The Global Incidence of Lip, Oral Cavity, and Pharyngeal Cancers by Subsite in 2012

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ABSTRACT: By using data from the International Agency for Research on Cancer publication Cancer Incidence in 5 Continents and GLOBOCAN, this report provides the first consolidated global estimation of the subsite distribution of new cases of lip, oral cavity, and pharyngeal cancers by country, sex, and age for the year 2012. Major geographically based, sex-based, and age-based variations in the incidence of lip, oral cavity, and pharyngeal cancers by subsite were observed. Lip cancers were highly frequent in Australia (associated with solar radiation) and in central and eastern Europe (associated with tobacco smoking). Cancers of the oral cavity and hypopharynx were highly common in south-central Asia, especially in India (associated with smokeless tobacco, bidi, and betel-quid use). Rates of oropharyngeal cancers were elevated in northern America and Europe, notably in Hungary, Slovakia, Germany, and France and were associated with alcohol use, tobacco smoking, and human papillomavirus infection. Nasopharyngeal cancers were most common in northern Africa and eastern/southeast Asia, indicative of genetic susceptibility combined with Epstein-Barr virus infection and early life carcinogenic exposures (nitrosamines and salted foods). The global incidence of lip, oral cavity, and pharyngeal cancers of 529,500, corresponding to 3.8% of all cancer cases, is predicted to rise by 62% to 856,000 cases by 2035 because of changes in demographics. Given the rising incidence of lip, oral cavity, and pharyngeal cancers and the variations in incidence by subsites across world regions and countries, there is a need for local, tailored approaches to prevention, screening, and treatment interventions that will optimally reduce the lip, oral cavity, and pharyngeal cancer burden in future decades. CA Cancer J Clin 2017;67:51-64. © 2016 American Cancer Society.

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Introduction

Globally, lip, oral cavity, and pharyngeal cancers have been estimated to be responsible for 529,500 incident cases and 292,300 deaths in 2012, accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths. Lip, oral cavity, and pharyngeal cancers constitute a broad range of tumors with diverse etiologies by world region. In developed countries, approximately 75% of lip, oral cavity, and pharyngeal cancers are attributable to tobacco smoking and alcohol consumption. In developing countries, risk factors for lip, oral cavity, and pharyngeal cancers also include the chewing of betel quid with or without tobacco (oropharyngeal and oral cavity cancers); the use of pipes to smoke tobacco; the consumption of nitrosamine-rich foods, including salted fish; and infection, eg, Epstein-Barr virus (EBV) (nasopharyngeal cancer). In addition, infection with high-risk human papillomavirus (HR-HPV) types (ie, HPV16 and HPV18) explains 17% to 56% of oropharyngeal cancers in developed countries and, to a lesser extent (13%), oropharyngeal cancers in less developed countries. Other determinants are linked to environmental exposures, eg, ultraviolet radiation (UVR) (lip cancer) or deficiencies in dietary intake, eg, fruits and nonstarchy vegetables (oral cavity and pharyngeal cancers). International differences in the distribution of lip, oral cavity, and pharyngeal cancers may allude to differences in etiology, diagnostic workup, prognosis...
and, treatment. Existing studies have been limited to cancer registry comparisons that currently lack global coverage.\(^7\)\(^9\)

There is a critical need to first develop a better understanding of the geographical distribution of new cases of lip, oral cavity, and pharyngeal cancers by major subsites to determine and provide an appropriate allocation of health care resources at the local level. Accordingly, this study describes and compares the country-specific, sex-specific, and age-specific incidence rates of lip, oral cavity, and pharyngeal cancers by subsite globally, examining their major causes as well as the prospects for effective interventions to reduce the future burden.

**Materials and Methods**

Estimated new cases and corresponding population data were extracted from GLOBOCAN for lip and oral cavity cancers (International Classification of Diseases 10th revision [ICD-10] codes C00-C08), nasopharyngeal cancer (C11), and other pharyngeal cancers (C09-C10, C12-C14) for 184 countries, by sex and for 10 age groups (ages 0-14, 15-39, 40-44, ,70-74, and ≥75 years) for the year 2012.\(^1\) We extracted data for more detailed lip, oral cavity, and pharyngeal cancer categories from Volume X of Cancer Incidence in 5 Continents (CI5-X\(^10\)), which were reported at the 3-digit ICD-10 level by sex and for 18 five-year age groups. These data were available from national registries or from 1 or more regional registries in 68 countries and were supplemented by data from the African Cancer Registry Network (AFCRN) (afcrn.org) for the sub-Saharan Africa region as well as the cancer registry data used to build national estimates in GLOBOCAN, resulting in a total of 119 countries with available data.

