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ORIGINAL ARTICLE

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

Neerav Goyal[1] | Max Hennessy[1] | Erik Lehman[1] | Wenxue Lin[1] | Antonio Agudo[2] | Wolfgang Ahrens[3] | Stefania Boccia[4,5] | Paul Brennan[6] | Hermann Brenner[7,8,9] | Gabriella Cadoni[10,11] | Cristina Canova[12] | Chu Chen[13] | David Conway[14] | Maria Paula Curado[15] | Luigino Dal Maso[16] | Alexander W. Daudt[17] | Valeria Edefonti[18] | Eleonora Fabianova[19] | Leticia Fernandez[20] | Silvia Franceschi[6] | Werner Garavello[21] | Maura Gillison[22] | Richard B. Hayes[23] | Claire Healy[24] | Rolando Herrero[6] | Ivana Holcatova[25] | Jossy L. Kanda[26] | Karl Kelsey[27] | Bo T. Hansen[28] | Rosalina Koifman[29] | Pagona Lagiou[30] | Carlo La Vecchia[18] | Fabio Levi[31] | Guojun Li[32] | Jolanta Lissowska[33] | Rossana Mendoza López[34] | Danièle Luce[35] | Gary Macfarlane[36] | Dana Mates[37] | Keitaro Matsuo[38] | Michael McClean[39] | Ana Menezes[40] | Gwenn Menvielle[41] | Hal Morgenstern[42] | Kirsten Moysich[43] | Eva Negri[44] | Andrew F. Olshan[45] | Tamas Pandics[46] | Jerry Polesel[16] | Mark Purdue[47] | Loredana Radoi[48] | Heribert Ramroth[49] | Lorenzo Richiardi[50] | Stimson Schantz[47] | Stephen M. Schwartz[13] | Diego Serraino[16] | Oxana Shangina[51] | Elaine Smith[52] | Erich M. Sturgis[53] | Beata Świątkowska[54] | Peter Thomson[55] | Thomas L. Vaughan[13] | Marta Vilensky[56] | Deborah M. Winn[57] | Victor Wunsch-Filho[58] | Guo-Pei Yu[59] | Jose P. Zevallos[60] | Zuo-Feng Zhang[61] | Tongzhang Zheng[62] | Ariana Znaor[6] | Paolo Boffetta[63,64] | Mia Hashibe[65] | Yuan-Chin A. Lee[65] | Joshua E. Muscat[1]

[1]College of Medicine, The Pennsylvania State University, Hershey, Pennsylvania, USA

[2]Institut Catala Oncologia, Barcelona, Spain

[3]Faculty of Mathematics and Computer Science, Institute of Statistics, Leibniz Institute for Prevention Research and Epidemiology, BIPS, and University of Bremen, Bremen, Germany

[4]Sezione di Igiene, Dipartimento Universitario di Scienze della Vita e Sanità Pubblica, Università Cattolica del Sacro Cuore, Roma, Italia

[5]Department of Woman and Child Health and Public Health - Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia

[6]International Agency for Research on Cancer, World Health Organization, Lyon, France

[7]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

[8]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

[9]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

[10]Dipartimento Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

[11]Dipartimento Patologia Testa Collo e Organi di Senso, Facoltà Medicina e, Chirurgia Università Cattolica Sacro Cuore, Roma, Italy

[12]University of Padua, Padova, Italy

[13]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[14]Dental School, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

[15]Epidemiology- CIPE/ACCAMARGO, Sao Paulo, Brazil

[16]Cancer Epidemiology Unit, Centro di Riferimento Oncologico (CRO) Aviano, IRCCS, Aviano, PN, Italy

[17]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

[18]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[19]Regional Authority of Public Health in Banska Bystrica, Banska Bystrica, Slovakia

[20]Institute of Oncology and Radiobiology, Havana, Cuba

[21]Department of Otorhinolaryngology, School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

[22]Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[23]Division of Epidemiology, New York University School of Medicine, New York, New York, USA

[24]Trinity College School of Dental Science, Dublin, Ireland

[25]Institute of Hygiene and Epidemiology, Prague, Czech Republic

[26]Faculdade de Medicina do ABC, Hospital de Ensino, São Bernardo do Campo, SP, Brazil

[27]Brown University, Providence, Rhode Island, USA

[28]Cancer Registry of Norway, Oslo, Norway

[29]Escola Nacional de Saude Publica, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil

[30]School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[31]Institut Universitaire de Medecine Sociale et Preventive (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

[32]UT-M.D. Anderson Cancer Center, Houston, Texas, USA

[33]Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[34]Faculdade de Medicina da, Universidade de São Paulo, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

