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Risk factors for head and neck cancer in more and less developed countries: Analysis from the INHANCE Consortium

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Abstract

Objective. We analyzed the pooled case-control data from the International Head and Neck Cancer Epidemiology (INHANCE) consortium to compare cigarette smoking and alcohol consumption risk factors for head and neck cancer between less developed and more developed countries.

Subjects and Methods. The location of each study was categorized as either a less developed or more developed country. We compared the risk of overall head and neck cancer and cancer of specific anatomic subsites associated with cigarette smoking and alcohol consumption. Additionally, age and sex distribution between categories was compared.

Results. The odds ratios for head and neck cancer sites associated with smoking duration differed between less developed and more developed countries. Smoking greater than 20 years conferred a higher risk for oral cavity and laryngeal cancer in more developed countries, whereas the risk was greater for oropharynx and hypopharynx cancer in less developed countries. Alcohol consumed for more than 20 years conferred a higher risk for oropharynx, hypopharynx and larynx cancer in less developed countries. The proportion of cases that were young (<45 years) or female differed by country type for some HNC subsites.

Conclusion. These findings suggest the degree of industrialization and economic development affects the relationship between smoking-and alcohol with head and neck cancer.

Introduction

Countries can be classified as to development status based on Gross Domestic Product (GDP) per capita, which reflects availability and use of natural resources, degree of industrialization and economic development, quality and access to medical care, and social and economic development[1]. On a global basis, per-capita income and economic development differ substantially between less developed and more developed countries (as defined by the United Nations), and this classification has been used as the basis for providing resources to support the economic and social development of developing countries[2]. The World Bank has its own classification system by four gross national income groups — high, upper-middle, lower-middle, and low, where lower middle and low incomes are considered less developed countries[3].

Challenges facing less developed countries include rapid urban development, outdoor and indoor air pollution control, crowding, and their associated effects on lifestyle. For example, 92% of industrial pollution-related deaths occur in low- and middle-income countries and, especially among poorer individuals in all countries[4]. Lifestyle contributions to cancer are a major concern, especially as cancer control efforts are substantially underfunded in developing countries that are experiencing aging populations and increased tobacco use in some areas. Many less developed countries lack cancer registries and other rigorously-collected health data, and determining the causes and prevention of cancer has been challenging due to the lack of resources[5].

Head and neck cancer (HNC) is the seventh most common cancer worldwide[6], and its incidence is increasing each year, with an estimated number of 878,348 in 2020[7]. For countries with established cancer registries, HNC rates (oral cavity, oropharynx, other HNC) increased from 1983 to 2002 in some countries but decreased in others[8]. The 2020 age-standardized rates of oral cavity cancer varied considerably by country. For example, in men the rates were 1.6 per 100,000 in Western Africa and 13.3 per 100,000 in South Central Asia[7]. It is projected that future rates will decrease with associated declines in cigarette consumption[9].

The comparative epidemiology of HNC in less and more developed countries is not well documented[10]. Tobacco and alcohol use are the major risk factors worldwide, and the population attributable risk of HNC due to tobacco and alcohol in studies conducted in Europe and the Americas is 72%[11]. Other risk factors include low fruit and vegetable intake, poor oral hygiene, hormonal factors, and occupational exposures, as well as the role of genetic variation are not fully characterized[12]. Human papillomavirus (HPV) is associated primarily with oropharyngeal HNC.

To determine whether more developed and less developed countries have different risk factor profiles for HNC and HNC subsites, we used pooled data from 32 case-control studies.

The INHANCE Database

The current study included pooled datasets from the INHANCE Consortium (data version 1.5) that contained information on demographic and lifestyle characteristics, including tobacco smoking and alcohol drinking, and tumor information. Descriptions of the studies included in the INHANCE Consortium can be found on the database website (http://www.inhance.utah.edu, accessed April 1, 2021). The dataset for the current analysis included 32 case-control studies, most of which were age and gender frequency-matched; the study populations come from Asia, Europe, North America and South America. The pooling and harmonization methods have been previously described.[13,14] The majority of cases were classified by ICD-9, ICD-10, or ICD-O codes. This included some cases with overlapping areas of oral cavity and pharynx, who were classified as having overlapping HNC. Informed consent and institutional review board approval were obtained at each study center, and all identifying information was removed before data were transferred for pooling. An approval was also obtained from the institutional review board at the Pennsylvania State University for use of this specific de-identified dataset. Within each study population, subject demographic information and risk factors for HNC were collected by patient questionnaire, trained interviewers, or by the subject's physicians. Data on each case's tumor characteristics were obtained from pathology records.