The incidence of lip, oral cavity, and pharyngeal cancers by subsite was estimated using country-specific data, if such data were available, by applying sex-specific and age-specific proportions of lip, oral cavity, and pharyngeal cancers by subsite, as reported in the CI5-X database, to the overall incident cases of lip and oral cavity cancers (C00-C08) and other pharyngeal cancers (C09-C10, C12-C14) obtained from the GLOBOCAN database (nasopharyngeal cancers [C11] are reported in GLOBOCAN). For lip, oral cavity, and pharyngeal cancers, these data are limited to 3-digit ICD-10 codes because of contractual data confidentiality agreements between the International Agency for Research on Cancer (IARC) and cancer registries. Thus, this coding scheme represents a simplification of the generally used 4-digit ICD-10 classification scheme for lip, oral cavity, and pharyngeal cancers by subsite (see Limitations, below). For the 65 countries in which registry data were lacking, regional (based on the 21 GLOBOCAN regions\(^3\)), average proportions of lip, oral cavity, and pharyngeal cancers by subsite were estimated by sex and for 3 broad age groups (ages 0-54, 55-74, and ≥75 years) and were applied to the GLOBOCAN country-specific estimates.

The subsites of lip, oral cavity, and pharyngeal cancers reported in this study are as follows: lip (C00), oropharynx (C01, C09-D10), oral cavity (C02-C06), parotid gland and other and unspecified major salivary gland (PGOSG) (C07-C08), nasopharynx (C11), hypopharynx (C12-C13), and other and ill-defined sites in the lip, oral cavity and pharynx (C14) (for incidence data respecting cancers of other and ill-defined sites in the lip, oral cavity, and pharynx, see Figs. S1 to S4 and Tables S1 to S11 in the online supporting information).\(^11\) In a few instances where registry data within a country were sparse, registry data from neighboring countries were combined (see Table S12 in the online supporting information). Projections of the incidence of lip, oral cavity, and pharyngeal cancers for the year 2035 were performed by applying population projections from the United Nations Development Program to the estimated age-specific incidence rates per 100,000 person-years in 2012, assuming fixed cancer rates up to the year 2035.

The results are presented for the following 10 geographical regions: 1) sub-Saharan Africa, 2) Oceania, 3) northern Africa and western Asia, 4) Latin America and the Caribbean, 5) eastern/southeast Asia, 6) northern and western Europe, 7) southern Europe, 8) northern America, 9) south-central Asia, and 10) central and eastern Europe. The age-standardized rate (ASR) for each lip, oral cavity, and pharyngeal cancer subsite was computed using the world standard.\(^12\) Results are also presented by quartiles (very high, high, medium, and low) of the Human Development Index (HDI), a composite measure of life expectancy, education, and per capita income in a given country, based on data obtained from the United Nations Development Program for 2012.\(^13\)

**Results**

An estimated 529,500 patients were newly diagnosed with a lip, oral cavity, or pharyngeal cancer (70.8% or 375,000 men and 29.2% or 154,400 women) in 2012, a figure which is predicted to rise by 62% to 856,000 cases by 2035 because of changes in demographics (for projections to 2035, see Fig. S3 in the online supporting information). The subsite of lip, oral cavity, and pharyngeal cancers with the highest frequency was cancers of the oral cavity (202,000 cases) followed by cancers of the oropharynx (100,500 cases); naso-pharynx (86,700 cases); hypopharynx (60,800 cases); PGOSG (40,100 cases); lip (23,700 cases); and other and ill-defined cancers of the lip, oral cavity, and pharynx (15,800 cases). The relative contribution of each subsite varied markedly by world region (Fig. 1), sex, and age.