[35]Univ Rennes, INSERM, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, Pointe-à-Pitre, France

[36]University of Aberdeen Dental School, Aberdeen, UK

[37]National Institute of Public Health, Bucharest, Romania

[38]Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[39]Boston University School of Public Health, Boston, Massachusetts, USA

[40]Universidade Federal de Pelotas, Pelotas, Brazil

[41]INSERM, Sorbonne Université, Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, Paris, France

[42]Departments of Epidemiology and Environmental Health Sciences, School of Public Health and Department of Urology, Medical School, University of Michigan, Ann Arbor, Michigan, USA

[43]Roswell Park Cancer Institute, Buffalo, New York, USA

[44]Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

[45]University of North Carolina School of Public Health, Chapel Hill, North Carolina, USA

[46]National Public Health Center, Budapest, Hungary

[47]New York Eye and Ear Infirmary, New York, New York, USA

[48]INSERM UMR 1018, Centre for Research in Epidemiology and Population Health (CESP), Cancer Epidemiology, Genes and Environment Team, Villejuif, France

[49]Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg, Germany

[50]University of Turin, Turin, Italy

[51]Cancer Research Centre, Moscow, Russia

[52]College of Public Health, University of Iowa, Iowa City, Iowa, USA

[53]Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, Texas, USA

[54]Nofer Institute of Occupational Medicine, Lodz, Poland

[55]University of Hong Kong, Hong Kong, China

[56]Institute of Oncology Angel H. Roffo, University of Buenos Aires, Buenos Aires, Argentina

[57]National Cancer Institute, Bethesda, Maryland, USA

[58]Universidade de Sao Paulo, Sao Paulo, Brazil

[59]Department of Otolaryngology, School of Medicine, New York Medical College, Valhalla, New York, USA

[60]Division of Head and Neck Surgical Oncology, Department of Otolaryngology/Head and Neck Surgery, Washington University School of Medicine, St. Louis, Missouri, USA

[61]UCLA School of Public Health, Los Angeles, California, USA

[62]Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island, USA

[63]Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York, USA

[64]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[65]Division of Public Health, Department of Family & Preventive Medicine and Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah, USA

Correspondence
Neerav Goyal, Department of Otolaryngology-Head and Neck Surgery, College of Medicine, The Pennsylvania State University, 500 University Drive, H091, Hershey, PA 17033-0850, USA.
Email: ngoyal1@pennstatehealth.psu.edu

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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.

KEYWORDS
alcohol use, head and neck cancer, INHANCE, smoking, socioeconomic status

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1 | 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 (Fan et al., 2018). 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 (Syed et al., 2012). 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 (Reynolds, 2018).

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 (Landrigan et al., 2018). 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 (Hanna & Kangolle, 2010).

Head and neck cancer (HNC) is the seventh most common cancer worldwide (Rettig & D'Souza, 2015), and its incidence is increasing each year, with an estimated number of 878,348 in 2020 (Bray et al., 2018). For countries with established cancer registries, HNC rates (oral cavity, oropharynx, and other HNC) increased from 1983 to 2002 in some countries but decreased in others (Simard et al., 2014). 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 (Bray et al., 2018). It is projected that future rates will decrease with associated declines in cigarette consumption (Lee & Hashibe, 2014).

The comparative epidemiology of HNC in less and more developed countries is not well documented (Gupta et al., 2016). 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% (Hashibe et al., 2009). 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 (Bravi et al., 2021). 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.

2 | Methods

2.1 | 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;

TABLE 1 Selected characteristics of HNC cases and controls from less developed and more developed countries, INHANCE database

Characteristic	Overall (n = 61,297)	Less developed		More developed	
		Cases (n = 5251)	Controls (n = 4882)	Cases (n = 20,005)	Controls (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	15,410 (25.2%)	1120 (21.4%)	1601 (33.0%)	4269 (21.3%)	8420 (27.0%)
Male	45,842 (74.8%)	4114 (78.6%)	3257 (67.0%)	15,734 (78.7%)	22,737 (73.0%)
BMI (kg/m^2)[a]	25.1 ± 4.6	22.3 ± 4.4	24.5 ± 4.8	24.6 ± 4.7	25.8 ± 4.4
Age started smoking (years)[a]	18.4 ± 5.8	16.6 ± 6.1	17.5 ± 6.4	18.0 ± 5.2	19.26 ± 6.0
Age stopped smoking (years)[a]	50.9 ± 13.4	55.0 ± 11.1	48.1 ± 13.7	54.1 ± 12.0	47.7 ± 14.1
Duration of smoking (years)[a]	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)[a]	33.0 ± 15.6	30.5 ± 16.2	22.4 ± 18.4	35.8 ± 14.0	33.5 ± 15.3

[a]Mean ± standard deviation.