Variable Definitions

Smoking status variables included never, former, and current smokers. We further classified it as Ever (No) and Ever (Yes). Never smokers were classified as Ever (No). Former and current smokers were classified as Ever (Yes). The large sample size enabled us to examine ever smoking history in tumor subsites in the oral cavity and oropharynx **(**Table 6). For all subjects, descriptive statistics are shown in Table 1. For smoking variables, these included age started and stopped smoking, and mean duration in years. For the binary logistic regression models, duration of smoking was classified into two 20-year intervals (≤20 years and >20 years, Table 2). Years of alcohol consumption are shown in Table 1. Alcohol drinking duration in logistic models was also classified into two intervals (≤20 years and >20 years). For the variable age, it was modelled as a continuous covariate in most analyses. For table 4, because age was the variable of interest, we classified it as a binary variable (less than 45 vs. older than 45) for our analysis.

Drinking duration in models was classified into two intervals (<20 years, >20 years). Country type (location of the study) was classified as either more developed or less developed, based on United Nations classification.[15] In the current study, less developed countries included Argentina, Bangladesh, Brazil, China, Cuba, Granada, India, and Sudan. More developed countries included Australia, Canada, Croatia, Greece,

France, Italy, Japan, Spain, Germany, Hungary, Poland, Romania, Russia, Slovakia, the United Kingdom and the United States.

For the main analyses, HNC was grouped into five tumor site categories: oral cavity cancer (OCC), oropharynx cancer (OPC), hypopharynx cancer (HPC), laryngeal cancer (LC), and overlapping HNC. We also conducted a descriptive analysis of smoking prevalence for just oral cavity cancer (OCC) and oropharyngeal cancer (OPC) by their subsites, to explore whether smoking history may further vary by subsite and between more developed and less developed countries.

Statistical Analysis

Descriptive statistics of subject characteristics included means and their standard deviations. Logistic regression models were fit to determine odds ratios (OR) and 95% confidence intervals (95% CI) associated with cigarette smoking years and drinking years, respectively, separately for more developed and less developed countries. In addition to the main effects, a multiplicative interaction term between each of the exposure variables (cigarette smoking years, alcohol consumption years) and country type (more vs less developed) was included in the model. The fits for models with the interaction term with country type were compared to the respective models that did not include the interaction term; the -2 log likelihoods of differences between the two models and corresponding p-values were calculated as tests of the null hypothesis of no multiplicative interaction. Due to overlap between study center and country type, it was not possible to adjust simultaneously for the former. The logistic regression analyses were therefore adjusted for geographic region where each individual study location was assigned to one of four regions (Europe, North America, Central/South America, Asia and other). The risks for HNC and its subsites were adjusted for the age (continuous), sex (categorical), and average cigarettes smoked per day (continuous). The risks associated with cigarette smoking duration were further adjusted for alcohol drinking duration but the findings were similar to the risks that were not adjusted for alcohol drinking. Due to missing data for alcohol duration in some subjects (n=8089 for developed countries, 371 for developing), final models for smoking duration are presented without adjustment for alcohol duration using the full dataset. The analysis for consumption of alcohol was conducted using the same approach, using the dichotomous indicator variable for the categories of alcohol duration to test for interaction with country type.

For thesubsite analysis, cases with missing ICD subsite codes, or with codes that indicated unspecified or overlapping subsites were excluded (n=795 for developing counties and 7658 for developed countries). For this analysis, OCCs were grouped into three subcategories including: 1. Gingivo-buccal/hard palate,

retromolar; 2. Oral (anterior) tongue; 3. Floor of mouth. OPCs were subcategorized into: 1. Posterior or base of tongue, 2. Soft palate/oropharyngeal wall; 3. Tonsil. The large INHANCE database was examined for comparing the percent of ever smokers by subsite between developing and developed countries. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Significance was set at a p-value of < 0.05.

