

Global burden of oral cavity and pharyngeal cancers

Chairs: Newell Johnson, *Emeritus Professor, Griffith University (Australia)*
and Anil Chaturvedi, *Division of Cancer Epidemiology and Genetics, National Cancer Institute (USA)*

Moderator: Ross Kerr, *New York University College of Dentistry (USA)*

Regional Delegates North America:

Alessandro Villa, *Harvard School of Dental Medicine (USA)*
Ajit Auluck, *University of British Columbia*

Regional Delegates Europe:

Pedro Diz Dios, *Santiago de Compostela University (Spain)*
Marco Meleti, *University of Parma (Italy)*

Regional Delegates Asia:

Honghua, *Peking University School of Stomatology (China)*
WM Tilikaratne, *University of Peradeniya (Sri Lanka)*

Regional Delegates Far East/ Australasia:

Cheung Sok Ching, *Cancer Research Initiatives Foundation (Malaysia)*
Camile Farah, *University of Western Australia (Australia)*

Regional Delegates Africa/Middle East:

Jos Hille, *National Health Laboratory Service (South Africa)*
Omar Kujan, *Al-Farabi College (Middle East)*

Regional Delegates South America:

Luiz Kowalski, *AC Camargo Cancer Center (Brazil)*
Hector Lanfranchi, *University of Buenos Aires (Argentina)*
Pablo Vargas, *University of Campinas (Brazil)*

Introduction

Cancers oral cavity and the pharynx include tumors arising from the mucosal surfaces of the mouth, salivary glands, oropharynx, nasopharynx, and hypopharynx (1). These cancers collectively contribute to substantial morbidity and mortality worldwide, with an estimated 526,481 annual incident cases (2). The traditional risk factors for oral cavity and pharyngeal cancers include tobacco smoking and chewing, betel-quid chewing with or without tobacco, and alcohol use (1;3;4). Other emerging risk factors include a diet low in fruit and vegetable consumption and poor oral hygiene (1;4). Other risk factors show anatomic site heterogeneity in etiologic associations; examples include the association of ultraviolet radiation with lip cancer, of Epstein-Barr Virus with nasopharyngeal carcinoma, and human papillomavirus (HPV) with oral cavity cancers and oropharyngeal cancers (1;4). Notably, the etiologic role of HPV shows anatomic site heterogeneity, with stronger associations for oropharyngeal cancers and weaker associations for oral cavity cancers (5).

Consistent with the wide geographic and temporal heterogeneity in the worldwide prevalence of the key risk factors for oral cavity and pharyngeal cancer, the incidence of these cancers shows wide variability by geographic region and calendar era (1;4;6). Wide geographic variability is also observed in the incidence of the constituent anatomic subsites. Historically, the incidence of oral cavity and pharyngeal cancers has been highest in South and South-east Asia, Western and Central Europe, and South America (6).

Despite the amenability of oral cavity and pharyngeal cancers, particularly oral cavity cancers, for early detection through visual inspection, these cancers are often diagnosed at advanced stages, resulting in poor survival outcomes. The inaugural Global Oral Cancer Forum, sponsored by the Henry-Schein Foundation, recently convened scientists from around the world working on oral cancer in New York City (March 4-5, 2016) to discuss the state-of-the-science on the global burden of oral cavity cancers and tools for early detection and prevention. The current report arises from the epidemiology group of the Forum, and describes the

historical, current, and future burden of oral cavity cancers worldwide as well as a summary of the discussions at the Forum.

Methods

Geographic regions and data sources: We included data from six broad regions worldwide—North America (USA and Canada), South America, Asia, Oceania and South-East Asia, Europe, the Middle east, and Africa. We primarily utilized data from the Cancer Incidence in Five Continents (Volumes and calendar periods varying by registry), Cancer Mortality Databases, as well as the GLOBOCAN 2012, all of which are maintained by the International Agency for Research on Cancer, World Health Organization (2). Data for the United States were based on data from 13 cancer registries (years 1992-2012) covered by the US National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program (7). These registries collectively cover ~18% of the US population. Data for Canada were derived from the Canadian regional Cancer registries (1992-2012), which cover ~97% of the Canadian population. When population-based cancer registry data were unavailable, data were derived from hospital-based registries or were imputed from neighboring regions with available data (2).

Anatomic sites: The Forum specifically focused on cancers of the oral cavity, including those arising from the lip (International Classification of Diseases version-10 code C00), tongue (C01 and C02), gum (C03), floor of mouth (C04), palate (C05), and other/unspecified parts of the mouth. Where available, data were also included for the oropharynx (base of tongue [C01], soft palate {C05.1 and 5.2}, tonsil [C09], and other parts of the oropharynx [C10]), salivary gland (C07 and C08), and other parts of the pharynx (C12 and C13). Cancers of the nasopharynx were not included in the current review. Of note, for a majority of the global regions, cancers of the tongue included the base of tongue.