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[a]
All	More developed	≤20	4463 (19.9)	Ref	<0.0001
		>20	15,334 (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)	

Note: Adjusted for sex, age, cigarettes per day, and geographic grouping.
[a]Interaction between smoking years and country type.

the study populations come from Asia, Europe, North America and South America. The pooling and harmonization methods have been previously described (Conway et al., 2009; Hashibe et al., 2007). 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.

2.2 | 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 (DESA, 2017) 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.

2.3 | 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 the subsite 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 the following: (1) Gingivo-buccal/hard palate, retromolar; (2) Oral (anterior) tongue; and (3) Floor of mouth. OPCs were subcategorized into the following: (1) Posterior or base of tongue; (2) Soft palate/oropharyngeal wall; and (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.

3 | 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.

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[a]
All	More developed	≤20	3643 (27.5)	Ref	0.9030
		>20	12,965 (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)	

Note: Adjusted for sex, age, cigarettes per day, and geographic grouping.

[a]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: More developed	Country type: Less developed	OR	*p*-value
All	<45 years	1614 (8.1%)	546 (10.4%)	1.3 (1.1, 1.4)	<0.0001
	≥45 years	18,391 (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%)		

Note: 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: More developed	Country type: Less developed	OR	*p*-value
All	Male	15,734 (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%)		
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%)		

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

3.1 | 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).

3.2 | 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).

3.3 | 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).

3.4 | 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).

3.5 | 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).

3.6 | Overlapping HNC

The association of smoking cigarettes >20 years vs. ≤20 years was slightly more in more developed vs. less developed countries

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%)

Note: Excludes sites not otherwise specified.

(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).

3.7 | 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 with 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 (Parkin & Bray, 2006), 82.1% and 83.0% of patients with base of tongue cancers were ever smokers in less and more developed countries, respectively.

4 | 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 with 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 (Sapkota et al., 2007; Schottenfeld & Fraumeni, 2008). Bidis are generally unfiltered and while they contain less tobacco than conventional cigarettes, they emit higher concentrations of tar and nicotine (Watson et al., 2003). 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 eightfold when combined with other smokeless tobacco, and about threefold when used exclusively (Guha et al., 2014; Stepanov et al., 2005; Wen et al., 2005). 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 (Lee et al., 2019). Data from other studies suggest an interactive effect of smoking and chewing (Liu et al., 2015; Thomas et al., 2007; Wen et al., 2005). 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 (Lee et al., 2019).

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 (Wyss et al., 2016). Snuff use was associated with a threefold 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 (Purdue et al., 2009).

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 (Gaudet et al., 2012).

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 (Chaturvedi et al., 2013; Enomoto et al., 2016; Martel et al., 2017). 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 (Chaturvedi et al., 2013). 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 (Anantharaman et al., 2016; Smith et al., 2012).

The mean age of HNC at diagnosis was slightly younger in less developed countries, consistent with another report (Joshi et al., 2014). It has been suggested that the etiology of HNC may differ somewhat in people ages 45 and younger (Toporcov et al., 2015). 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 (https://www.who.int/heli/risks/ehindevcoun/en/index1.html; Goodson et al., 2015; Wong et al., 2014). 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 (Freedman et al., 2008; Platek et al., 2017; The Lancet Oncology, 2011).

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 (Di Credico et al., 2019; Lubin et al., 2007). 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 (Wyss et al., 2013).

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 (Anderson et al., 2015). The SES literature shows that HNC incidence is increased in lower SES relative to higher SES populations in Western countries (Al-Dakkak, 2010; Andersen et al., 2008; Edwards & Jones, 1999; Hwang et al., 2013; Purkayastha et al., 2016; Tataru et al., 2017). 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 (Conway et al., 2015). 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 (Hashim et al., 2016).

In addition, potential misclassification of HNC subsites needs to be considered when interpreting findings (Sankaranarayanan et al.,

1998). 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 (Fakhry et al., 2018).

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 (Kurkure & Yeole, 2006).