Results

The dataset included 25,256 cases and 36,041 controls. Table 1 shows selected characteristics of the subjects including age and sex. About 79% of cases in both groups were men. Mean and median years of smoking in cases were similar between the two groups, whereas mean years of alcohol use was 32 in less developed countries and 36 in more developed countries. Mean BMI was slightly lower in cases than controls for both developing and developed countries, which is consistent with other findings.

Smoking and alcohol on HNC

The association with more than 20 years of cigarette smoking vs. 20 years or less was increased in both more developed (OR=3.8, 95% CI 3.6-4.0) and in less developed countries (OR=2.7, 95% CI 2.4-2.9; interaction p-value <0.0001; Table 2). For alcohol consumption, no differences were found by country development status (Table 3). In the case-only analysis, cases with older age (≥ 45) were more likely to be associated with developed countries (OR=1.3, 95% CI 1.1-1.4; Table 4). There was evidence of confounding by age. The crude OR was about 1.0 and the age-stratified ORs were both 1.2. The case-only OR for developed countries associated with female sex was 1.2 (95% CI 1.0-1.2; Table 5).

Oral Cavity Cancer (OCC)

The OR for OCC for 20+ years of smoking cigarettes vs ≤20 years was 3.3 (95% CI 3.1-3.6) in more developed counties and 2.0 (95% CI 1.8-2.2) in less developed countries (interaction p-value <0.0001, Table 2). The association of >20 years of alcohol consumption was similar for less and more developed countries (Table 3). In case-only analysis, the OR for developed countries with older age (≥ 45) was 1.2 (95% CI 1.0-1.4; Table 4). The case-only OR for developed countries associated with female sex was 1.4 (95% CI 1.2-1.5; Table 5).

Oropharyngeal Cancer (OPC)

The odds ratios associated with cigarette smoking >20 years vs. ≤20 years were 5.4 (95% CI 4.4-6.7) in less developed countries and 3.3 (95% CI 3.1-3.6) in more developed countries (Table 2). The association of OPC with >20 years of alcohol use was slightly greater in less developed countries (Table 3). In case-only analysis, the odds ratio for more developed countries associated with female sex was 1.3 (95% CI 1.1-1.6; Table 5).

Hypopharyngeal Cancer (HC)

The OR associated with >20 years cigarette smoking vs. ≤ 20 years was 7.7 (95% CI 5.3-11.3) in less developed countries and 5.8 (95% CI 5.0-6.6) in more developed countries (interaction p-value =0.156; Table 2). The OR for longer duration of alcohol consumption was slightly higher in less developed countries (Table 3). In the case-only analysis, the odds ratio for more developed countries associated with >45 years of age was 1.9 (95% CI, 1.2-2.9, Table 4). The OR was also significantly higher for female sex (Table 5).

Laryngeal Cancer (LC)

The positive association between years of smoking cigarettes (>20 vs. < 20 years) was a little stronger in more vs. less developed countries (OR=6.8 vs 4.8, interaction p-value =0.0009; Table 2). The odds ratio for longer alcohol duration was slightly higher in less developed countries (interaction p-value =0.0174; Table 3). The case-only analysis showed that the odds of being a female case were slightly higher in more developed countries (OR=1.3, 95% CI 1.1-1.5; Table 5).

Overlapping HNC

The association of smoking cigarettes > 20 years vs. ≤ 20 years was slightly more in more developed vs. less developed countries (interaction p-value =0.021; Table 2). There was no association with alcohol consumption (Table 3, interaction p-value =0.131). In case-only analysis, age and sex were not associated with country type (Tables 4 and 5, respectively).

Case-series analysis of ever smoking by oral cavity and oropharynx subsite

Table 6 shows cigarette smoking status (ever vs. never) for more and less developed countries separately for OCC and OPC. As expected, the majority of cases for both subsites were ever smokers. The percent ever smoking was lower for cancers of the gingiva and hard palate (59% for less developed countries and 78% for more developed countries) than other subsites. The proportion of ever smoking was also lower for oral tongue (72.9% for less developed countries and 75.2% for more developed countries) compared to other cancers such as base of tongue. For floor of mouth cancer, ever smoking proportion was 89.2% in less developed countries

and 94.1% in more developed counties. Within the oropharynx, the site most commonly associated with HPV[21], 82.1% and 83.0% of patients with base of tongue cancers were ever smokers in less and more developed countries, respectively.

