 1.19	0.89	0.70, 1.13
20–24	632/1823	1.01	0.84, 1.23	0.94	0.78, 1.15
15–19	1056/2725	1.01	0.83, 1.21	0.92	0.76, 1.11
10–14	324/615	1.00	0.80, 1.27	0.90	0.71, 1.14
< 10	58/74	1.02	0.67, 1.56	0.94	0.61, 1.44
Missing	70/103				
P_{trend}		0.78		0.51	
> 20 tobacco packyears					
≥30	304/280	1.00	Referent	1.00	Referent
25–29	570/507	1.14	0.90, 1.44	1.06	0.83, 1.34
20–24	2542/2591	1.23	1.00, 1.51	1.10	0.89, 1.35
15–19	6181/4499	1.22	1.00, 1.48	1.03	0.84, 1.26
10–14	3162/1866	1.18	0.96, 1.45	0.94	0.76, 1.17
< 10	610/286	1.20	0.93, 1.55	0.94	0.73, 1.22
Missing	216/82				
P_{trend}		0.49		0.03	

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

[b] Model was additionally adjusted for tobacco packyears and interaction between alcohol drinks per day and tobacco packyears.

Table 6
Age at start of using tobacco products and the risk of head and neck cancer, by duration of using tobacco products, in the INHANCE Consortium.

Smoking Duration	Cases/ Controls	Model without tobacco packyears		Model adjusted for tobacco packyears	
		OR[a]	95% CI	OR[b]	95% CI
1–19 years					
≥30	222/529	1.00	Referent	1.00	Referent
25–29	94/364	0.81	0.58, 1.12	0.76	0.54, 1.06
20–24	268/1092	0.85	0.65, 1.13	0.78	0.59, 1.04
15–19	526/1814	0.97	0.74, 1.26	0.88	0.66, 1.16
10–14	128/374	0.95	0.68, 1.34	0.86	0.61, 1.23
< 10	10/14	1.04	0.44, 2.46	1.00	0.41, 2.42
Missing	0/0				
P_{trend}		0.63		0.96	
20–39 years					
≥30	410/474	1.00	Referent	1.00	Referent
25–29	525/625	1.26	1.02, 1.56	1.06	0.85, 1.32
20–24	1790/2332	1.55	1.28, 1.86	1.21	0.99, 1.47
15–19	3531/3540	1.60	1.32, 1.93	1.14	0.93, 1.40
10–14	1231/1091	1.58	1.27, 1.96	1.03	0.82, 1.30
< 10	101/114	1.45	0.99, 2.12	0.90	0.61, 1.34
Missing	0/0				
P_{trend}		< 0.01		0.63	
≥40 years					
≥30	68/45	1.00	Referent	1.00	Referent
25–29	208/156	0.93	0.57, 1.51	0.86	0.51, 1.45
20–24	1217/1060	0.96	0.62, 1.50	0.79	0.49, 1.27
15–19	3355/2002	0.98	0.63, 1.52	0.72	0.44, 1.15
10–14	2230/1098	0.98	0.63, 1.54	0.67	0.41, 1.08
< 10	594/242	1.02	0.64, 1.64	0.68	0.41, 1.13
Missing	0/0				
P_{trend}		0.59		0.01	

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Model was adjusted for age, sex, race/ethnicity, education levels, alcohol drinks per day, duration of using chewing tobacco, duration of using snuff, and years since quitting tobacco use.

[b] Model was additionally adjusted for tobacco packyears and interaction between alcohol drinks per day and tobacco packyears.

cases might tend to recall an earlier age at start of using these products. This could have resulted in an overestimation of the risk associated with younger age at start. On the other hand, since the general legal age worldwide of buying tobacco was between 16 and 18 years old, individuals who started to smoke earlier than that age might report their age at starting smoking later. Thus, we might have underestimated the risk association of starting using tobacco products before the age of 16 to 18. However, we did not observe heterogeneity of the results between European studies and studies from other regions of the world, and we believe that reporting bias would be minimal. Another limitation of this study is that we were not able to adjust for the intensity of using chewing tobacco and snuff because the units were not comparable across studies (such as grams of tobacco or pinch of tobacco). Therefore, only the duration of chewing tobacco and snuff were adjusted for, and the results might be susceptible to residual confounding. However, the predominant tobacco habit was cigarette smoking, and we were able to fully adjust for frequency and duration of cigarette smoking.

The major strength of this study is the large sample size, which provides adequate statistical power to examine potential associations between age at start of using tobacco and head and neck cancer risk among ever tobacco users. We were also able to compare the associations across different head and neck cancer subsites. Furthermore, the detailed information on tobacco habits enabled us to adjust for potential confounding factors while accounting for the multicollinearity issue of various time-related factors.

In summary, the results from this large pooling project from the INHANCE consortium support an association between the risk of head and neck cancer and the younger age at start of using tobacco products, which is mediated by cumulative tobacco smoking. Even though a null association was observed between age at start of using tobacco products and the risk of head and neck cancer after adjusting for tobacco related factors, younger age at start of using tobacco products was closely related to longer duration or higher frequency of tobacco smoking, which are important risk factors of head and neck cancer.

Authorship contribution statement

C. Chang, S.C., M.H., and Y.A.L contributed to write, review, and/or revision of the manuscript; S.C. contributed to the analysis, and C. Chang performed statistical support; J.B., G.F., K.M., V.W., T.N.T., M.B.C., C.L.V., A.F.O., J.P.Z., D.S., J.M., E.M.S., G.L., H.M., F.L., L.D.M., E.S., K.K., M.M., T.L.V., P.L., H.R., C. Chen, S.M.S., D.M.W., C.B., V.E., W.G., E.N., R.B.H., M.P.P., S.B., G.C., O.S., R.K., M.P.C., M.V., B.S., R.H., S.F., S.B., L.F., A.M.B.M., A.W.D., D.M., S.S., G.Y., J.L., H.B., E.F., P.R., P. Brennan, and Z.Z. conducted research and provided single-study databases; P. Boffetta, Y.A.L., and M.H. are the INHANCE study coordinators; all authors approved the final version of the manuscript.

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Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

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