**Lip Cancers (C00)**

The estimated global ASR of lip cancer in 2012 was 0.3 per 100,000 (0.4 in men and 0.2 in women), with marked differences in the relative importance of lip cancer by region,
ranging from 2.1% to 29.2% of all lip, oral cavity, and pharyngeal cancers in south-central Asia and Oceania, respectively (Fig. 1). In terms of the number of newly diagnosed cases, the majority of global lip cancers (19.2% of all incident cases) occurred in central and eastern Europe. At the national level (both sexes combined), Papua New Guinea and Australia in Oceania had the highest ASRs of lip cancer, with 8.9 and 2.6 new cases per 100,000, respectively. Countries in central and eastern Europe (Serbia and the Ukraine) followed closely, ranking fourth and fifth globally, respectively (Figs. 2-4). The regions with the lowest incidence rates were eastern/southeast Asia and sub-Saharan Africa.

Among both sexes, the proportional incidence of lip cancer to all lip, oral cavity, and pharyngeal cancers was much greater in high and very high HDI countries (Fig. 5). The incidence of lip cancer was consistently elevated among men.
relative to women. The male:female (M:F) rate ratio was 2.5, with this ratio ranging from 5.4 for central and eastern Europe to 1.0 for eastern/southeast Asia (see Table S5 in the online supporting information). As with most other lip, oral cavity, and pharyngeal cancers, the incidence of lip cancer generally occurred at older ages, with 63.2% and 69.9% of all lip cancer cases occurring after age 60 years in men and women, respectively.

**Oropharyngeal Cancers (C01, C09-C10)**

Oropharyngeal cancer had an estimated global ASR of 1.4 per 100,000 for both sexes combined (2.3 for men and 0.5 for women) in 2012. The M:F rate ratio was 4.8, with this ratio ranging from 7.3 for central and eastern Europe to 2.4 for sub-Saharan Africa (see Table S5 in the online supporting information). Proportionally, the contribution of oropharyngeal cancer to all new lip, oral cavity, and pharyngeal cancers ranged from 8.2% in northern Africa and western Asia to 34.2% in northern America (Fig. 1). South-central Asia had the highest number of new oropharyngeal cancer cases (35.1% of global incident cases). At the country level, Hungary had the highest ASR of oropharyngeal cancer, with 5.0 new cases per 100,000 (Fig. 3). The European countries of Slovakia, Germany, and France had the second to fourth highest ASRs, respectively; whereas northern Africa and western Asia (for men) and eastern/southeast Asia (for women) had the lowest ASRs of oropharyngeal cancer (Figs. 2 and 3). Accordingly, countries with high HDI scores had the highest proportional incidence of oropharyngeal cancer for both men and women.

**Oral Cavity Cancers (C02-C06)**

The estimated ASR of oral cavity cancer was relatively large at 2.7 per 100,000 (3.7 in men and 1.8 in women) in 2012, with substantial differences by sex, age, and region. The proportion of oral cavity cancer (of all lip, oral cavity, and pharyngeal cancers) was lowest in northern Africa and western Asia (23.0%) and largest in south-central Asia.
Furthermore, incident cases of oral cavity cancer were highest in south-central Asia (40.9% of all incident cases). At the country level, Papua New Guinea had the highest ASR of oral cavity cancer, with 10.6 new cases per 100,000; however, the countries with the second, third, and fourth highest ASRs (Maldives, Sri Lanka, and Pakistan, respectively) were predominantly from the region of southern Asia (Figs. 2 and 3). The lowest rates were observed in Oceania (for men) and in eastern/southeast Asia (for women) (Figs. 2 and 3).

The proportion of oral cavity cancer by age also varied by HDI grouping; women in low HDI countries, where this cancer is common, had the highest proportional incidence, especially those women in older age groups and in the south-central Asia region (Fig. 5). The incidence of oral cavity cancer was consistently greater among men than among women, with an M:F rate ratio of 2.1, ranging from 5.2 for central and eastern Europe to 1.4 for northern Africa, western Asia, and Oceania.