Discussion

We found that the odds ratios associated with >20 years (vs ≤20 years) of cigarette smoking was greater in less developed countries for OPC and HPC, whereas >20 years cigarette smoking conferred a greater risk of OC and LC in more developed countries. In contrast, >20 years of alcohol consumption increased the odds of all HNC subsites except OC and overlapping HNC to a greater extent in less developed countries, compared to that in more developed countries.

When considering these findings, several factors need to be considered. There may be different forms or brands of cigarettes that vary by geography. Bidis (tobacco hand-wrapped in plant leaf) are cigarettes commonly used in South and Southeast Asia. They are packaged under different brand names and are often fruit-flavored. Bidis cause OC, HC and LC [22,23]. Bidis are generally unfiltered and while they contain less tobacco than conventional cigarettes, they emit higher concentrations of tar and nicotine[24]. INHANCE subjects who might have smoked bidi cigarettes include participants from India and Bangladesh. We did not assess the possible confounding effects of smokeless tobacco products. Chewing of betel quid or "paan" is common in parts of Asia. The areca nut is placed in a betel leaf, often in combination with smokeless tobacco products such as khaini, zarda, mawa in south-central Asia. These products have high concentrations of nitrosamines, and the OPC risk associated with betel nut chewing is about 8 fold when combined with other smokeless tobacco, and about 3 fold when used exclusively[25,26,27]. Betel quid use information was not routinely collected in INHANCE studies from Asia. The combined association for tobacco smoking and betel quid user is difficult to assess. as betel quid chewers are mostly a subgroup of cigarette smokers in Taiwan. A recent report found no evidence of a greater association than would be expected under either a multiplicative or additive model[28]. Data from other studies suggest an interactive effect of smoking and chewing [27,29,30]. The OR for HNC with betel quid use in never tobacco smokers is (OR = 13.71, 95% CI 3.62, 51.92) with a greater effect possibly for OC[28].

Likewise, there are smokeless tobacco products used in more developed countries that are not used in less developed countries. INHANCE studies showed that except for the oral cavity, chewing tobacco in the United States was not a risk factor in never smokers and did not modify HNC risk in ever smokers[31]. Snuff use was associated with a 3-fold risk for OCC in never smokers, but only about 2% of the U.S. study population used snuff, whereas use of the more toxic smokeless product betel quid is common in some less developed populations.

The association of longer vs. shorter duration of alcohol consumption was slightly higher for larynx and pharynx cancer in less developed countries than in more developed countries. In many less developed countries, traditionally and locally prepared beverages are being replaced by internationally-marketed products, especially beer. The risk of HNC did not vary much by beverage type in a previous INHANCE study, although the analysis was limited mostly to European and North American study centers[32].

BMI was lower in cases than in controls for both developing and developed countries. This is consistent with the literature. In the prospective American Cancer Society Cancer Prevention Study-II, low BMI was associated with HNC mortality but not incidence[33].

Differences in HPV infection by country type also need to be considered. The attributable fraction of HPV-associated HNC cancer (primarily OPC) has increased in more developed countries compared to less developed countries, particularly in younger men[34 35 36]. This is in contrast to the incidence of OCC in the same populations, in which either no change or a decrease in incidence was observed, as would be expected with decreased tobacco use[35]. Many of the INHANCE studies particularly in the more developed countries completed recruitment in the early 2000's when HPV-positive OPC was less common in more developed countries than it is today. We did not have information on HPV status in most studies and it is unclear from prior research whether there is an excess joint effect of smoking and HPV on OPC risk. Some data indicate an additive effect only, whereas other findings show that the odds ratio associated with heavy smoking is higher in subjects who are HPV seronegative than subjects who are HPV seropositive[37,38].

The mean age of HNC at diagnosis was slightly younger in less developed countries, consistent with another report[39]. It has been suggested that the etiology of HNC may differ somewhat in people ages 45 and younger[17]. Our case-only analyses suggested that while some analyses showed departure from multiplicativity between country type and age or sex, the effect was small.