Statistical analyses: Key metrics of the burden included age-standardized (world standard population) incidence rates and mortality rates per 100,000 population as well as the annual number of incident/new cases. Trends in incidence and mortality rates over time were

evaluated using log-linear regression models. In most regions, analyses were conducted both overall and stratified by sex.

Results

Globally, ~300,000 lip and oral cavity cancers occur annually. The burden of lip and oral cavity cancers is considerably higher in less economically developed than more economically developed countries, with the highest incidence observed in Melanesia, countries in South-Central Asia, Australia/New Zealand, and Western Europe. Worldwide, lip and oral cavity cancer incidence is significantly higher in men than women.

Burden of lip and oral cavity cancers across different regions worldwide

North America

Analyses of North American data included USA and Canada. These two countries have high-quality population-based cancer registries. Key prevalent risk factors in the US and Canada include cigarette smoking, the use of smokeless tobacco, alcohol use, and HPV infection.

In both countries, among men, the incidence of lip and oral cavity cancers has significantly declined during 1992-2012. This decline is most noticeable for most constituent anatomic sites—lip, other mouth, and other pharyngeal cancers. By contrast, the incidence of oral tongue cancer has remained stable over time, while the incidence of oropharyngeal cancer has significantly increased during 1992-2012 in US and Canadian men. Likewise, in women, the incidence of oral tongue cancer has significantly increased during 1992-2012 in the US, and the incidence of tongue, salivary gland, and oropharyngeal cancers has significantly increased during 1992-2012 in Canadian women. The most common anatomic site of cancer in the oral cavity is the anterior tongue.

The declining incidence of most lip and oral cavity cancers in the US and Canada is consistent with population-level declines in the prevalence of cigarette smoking over the past four

decades. These observations underscore the importance of primary prevention through behavioral modification. Recent studies have attributed the rising oropharyngeal cancer incidence to HPV infection, perhaps as a result of changes in sexual behaviors through the 1950s and 1960s. The reasons for rising incidence of oral tongue cancers in the US and Canada are currently unclear.

Northern and Eastern Europe

Analyses in Northern and Eastern Europe included data from population-based cancer registries in 22 countries (North: Denmark, Estonia, Finland, Ireland, Iceland, Latvia, Lithuania, Norway, UK, and Sweden and east: Russia, Belarus, Ukraine, Romania, Poland, Czech Republic, Slovakia, Moldova, Hungary, Bulgaria, Kazakhstan, and Siberia). Prevalent risk factors in all of these regions include smoking, smokeless tobacco use, alcohol, and HPV infection.

In most countries, the incidence of lip, oral cavity and pharynx cancers (combined) has declined in both men and women. Notable exceptions for men include rising incidence in the Czech Republic, Denmark, Lithuania, and the UK during 1995-2010. Likewise, incidence rates for women have significantly increased during 1995-2010 in Denmark and the Czech Republic. There is considerable geographic variation in the incidence of lip, oral cavity, and pharyngeal cancers in Northern and Eastern Europe—the highest incidence is observed in Denmark, Lithuania, Slovakia, and Hungary. The most common anatomic site of cancer is the anterior tongue and the pharynx.

Temporal trends in the incidence of lip, oral cavity, and pharynx cancers in Northern and Eastern Europe appear to parallel trends in the tobacco epidemic. For example, the high cancer burden tracks closely with the shift in the smoking epidemic to Eastern Europe as well as to women. Changing incidence of oropharyngeal cancers could also be attributed to HPV infection.

Western and Southern Europe

Analyses in Western and Southern Europe included variable-quality population-based cancer registry data from 20 countries (Austria, Belgium, France, Germany, Luxembourg, Netherlands,

Switzerland, Albania, Bosnia-Herzegovina, Croatia, Cyprus, Greece, Italy, Macedonia, Malta, Montenegro, Portugal, Serbia, Slovenia, Spain). Prevalent risk factors for lip, oral cavity and pharynx cancers include cigarette smoking, smokeless tobacco, alcohol, and HPV.

In most countries, the incidence of lip, oral cavity, and pharynx cancers declined since 1991, with declines being more pronounced in Southern Europe. There is wide geographic variability in the burden of lip, oral cavity, and pharynx cancers, with highest incidence observed in Croatia, Portugal, Spain, and Slovenia. The most common anatomic sites of cancer are the anterior tongue and pharynx.

The general declines in the incidence of lip, oral cavity, and pharynx cancers in Western and Southern Europe appear consistent with declines in cigarette smoking.

East Asia

Analyses in East Asia included variable-quality population-based cancer registry data from 5 countries (Mainland China, Hong Kong, Taiwan, Japan, and Mongolia). Prevalent risk factors include smoking, alcohol, HPV, and areca-nut/betel-quid chewing.