**PGOSG Cancers (C07-C08)**

The global ASR of PGOSG cancers was estimated to be 0.5 per 100,000 (0.6 in men and 0.4 in women) in 2012. The contribution of PGOSG cancers to the incidence of all lip, oral cavity, and pharyngeal cancers varied by region, ranging from 4.0% in south-central Asia to 14.3% in sub-Saharan Africa (Fig. 1). Northern America (for men) and Oceania (for women) had the highest incidence rates, while, because of population size, eastern/southeast Asia had the highest number of new PGOSG cancer cases (27.9% of all incident cases). At the country level, Papua New Guinea had the highest ASR of PGOSG cancers, with 3.2 per 100,000 (Figs. 2 and 3). The regions of northern Africa and western Asia (for men) and eastern/southeast Asia (for women) had the lowest incidence rates (Figs. 2 and 3). The incidence rate of PGOSG cancers only varied slightly by HDI country groupings (Fig. 5); however, women in high and very high HDI countries had noticeably higher proportional incidence rates of PGOSG cancers compared with countries in other HDI groupings.
Nasopharyngeal Cancers (C11)

Nasopharyngeal cancer had an estimated ASR of 1.2 per 100,000 (1.7 in men and 0.7 in women) in 2012. The relative contribution of nasopharyngeal cancer to the incidence of all lip, oral cavity, and pharyngeal cancers varied by region, ranging from 3.1% in northern and western Europe to 43.6% in eastern/southeast Asia (Fig. 1). Eastern/southeast Asia (for men and women) had the highest incidence rates as well as the majority of all new nasopharyngeal cancer cases (71.5% of all incident cases), with China contributing 53.5% of these cases. At the country level, Malaysia had the highest ASR of new nasopharyngeal cancer cases, with 7.2 per 100,000, followed by Singapore with 6.4 per 100,000. Furthermore, all of the other top 5 ASR countries (Indonesia, Vietnam, and Brunei Darussalam) were from the eastern/southeast Asia region (Figs. 2 and 3).

In medium HDI countries, which grouping includes China, the incidence of nasopharyngeal cancer was high in people ages birth to 39 years and well in older individuals, thus presenting a dual peak scenario—one peak at younger ages and another peak at older ages. This relationship was observed for the medium HDI country grouping even after removing China and India from the analysis (see Fig. S5 in the online supporting information). Nasopharyngeal cancer generally occurred at earlier ages compared with other lip, oral cavity, and pharyngeal cancers, with 68.4% and 68.7% of all nasopharyngeal cancer cases occurring before 60 years of age in men and women, respectively.

Hypopharyngeal Cancers (C12-C13)

The estimated rates of hypopharyngeal cancer varied greatly by sex, age, country, and region, with a generally low global
The incidence rate of hypopharyngeal cancer was 5 times greater among men than women, ranging from 23.0 for central and eastern Europe to 1.2 for northern Africa and western Asia. The relative contribution of hypopharyngeal cancer to the incidence of all lip, oral cavity, and pharyngeal cancers also varied by region, ranging from 3.7% in sub-Saharan Africa to 17.3% in south-central Asia. The south-central Asia region had the highest incidence of new hypopharyngeal cancers for both men and women (48.2% of all

FIGURE 5. Incidence Rates of Lip, Oral Cavity, and Pharyngeal Cancers (LOCP) by Sex, Age, Subsite, and Human Development Index (HDI) in 2012. International Classification of Diseases 10th Revision codes are indicated in the key for each subsite.
Lip, Oral Cavity, and Pharyngeal Cancers

incident cases). This relationship was also observed by HDI groupings, with countries with a low to medium HDI score having the greatest ASRs of hypopharyngeal cancer. At the country level, Bangladesh and Sri Lanka had the highest ASRs of hypopharyngeal cancer, with 4.8 and 2.8 new cases per 100,000, respectively. The other top 5 ASR countries (Hungary, Slovakia, and Romania) were all from central and eastern Europe.

Discussion
To our knowledge, this study is the first to quantify the global burden of lip, oral cavity, and pharyngeal cancers by subsite, as well as the distinct geographic variations by region and country. The ASRs of lip, oral cavity, and pharyngeal cancers also exhibit large variations by sex and age, and the rate disparities reported herein provide an evidence base from which to develop more tailored preventative, screening, and treatment approaches to reduce mortality from specific lip, oral cavity, and pharyngeal cancers in countries and regions where site-specific incidence is elevated.