The current study did not measure other factors that are associated with a country's degree of development or developmental changes. Less developed and more developed countries are defined according to assets, wealth and industrialization. Increasing industrial pollution in less developed countries poses a substantial cancer risk including HNC, with estimates that the incidence of up to 20% of all cancers is due to environmental chemical mixtures[40,41,42]. An increasing but still small proportion of cancer deaths in less developed countries are attributable to lifestyle changes including diet and physical inactivity, which have been associated with the risk of HNC[43,44,45].

The current study compares and contrasts overall and subsite-specific associations between tobacco and alcohol use and HNC risk between categories of less and more developed countries. Several INHANCE publications have employed extensive and novel statistical approaches to modeling cigarette smoking and other

exposures including spline and linear-exponential models, demonstrating further variation in risks by HNC subsite[46,47]. The current study was not designed to recreate those analyses, but to take a first look at comparing the associations as they may vary by country development. We did not control for pipe and cigar smoking, which were previously found not to increase HNC risk in current smokers in the INHANCE data[48].

The grouping of countries by level of development is often used as a measure of health disparity, and differs from socioeconomic status (SES) groupings, which is a measure of social position within a defined geographic area[49]. The SES literature shows that HNC incidence is increased in lower SES relative to higher SES populations in Western countries [50-55]. Using the World Bank classification system for developing and developed countries, low SES was associated with oral cancer risk in both high- and lower-income countries. In a previous INHANCE pooled analysis, low education was associated with an increased risk which that was not completely attenuated after adjusting for smoking and alcohol[56]. The INHANCE consortium pooled data provided the opportunity to examine a different aspect of economic position, namely that which separates countries by wealth, assets and degree of industrialization. It should be noted that Argentina, one of the sites in the current database is classified as a less developed country, although it has an emerging economy that may be more similar to more developed countries.

While INHANCE pooled studies are unique for allowing this type of comparison, there are several limitations. While the INHANCE consortium is large and studies were conducted in many different countries, the data are not a globally representative sample. For example, there is low representation from Africa. The inclusion criteria for age across studies was not uniform, usually defined as >18 or 18-80 years for most studies. This might have biased the age analysis for the case-only comparisons. The case-only analyses are also potentially biased if assumptions of independence between country type and the exposures are violated. This approach is more often used to assess gene-environment interactions, but has potential utility in the current analysis. Misclassification is a concern in case-only analysis but the variables for the current study are well defined. Several (n=13) but not all INHANCE studies had information on oral hygiene risk factors such as tooth loss and gum disease. We were not able to adjust for these variables, although the increased risks with poor hygiene indicators in INHANCE were similar across different geographic regions in a previous report[57].

In addition, potential misclassification of HNC subsites needs to be considered when interpreting findings[58]. The head and neck area is contiguous with boundaries between different sites being somewhat subjective. Some tumors are classified as overlapping but some site misclassification is described in the Surveillance, Epidemiology, and End Results (SEER) database[59].

In summary, our analyses of INHANCE data suggest that longer exposure to cigarette smoking and alcohol consumption confer somewhat higher risks among individuals from less developed countries, and

indicate the importance of sustained tobacco control efforts in both developing and developed countries. However, the success of these programs in low SES areas of some developing countries are considered to be dependent on elimination of poverty and improving social inequality[60].

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Table 1. Selected characteristics of HNC cases and controls from less developed and more developed countries,

		Less developed		More developed	
	Overall	Cases	Controls	Cases	Controls
Characteristic	(n = 61,297)	(n = 5,251)	(n = 4,882)	(n = 20,005)	(n = 31,159)
Mean age (years)	58.4 ± 11.3	57.7 ± 11.1	55.4 ± 13.3	58.9 ± 10.5	58.5 ± 11.4
Sex					
Female	15410 (25.2%)	1120 (21.4%)	1601 (33.0%)	4269 (21.3%)	8420 (27.0%)
Male	45842 (74.8%)	4114 (78.6%)	3257 (67.0%)	15734 (78.7%)	22737(73.0%)
BMI (kg/m^2) *	25.1 ± 4.6	22.3 ± 4.4	24.5 ± 4.8	24.6 ± 4.7	25.8 ± 4.4
Age started smoking (years) *	18.4 ± 5.8	16.6 ± 6.1	17.5 ± 6.4	18.0 ± 5.2	19.26 ± 6.0
Age stopped smoking (years) *	50.9 ± 13.4	55.0 ± 11.1	48.1 ± 13.7	54.1 ± 12.0	47.7 ± 14.1
Duration of smoking (years) *	23.0 ±18.9	30.4 ± 19.2	17.2 ±19.0	31.3 ± 16.7	17.4 ± 17.6
Duration of alcohol use (years) *	33.0 ± 15.6	30.5 ± 16.2	22.4 ± 18.4	35.8 ± 14.0	33.5 ± 15.3