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Neerav Goyal: Data curation; Formal analysis; Writing – original draft; Writing – review & editing. **Max Hennessy:** Data curation; Formal analysis; Writing – original draft; Writing – review & editing. **Erik Lehman:** Data curation; Formal analysis; Writing – original draft; Writing – review & editing. **Wenxue Lin:** Data curation; Writing – review & editing. **Antonio Agudo:** Data curation; Writing – review & editing. **Wolfgang Ahrens:** Data curation; Writing – review & editing. **Stefania Boccia:** Data curation; Writing – review & editing. **Paul Brennan:** Data curation; Writing – review & editing. **Hermann Brenner:** Data curation; Writing – review & editing. **Gabriella Cadoni:** Data curation; Writing – review & editing. **Cristina Canova:** Data curation; Writing – review & editing. **Chu Chen:** Data curation; Writing – review & editing. **David Conway:** Data curation; Writing – review & editing. **Maria Paula Curado:** Data curation; Writing – review & editing. **Luigino Dal Maso:** Data curation; Writing – review & editing. **Alexander W. Daudt:** Data curation; Writing – review & editing. **Valeria Edefonti:** Data curation; Writing – review & editing. **Eleonora Fabianova:** Data curation; Writing – review & editing. **Leticia Fernandez:** Data curation; Writing – review & editing. **Silvia Franceschi:** Writing – review & editing. **Werner Garavello:** Data curation; Writing – review & editing. **Maura Gillison:** Data curation; Writing – review & editing. **Richard B. Hayes:** Data curation; Writing – review & editing. **Claire Healy:** Data curation; Writing – review & editing. **Rolando Herrero:** Data curation; Writing – review & editing. **Ivana Holcatova:** Data curation; Writing – review & editing. **Jossy L. Kanda:** Data curation; Writing – review & editing. **Karl Kelsey:** Data curation; Writing – review & editing. **Bo T. Hansen:** Data curation; Writing – review & editing. **Rosalina Koifman:** Data curation; Writing – review & editing. **Pagona Lagiou:** Data curation; Writing – review & editing. **Carlo La Vecchia:** Data curation; Writing – review & editing. **Fabio Levi:** Data curation; Writing – review & editing. **Jolanta Lissowska:** Data curation; Writing – review & editing. **Rossana Mendonza López:** Data curation; Writing – review & editing. **Daniele Luce:** Data curation; Writing – review & editing. **Gary Macfarlane:** Data curation; Writing – review & editing. **Dana Mates:** Data curation; Writing – review & editing. **Keitaro Matsuo:** Data curation; Writing – review & editing. **Michael McClean:** Data curation; Writing – review & editing. **Ana Menezes:** Data curation; Writing – review & editing. **Gwenn Menvielle:** Data curation; Writing – review & editing. **Hal Morgenstern:** Data curation; Writing – review & editing. **Kirsten Moysich:** Data curation; Writing – review & editing. **Eva Negri:** Data curation; Writing – review & editing. **Andrew F. Olshan:** Data curation; Writing – review & editing. **Tamas Pandics:** Data curation; Writing – review & editing. **Jerry Polesel:** Data curation; Writing – review & editing. **Mark Purdue:** Data curation; Writing – review & editing. **Loredana Radoi:** Data curation; Writing – review & editing. **Heribert Ramroth:** Conceptualization; Writing – review & editing. **Franco Merletti:** Data curation; Writing – review & editing. **Stimson Schantz:** Data curation; Writing – review & editing. **Stephen Schwartz:** Data curation; Writing – review & editing. **Diego Serraino:** Data curation; Writing – review & editing. **Oxana Shangina:** Data curation; Writing – review & editing. **Elaine Smith:** Data curation; Writing – review & editing. **Beata Świątkowska:** Data curation; Writing – review & editing. **Peter J. Thomson:** Data curation; Writing – review & editing. **Thomas I. Vaughan:** Data curation; Writing – review & editing. **Marta Vilensky:** Data curation; Writing – review & editing. **Deborah Winn:** Data curation; Writing – review & editing. **Victor Wunsch-Filho:** Data curation; Writing – review & editing. **Guo-Pei Yu:** Data curation; Writing – review & editing. **Josè Zevallos:** Data curation; Writing – review & editing. **Zuo-Feng Zhang:** Data curation; Writing – review & editing. **Tongzhang Zheng:** Data curation; Writing – review & editing. **Ariana Znaor:** Data curation; Writing – review & editing. **Paolo Boffetta:** Data curation; Writing – review & editing. **Mia Hashibe:** Data curation; Writing – review & editing. **Yuan-Chin A. Lee:** Data curation; Writing – review & editing. **Joshua E. Muscat:** Data curation; Writing – original draft; Writing – review & editing.

PATIENT CONSENT STATEMENT

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.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.14196.

DATA AVAILABILITY STATEMENT

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).

ORCID

Neerav Goyal https://orcid.org/0000-0001-7783-1097
Valeria Edefonti https://orcid.org/0000-0002-1995-1477
Mia Hashibe https://orcid.org/0000-0002-6903-2049

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