There are 2 main causes of lip cancer: UVR exposure, which is considered the main risk factor, and the transfer of heat from using pipes to smoke or resting a cigarette on the lower lip while smoking. In Australia (among fair-skinned populations), as well as in some European countries (particularly in Spain and Portugal), UVR is a key causative factor, through both occupational and recreational exposure, although the latter only modestly increases risk. Tobacco smoking is a risk factor for lower lip cancer in northern America, southern Europe, and central and eastern Europe and for high incidence rates of lip cancer among the indigenous populations of Australia and New Zealand. In global terms, incidence rates are either stable or decreasing, which may be because of an increased awareness of the need for solar protection or a decline in smoking rates. A decrease in the M:F ratio for incident cases has been observed, in part as a result of falling incidence rates among men and, in some regions, rising incidence rates among women. Cancers of the upper lip are much more common among women: many of these cancers are basal cell carcinomas, and young females in particular are at a higher risk of basal cell carcinoma of the upper lip (probably because of recreational UVR exposure). It has been postulated that this gender difference in upper lip cancer incidence is because of the protective effect of the presence in men of hair above the lip.

Tobacco smoking, alcohol consumption, and HR-HPV infection are the major risk factors for oropharyngeal and oral cavity cancers, with tobacco smoking and alcohol consumption having synergistic effects. In the Indian subcontinent (particularly in India and Sri Lanka) and in large parts of southern Asia (particularly in southern China and Thailand), where the incidence of these cancers is highest, tobacco smoking and chewing, with or without betel quid, are the premier causes. Male immigrants from India to the United Kingdom also have a higher risk of oral cancer than the host population, and the rates of oral cancers tend to be higher in areas of Europe where there are large Asian populations. Alcohol consumption is currently and historically the greatest in the northern America and European regions (especially in central and eastern Europe), where oropharyngeal cancer incidence rates are the highest. Finally, the frequency of HR-HPV infection of the oropharynx, which plays an increasing role in oropharyngeal cancer incidence in western countries, is highest in northern America (prevalence varying between 44% and 90%), followed by Asia, Oceania, and Europe (prevalence from 36% to 45% across regions), and is lowest in Latin America and the Caribbean (prevalence around 15%). Rates of HR-HPV–related oropharyngeal cancer have been increasing in northern America and in European regions in particular.

Five-year survival rates for cancers of the oral cavity and oropharynx are approximately 50% for Europe and are expected to be lower in developing countries. Furthermore, prognosis depends largely on how early the cancer is diagnosed and the specific site of the carcinoma. For example, cancers of the tongue, which has a rich blood supply and lymphatic drainage, are much more likely to metastasize than other cancers. HR-HPV positivity impacts on survival, with HR-HPV–related oral cavity cancers associated with a better prognosis. Thus, given the prevalence and impact of various factors on the risk of oral cavity cancers, early detection and prevention are important.

PGOSG cancers are relatively rare and represent a categorization of neoplasms that are morphologically and clinically diverse, with the majority of research limited to case-series analyses. There are many hypotheses concerning the risk factors for PGOSG cancers, but, in many cases, the etiology of these cancers is difficult to determine. Currently, only occupational exposures (eg, working in the rubber industry) have been declared carcinogenic. Previous research has also suggested that exposure to ionizing radiation (such as repeated exposure to radiation from medical or dental radiographic examinations) is a risk factor for cancer of the salivary gland. For example, it has been hypothesized that the recently observed increase in incidence, especially in high-income countries such as the United States, is because of increasing exposure to ionizing radiation. Although radiological imaging is an indispensable diagnostic tool, assessing the need for radiological imaging and altering the radiation dose should be considered; however, this practice is currently...
Nasopharyngeal cancers have a unique, complex, and enigmatic etiology and are mainly hypothesized to be caused by genetic factors, EBV exposure, tobacco smoking, occupational exposure to wood dust and formaldehyde, and the consumption of nitrosamine-rich foods, including salted fish. Genetic factors are hypothesized to be responsible for the high incidence rates of nasopharyngeal cancers in south-central Asia and eastern/southeast Asia. A combination of genetic susceptibility and highly carcinogenic risk factors, including consumption of salted fish, is hypothesized to cause the high rates of nasopharyngeal cancers observed in the southeast region of China compared with other regions of that country. The distinct age patterns further illustrate its different etiology: ie, nasopharyngeal cancers show 2 peaks of incidence in low-risk countries (at ages 15-34 years and 55-69 years) and 1 peak in high-risk countries (at ages 55-75 years). The earlier peak of incidence in adolescence/early adulthood may be indicative of cancers caused by germ-line alterations in a gene that greatly increase the risk of these cancers in people who also have an EBV infection or other carcinogenic exposure. Conversely, nasopharyngeal cancers that are more commonly diagnosed at an older age have been related to tobacco and alcohol use and to formaldehyde exposure.