* mean ± standard deviation

INHANCE database

Table 2. Odds ratios for head and neck cancer subtypes by years of smoking, for more developed and less developed countries, INHANCE database

Head & Neck Cancer site	Country	Smoking Years	N (%) Cancer	Odds ratio (95% CI)	Interaction P-value*
All	More developed	≤20	4463 (19.9)	Ref	<0.0001
		>20	15334 (54.1)	3.8 (3.6, 4.0)	
	Less developed	≤20	1379 (32.8)	Ref	
		>20	3760 (65.2)	2.7 (2.4, 2.9)	
Oral cavity	More developed	≤20	1375 (7.1)	Ref	<0.0001
		>20	3614 (21.7)	3.3 (3.1, 3.6)	
	Less developed	≤20	915 (24.5)	Ref	
		>20	1226 (37.9)	2.0 (1.8, 2.2)	
Oropharynx	More developed	≤20	1422 (7.4)	Ref	<0.0001
		>20	3942 (23.2)	3.3 (3.1, 3.6)	
	Less developed	≤20	125 (4.2)	Ref	
		>20	718 (26.3)	5.4 (4.4, 6.7)	
Hypopharynx	More developed	≤20	282 (1.6)	Ref	0.1561
		>20	1618 (11.1)	5.8 (5.0, 6.6)	
	Less developed	≤20	30 (1.1)	Ref	
		>20	304 (13.2)	7.7 (5.3, 11.3)	
Larynx	More developed	≤20	662 (3.6)	Ref	0.0009
		>20	4737 (26.7)	6.8 (6.2, 7.4)	
	Less developed	≤20	160 (5.4)	Ref	
		>20	1124 (35.9)	4.8 (4.0, 5.8)	
Overlapping H&N	More developed	≤20	33 (0.2)	Ref	0.0210
		>20	142 (1.1)	4.6 (3.1, 6.8)	
	Less developed	≤20	37 (1.3)	Ref	
		>20	119 (5.6)	2.4 (1.6, 3.7)	

Adjusted for sex, age, cigarettes per day, and geographic grouping. *Interaction between smoking years and country type.

Table 3. Odds ratios for head and neck cancer subtypes by years of drinking, for more developed and less developed countries, INHANCE database

Head & Neck Cancer site	Country	Drinking Years	N (%) Cancer	Odds ratio (95% CI)	Interaction P-value*
All	More developed	≤20	3643(27.5)	Ref	0.9030
		>20	12965 (43.5)	1.7 (1.6, 1.8)	
	Less developed	≤20	1658 (38.3)	Ref	
		>20	3377 (62.1)	1.7 (1.5, 1.9)	
Oral cavity	More developed	≤20	1144 (10.6)	Ref	0.4008
		>20	3127 (15.6)	1.6 (1.5, 1.7)	
	Less developed	≤20	983 (26.9)	Ref	
		>20	1112 (35.1)	1.5 (1.5, 1.7)	
Oropharynx	More developed	≤20	948 (9.0)	Ref	0.0115
		>20	3762 (18.2)	2.0 (1.8, 2.2)	
	Less developed	≤20	197 (6.9)	Ref	
		>20	631 (23.5)	2.6 (2.1, 3.1)	
Hypopharynx	More developed	≤20	195 (2.0)	Ref	0.0240
		>20	1258 (6.9)	2.5 (2.2, 3.0)	
	Less developed	≤20	51 (1.9)	Ref	
		>20	274 (11.7)	3.8 (2.7, 5.2)	
Larynx	More developed	≤20	815 (7.8)	Ref	0.0174
		>20	3708 (18.0)	1.7 (1.5, 1.8)	
	Less developed	≤20	279 (9.5)	Ref	
		>20	976 (32.2)	2.1 (1.8, 2.4)	
Overlapping H&N	More developed	≤20	31 (0.3)	Ref	0.1313
		>20	129 (0.8)	1.4 (0.9, 2.1)	
	Less developed	≤20	28 (1.0)	Ref	
		>20	128 (5.9)	2.1 (1.4, 3.4)	

Adjusted for sex, age, cigarettes per day, and geographic grouping. *Interaction between drinking years and country type.