The incidence of lip, oral, and oropharyngeal cancers significantly declined in Hong Kong in recent years, while incidence rates have significantly increased in Taiwan and Japan. There is wide regional variability in cancer incidence, with the highest incidence rates in Taiwan. Unlike in North America and Europe, the most common anatomic sites of cancers are gum, floor of mouth, palate, and buccal mucosa.

The high and rising incidence in Taiwan is attributable to high prevalence of betel-quid chewing and smoking. The predominance of buccal and gingival cancers in this region also arises from the unique exposure to betel-quid. HPV infection could also have contributed to the rise in incidence of oropharyngeal cancers in Taiwan and Japan.

South Asia

Analyses in South Asia were restricted to 2 countries with regional cancer registries (India and Sri Lanka). Estimates for all other countries in the region represent extrapolations. Prevalent risk factors in this part of the work include areca-nut chewing with or without tobacco, smoking, alcohol, and HPV.

The incidence of oral and pharyngeal cancers has significantly declined since the 1980s in Sri Lanka. In India, incidence rates have increased in recent years in men, but declined in women. Similar to South-East Asia, the common anatomic sites of cancer are the buccal mucosa, gingiva, and tongue.

The high incidence of oral and pharyngeal cancers in South Asia is attributable to exposure to a unique risk factor—chewing areca-nut with or without tobacco (paan and gutka). Notably, oral and pharyngeal cancer remains one of the most common cancers in men in South Asia, and incidence remains relatively high compared to the rest of the world.

Middle East and Africa

Analyses in the Middle East and Africa included a few countries with population-based cancer registry data and most with extrapolations from neighboring regions. Prevalent risk factors in this region include cigarette smoking, smokeless tobacco (toombak, khat), mate, and alcohol.

Temporal trends in incidence are only available from South Africa, where incidence of lip and oral cavity cancers has significantly declined since the late 1980s in both men and women. However, this trend was heterogeneous by ethnicity. Notably, lip and oral cavity cancer incidence increased significantly in colored men and women. There is wide variability in the regional burden of lip and oral cavity cancers, with highest incidence observed in Djibouti, Somalia, Sudan, Madagascar, Botswana, Mauritius, and Mozambique. There is geographic variability in the primary anatomic site: cancers of the oral mucosa are common in Central Africa, alveolar ridge and tongue cancers in East, West, and South Africa.

The analyses highlight the paucity of data in Africa, and underscore the need for additional studies.

South America

Analyses in South America included variable-quality population-based/regional cancer registry data from Argentina, Brazil, Chile, Colombia, Ecuador, Peru, and Uruguay. Prevalent risk factors in this region include cigarette smoking, alcohol, HPV, and mate.

The incidence of oral and pharyngeal cancers declined since 1999 in most countries for men. A similar decline was observed for women, with the exception of rising incidence in Brazil, and Peru. The most common anatomic site of cancer is the tongue. Incidence varied across countries and was highest in Brazil and Uruguay.

Summary of general patterns globally

- The analyses highlight substantial global and temporal variations in the incidence of oral cavity and pharyngeal cancers.
- Incidence remains high in less economically developed countries, where the prevalence of key risk factors, such as cigarette smoking, tobacco chewing, and alcohol use remain high.
- Significant declines in the incidence of oral and pharyngeal cancers in developed countries, such as USA, Canada, and parts of Western and Southern Europe are consistent with declines in cigarette smoking over the past 4 decades. These observations underscore the potential for primary prevention of oral and pharyngeal cancers through behavioral modification.
- Global incidence trends appear to parallel trends in the prevalence of key risk factors. This is exemplified by an increase in oral and pharyngeal cancers in women in certain European countries, which parallels the later occurrence of the tobacco epidemic in women.

- In recent years, particularly in Western countries, HPV has emerged as a major risk factor for oropharyngeal cancers. This observation highlights the potential for primary prevention through prophylactic HPV vaccination.
- The analyses highlight the paucity of high-quality cancer registry data in the regions of the world with high burden of oral and oropharyngeal cancers. Furthermore, the ability to accurately distinguish between oral cavity and oropharyngeal cancers in most regions of the world precluded an accurate assessment of the burden of these cancers.
- The analyses highlight the late stage of clinical diagnosis of cancer, which results in poor survival outcomes.