Survival from nasopharyngeal cancers is low compared with survival from other lip, oral cavity, and pharyngeal cancers, because metastasis is more common in nasopharyngeal cancers, with estimates of 5-year absolute survival ranging from 46% to 61% when a patient is treated with chemotherapy and 40% to 72% when patients are treated with chemotherapy and radiotherapy. However, prognosis depends on the extent of the disease when treatment commences, as individuals with stage I and II cancers have much better survival rates than those with stage III and IV cancers. Prognosis may depend on the pathology type of nasopharyngeal cancer, with those classified as World Health Organization (WHO) type I (keratinizing squamous cell carcinoma) having a higher overall survival rate compared with those classified as WHO types II (nonkeratinizing carcinoma) and III (undifferentiated carcinoma). These differences in survival rates may result from type III nasopharyngeal cancer being more aggressive and more likely to undergo distant metastasis; however, this finding of a difference in the survival rate is not universally observed, because type II and III nasopharyngeal cancers are more radiosensitive and may have better treatment outcomes than type I cancers.

Hypopharyngeal cancers are relatively uncommon in most parts of the world. The main risk factors are tobacco use and alcohol consumption. While deficiencies in fruits and vegetables as well as other dietary components are postulated risk factors, other confounding factors associated with diet cannot be ruled out through these analyses. Geographical differences may be associated with higher tobacco smoking and alcohol use in the European regions. In addition, the incidence of hypopharyngeal cancers was elevated in the south-central Asia region, with India having a very high incidence among men. Furthermore, risk is high in male immigrants from south-central Asia to Sweden. This may be due in part to tobacco use, and particularly to the use of smokeless tobacco and bidi (made of low-grade tobacco), because latter leads to a much higher risk of these cancers than tobacco smoking.

Risk Factor Prevention

The marked regional differences in the distributions and patterns of lip, oral cavity, and pharyngeal cancers by subsite indicate that a large proportion of these cancers are potentially avoidable. Furthermore, if current rates remain unchanged, the absolute burden of lip, oral cavity, and pharyngeal cancers is predicted to increase globally because of population aging and population growth, with the largest increase in new lip, oral cavity, and pharyngeal cancer cases predicted in the south-central Asia region. This increase is projected to disproportionately affect developing countries because of a transition of the burden of disease in those countries from infectious diseases to noncommunicable diseases. Many countries (in particular those undergoing transition) lack both population-based cancer registries and the interoperability of health information systems to capture these data. Furthermore, many countries lack information on the risk factors for lip, oral cavity, and pharyngeal cancers, including the population patterns of tobacco use, alcohol consumption, and HR-HPV infections. Thus, there is a need for expanded and improved surveillance systems for disease-driven databases, eg, for incidence, mortality, and survival data, as well as for risk factors. These data are necessary to plan, implement, and evaluate cancer prevention and control activities.

The implementation of cost-effective policies to reduce alcohol use and tobacco use, such as increasing prices (through taxation), restricting marketing, and counter-advertising, could help to prevent a large number of lip, oral cavity, and pharyngeal cancers as well as a large proportion of other tobacco-related and alcohol-related diseases and injuries that contribute to the global burden of disease. Furthermore, tobacco public health policy...
changes must be comprehensive, in that they should cover all forms of tobacco use,\textsuperscript{95,97} including bidi and smokeless tobacco, which are especially popular in eastern/southeast Asia.\textsuperscript{88} Clinicians can also screen for tobacco use and harmful alcohol consumption among patients, with the aim of implementing brief interventions and/or prescribing smoking-cessation medications (in the case of tobacco).\textsuperscript{98-100}

Despite the high incidence rates of oral cavity cancers, the overall incidence of such cancers has been decreasing in most parts of the world, which is consistent with decreases in tobacco and betel quid use.\textsuperscript{9,41,101,102} However, the incidence of oropharyngeal cancers has been increasing, especially among men in developed countries (which is hypothesized to be because of HR-HPV infection).\textsuperscript{9,41}

Thus, increasing the coverage of HR-HPV prevention programs (ie, vaccination programs for both men and women) shows great promise for controlling the rise of oropharyngeal cancers.\textsuperscript{103,104} Immunization against the most common HR-HPV types can prevent a large proportion of HR-HPV–related cancers (in some cases, approximately 80%-90%), especially for oropharyngeal cancers, which are predominantly caused by HR-HPV type 16.\textsuperscript{5,42}