Table 4. Case-only odds ratios between age and more developed country status, INHANCE database

Cancer site	Age	Country Type		OR	p-value
		More developed	Less developed		
All	<45 years	1614 (8.1%)	546 (10.4%)	1.3 (1.1, 1.4)	<0.0001
	≥45 years	18391 (91.9%)	4705 (89.6%)		
Oral cavity	<45 years	501 (10.0%)	287 (13.2%)	1.2 (1.0, 1.4)	0.0216
	≥45 years	4524 (90.0%)	1887 (86.8%)		
Oropharynx	<45 years	446 (8.3%)	88 (10.2%)	1.3 (1.0, 1.7)	0.0366
	≥45 years	4951 (91.7%)	775 (89.8%)		
Hypopharynx	<45 years	97 (5.0%)	30 (8.6%)	1.9 (1.2, 2.9)	0.0042
	≥45 years	1839 (95.0%)	319 (91.4%)		
Larynx	<45 years	280 (5.1%)	71 (5.4%)	1.1 (0.8, 1.4)	0.7064
	≥45 years	5196 (94.9%)	1250 (94.6%)		
Overlapping H&N	<45 years	16 (9.1%)	21 (13.5%)	1.6 (0.8, 3.2)	0.1945
	≥45 years	159 (90.9%)	135 (86.5%)		

Adjusted for sex and cpd. OR reflects departure from multiplicativity between country type and age.

Table 5. Case-only odds ratios between sex and more developed country status, INHANCE database

Cancer site	Gender	Country Type		OR	p-value
		More developed	Less developed		
All	Male	15734 (78.7%)	4114 (78.6%)	1.2 (1.0, 1.2)	0.0006
	Female	4269 (21.3%)	1120 (21.4%)		
Oral cavity	Male	3477 (69.2%)	1484 (68.5%)	1.4 (1.2, 1.5)	<0.0001
	Female	1546 (30.8%)	681 (31.5%)		
Oropharynx	Male	4268 (79.1%)	721 (83.7%)	1.3 (1.1, 1.6)	0.0033
	Female	1129 (20.9%)	140 (16.3%)		
Hypopharynx	Male	1706 (88.2%)	318 (91.1%)	1.5 (1.0, 2.3)	0.0412
	Female	229 (11.8%)	31 (8.9%)		

Adjusted for age and cigarettes per day. OR reflects departure from multiplicativity between country type and gender.

Larynx	Male	4753 (86.8%)	1172 (89.0%)	1.3 (1.1, 1.5)	0.0152
	Female	724 (13.2%)	144 (11.0%)		
Overlapping H&N	Male	132 (75.4%)	124 (79.5%)	1.3 (0.7, 2.4)	0.3935
	Female	43 (24.6%)	32 (20.5%)		

Table 6. Ever smoking status by tumor subsite in oral cavity and oropharynx in less developed and more developed countries, INHANCE database

	Less developed		More developed	
HNC Subsite	No	Yes	No	Yes
Oral cavity				
Gingivo-buccal/hard palate	400 (41.0%)	575 (59.0%)	352 (22.3%)	1226 (77.7%)
Oral tongue	191 (27.1%)	513 (72.9%)	571 (24.8%)	1734 (75.2%)
Floor of mouth	54 (10.8%)	446 (89.2%)	78 (5.9%)	1246 (94.1%)
Oropharynx				
Base of tongue	64 (17.9%)	293 (82.1%)	188 (17.0%)	917 (83.0%)
Soft palate/ oropharyngeal wall	15 (6.6%)	212 (93.4%)	90 (8.8%)	938 (91.2%)
Tonsil	34 (11.6%)	258 (88.4%)	230 (15.0%)	1311 (85.0%)

Excludes sites not otherwise specified.