Table 1: Burden of lip, oral cavity, and pharyngeal cancers by region

Region, country	Nature of data and population coverage	Key prevalent risk factors	Incidence trends over time, overall	Incidence trends over time, Men	Incidence trends over time, Women	Predominant anatomic site	Regional disparities	Comments
North America	Population-based cancer registries, ~18% of US population and ~97% of Canadian population	Smoking, smokeless tobacco, alcohol, HPV	Declining incidence for oral cavity cancers Rising incidence for oropharyngeal cancers	Declining incidence for oral cavity cancers Rising incidence for oropharyngeal cancers	US: Declining incidence for oral cavity and oropharyngeal cancers Canada: Stable incidence for oral cavity cancers and rising incidence of oropharyngeal cancers	Anterior tongue Oropharynx	Discrepant trends for women in the US vs. Canada for oral cavity as well as oropharyngeal cancers	Declining incidence over the past 3-4 decades is attributable to declines in cigarette smoking, highlighting primary prevention through behavioral modification.
Northern and Eastern Europe	Population-based cancer registries in a vast majority of countries	Smoking, smokeless tobacco, alcohol, HPV		Rising incidence of oral cavity and pharynx cancers in Czech Republic,	Rising incidence of oral cavity and pharynx cancers in	Anterior tongue and pharynx	Highest incidence in Denmark, Lithuania, Slovakia, and	Temporal trends in incidence closely track trends in the

	(except Russia and Poland)			Denmark, Lithuania, and UK. Stable/declining incidence in other countries	Denmark and Czech Republic.		Hungary	tobacco epidemic—high prevalence in eastern Europe and in women. Part of the increase also attributable to HPV infection
Western and Southern Europe	Population-based and regional cancer registries. Variable quality of available data	Smoking, smokeless tobacco, alcohol, HPV	General declines in the incidence of lip and oral cavity cancers			Anterior tongue and pharynx	Wide variability in incidence across countries. Highest incidence in Croatia, Portugal, Spain, and Slovenia.	Declining incidence attributable to declines in tobacco use.
East Asia	Population-based cancer	Smoking, alcohol,	Regional variability in			Other mouth cancers	High incidence in	Rising incidence in

	registries in recent years. No long-term data	HPV, areca-nut chewing	trends. Rising incidence of oral cavity and pharynx cancers in Taiwan			(gum, floor of mouth, palate, buccal mucosa). High incidence of nasopharynx cancers in China and Taiwan.	Taiwan and Hong Kong.	some regions (Taiwan) attributable to high prevalence of smoking, areca-nut chewing, and alcohol. Growing relevance of HPV in some regions.
South Asia	Regional cancer registries	Betel-nut and tobacco chewing, smoking, and alcohol	General declines in the incidence of oral cavity and pharynx cancers in Sri Lanka and India.			Buccal cancers	Some regional variability within India	Despite declines, there remains a high prevalence of chewing tobacco and smoking.
Middle	Few	Smoking				Tongue	Highest	Generally

east and Africa	population-based/regional cancer registries	and smokeless tobacco, mate, alcohol				cancers	incidence in Djibouti, Somalia, and Sudan	lower incidence compared to the rest of the world.
Sub-Saharan Africa	A few population-based cancer registries initiated over the past 5-6 years.	Smoking, chewing tobacco, toombak, khat, alcohol		South Africa: Declining incidence in recent years. Racial ethnic disparities: increasing incidence in colored males.	South Africa: Declining incidence in recent years. Racial ethnic disparities: increasing incidence in colored males.	Alveolar ridge and tongue	Highest incidence of lip and oral cavity cancers in Madagascar, Botswana, Mauritius, and Mozambique	Geographic variability in predominant anatomic site. Central: oral mucosa, East: alveolar ridge and tongue, West: alveolar ridge, South: Alveolar ridge and tongue.
South America	Population-based/regional cancer registries	Tobacco smoking, alcohol, HPV		General declines in incidence since 1992 in most countries	Variable trends in incidence since 1992 across countries. Rising incidence in Brazil and Peru	Tongue cancers	Highest incidence of lip, oral cavity, and pharynx cancers in Brazil and Uruguay.	High prevalence of tobacco use in many South American countries.

Reference List

1. Sankaranarayanan R, Ramadas K, Amarasinghe H, Subramanian S, Johnson N. Oral Cancer: Prevention, Early Detection, and Treatment. 2015.
2. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int.J.Cancer* 2015;136:E359-E386.
3. Hashibe M, Brennan P, Benhamou S et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J.Natl.Cancer Inst.* 2007;99:777-89.
4. Johnson NW, Warnakulasuriya S, Gupta PC et al. Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions. *Adv.Dent.Res* 2011;23:237-46.
5. Ndiaye C, Mena M, Alemany L et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. *Lancet Oncol.* 2014;15:1319-31.
6. Chaturvedi AK, Anderson WF, Lortet-Tieulent J et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers
CHATURVEDI2013. *J.Clin.Oncol.* 2013;31:4550-9.
7. Cancer Incidence in Five Continents, Volumes I to IX: IARC CancerBase No. 9. Lyon, France:
International Agency for research on Cancer 2010 [2010. Available from URL: <http://ci5.iarc.fr>.