However, when factoring in anogenital cancers (particularly cervical cancers), given the geographical differences in the frequency of specific HR-HPV types, vaccines may need to act against a large number of types to be cost effective.\textsuperscript{105} In particular, low-income countries (LICs) can take advantage of the Global Alliance for Vaccines and Immunization program, which aims to improve access in LICs to vaccines by negotiating low prices and co-financing to improve affordability.\textsuperscript{106} Such vaccination programs would reduce the incidence of oropharyngeal cancers and would also have a protective effect against anogenital cancers\textsuperscript{107} as well as other morbidities.\textsuperscript{108} Furthermore, such programs have been shown to be cost effective in LICs\textsuperscript{109} as well as in high-income countries.\textsuperscript{108}

In addition, given the burden of lip cancer observed in this study, there is also a need to further disseminate information about the risks of exposure to UVR.\textsuperscript{110} The implementation of occupational sun safety (which is low in countries with high rates of new lip cancer cases, such as Australia\textsuperscript{5}) and general public educational programs have been observed to be effective in changing sun-exposure risk behavior.\textsuperscript{111,112} For example, the “Slip! Slop! Slap!” sun-protection educational program in Australia has been associated with a reduction in the incidence rates of melanoma among those ages 54 years and younger and a stabilization of the rates for those ages 55 years and older (in whom the rates previously were increasing), suggesting a positive impact of changes in risk behaviors on cancer risk.\textsuperscript{25,26} Furthermore, banning the use of indoor tanning (in Brazil and Australia) or restricting access to these devices by minors (in Austria, Belgium, Finland, France, Germany, Iceland, Italy, Norway, Portugal, Spain, the United Kingdom, and the United States [for some states]) also has the potential to reduce lip cancer and melanoma of the skin, especially for those ages 30 years and younger, in whom the risk is affected more by UVR.\textsuperscript{113}

**Early Diagnosis and Screening**

Early recognition of the symptoms and signs, as well as prompt diagnosis, of lip, oral cavity, and pharyngeal cancers and of precancerous lesions and tumors are vital to patient survival.\textsuperscript{14} However, in developing countries, there is often a lack of resources, including inadequate cancer screening and treatment facilities and a scarcity of trained personnel (in particular, pathologists, histotechnologists, and cytotechnologists).\textsuperscript{114} Therefore, improving health resources and access to them in developing countries should be a priority. First, there is no standard or routine screening test to diagnose lip, oral cavity, and pharyngeal cancers,\textsuperscript{115} and no screening guidelines have been provided for the early detection of lip, oral cavity, and pharyngeal leukoplakia and erythroplakia lesions or cancers.\textsuperscript{116} A recent Cochrane review found only one published community randomized-control study in which the primary aim was to assess the effects of oral cavity cancer screening on mortality.\textsuperscript{117} That study, which was performed in India, found that visual oral screening of high-risk groups could reduce oral cavity cancer mortality by at least 29\%.\textsuperscript{118} However, additional studies are required to assess the effectiveness of screening programs based on the number of deaths prevented versus the costs of screening program as well as the potential harms caused by overdiagnosis and overtreatment.\textsuperscript{118} Therefore, although there is no evidence of effectiveness,\textsuperscript{119} visual inspection for oral leukoplakia and erythroplakia lesions and for oral tumors during dental visits or regular family physician appointments in high-risk groups may be able to reduce oral cavity cancer mortality.\textsuperscript{120} Second, the screening of high-risk individuals (migrants from endemic regions as well as individuals who have a familial risk of nasopharyngeal cancer) for raised levels of antibodies against EBV (a marker for nasopharyngeal cancer risk) may decrease morbidity and mortality from this cancer.\textsuperscript{121} Finally, to assist in the rapid detection of likely lip, oral cavity, and pharyngeal cancers, referral criteria have been developed to aid in prioritizing the biopsy (which is required for diagnosis) of highly probable malignant lesions.\textsuperscript{322}

**Survivorship Care**

The good prognosis of lip, oral cavity, and pharyngeal cancers, especially if diagnosed early, makes follow-up care for the survivors an issue that is growing in importance.\textsuperscript{123} In particular, survivors require coordinated, high-quality, comprehensive follow-up care that is adapted to their specific preferences and targeted to their risk of cancer reoccurrence,
with the ultimate goal of increased survival and quality of life (see Cohen et al).123

Limitations
There are limitations that are inherent in the estimates of incidence obtained from GLOBOCAN; although they are based on the best available data, the country-specific estimates should be interpreted with caution, especially for those countries where the estimations are based on potentially biased, insufficient, and/or proxy data.1 In some instances, the national estimates of the incidence of lip, oral cavity, and pharyngeal cancers are based on regional data that may or may not be representative of the entire country. Furthermore, in some countries with small populations and in countries with sparse data, site-specific lip, oral cavity, and pharyngeal cancer cases may be rare and, thus, subject to substantial random variation; we used 3 large age groups when estimating lip, oral cavity, and pharyngeal cancers by subsite as well as combined registry data in some instances.

Because of these data limitations, the topological groupings were also based on aggregate categories, such as oral cavity cancers, which did not necessarily reflect geographically based, age-based, and sex-based variations in subsite cancers (eg, tongue cancers, which are more common in Europe, the Americas, Oceania, and India).10 In addition, the coding scheme used was a 3-digit ICD-10 classification scheme for lip, oral cavity, and pharyngeal cancers that was developed and published by the WHO.124 This is important for malignant neoplasm of other and unspecified parts of tongue (C02) or for malignant neoplasm of palate (C05), which, in each instance, involves cancers of both the oral cavity and the oropharynx. However, an analysis using data reported by the Surveillance, Epidemiology, and End Results program indicates that the majority of malignant neoplasms of other and unspecified parts of tongue can be attributed to oral cavity cancers (C02.0-C02.3), while malignant neoplasms of palate will be split approximately evenly between oral cavity (C05.0) and oropharyngeal (C05.1-C05.2) cancers. In the United States, from 2003 to 2013, the percentage of all 4-digit oropharyngeal and unspecified (oral cavity/oropharyngeal) cancers coded within C02 and C05 represented 8.6% of all lip, oral cavity, and pharyngeal cancers (see Table S13 in the online supporting information). Therefore, attributing these C02 and C05 cancers solely to the oral cavity, as coded using 3 digits of ICD coding, may lead to an overestimation of the total number of new oral cavity cancers and an underestimation of the total number of new oropharyngeal cancers, depending on exposure to etiological factors for oral cavity cancer and/or oropharyngeal cancer within a country. Furthermore, other cancer coding systems exist, with the TNM system in particular requiring more detailed topological information.11,77,124 Finally, with respect to the C15-X data, determining the topographical codes for lip, oral cavity, and pharyngeal cancers was a complex task. For lip cancers on the vermilion border (the area between the skin of the lip and the labial mucosa),126 most will have been recorded correctly; however, a proportion of such cancers will have been misclassified as skin cancer.126 For oral cavity and pharyngeal cancers, reliable identification of the origin of tumors that arise along the plane of the superior surface of the soft palate to the superior surface of the hyoid bone is often not possible, thereby creating a degree of unreliability in the reporting of cancer cases for these subsites.127 In addition, PGOSG cancers, as coded by the ICD-10, do not include cancers of the minor salivary glands (which etiologically have not been observed to be associated with tobacco use, alcohol consumption, or HR-HPV infection); however, the salivary glands, which are distributed in the upper aerodigestive tract, have been considered in other studies of lip, oral cavity, and pharyngeal cancers.126 Finally, cutaneous squamous cell carcinomas (primarily the reoccurrence of these carcinomas) of the lymph node basin of the parotid gland are commonly inaccurately coded as primary malignancies of this gland.128

Conclusion
This study outlines the incidence of lip, oral cavity, and pharyngeal cancers according to the major subsites. The pattern and distribution of the incidence of these cancers by subsite differ markedly across and within regions, due in part to differences in etiology. These differences highlight the potential for reducing the incidence of lip, oral cavity, and pharyngeal cancers. The cornerstone of reducing the incidence of and mortality from lip, oral cavity, and pharyngeal cancers will be risk factor prevention (through the control of tobacco use and alcohol consumption, as well as through vaccination against HPV infection for oropharyngeal cancer prevention), early diagnosis (through screening of high-risk populations for oral cavity cancers), and risk reduction (through education programs for both clinicians and patients). Given the variability of the incidence of lip, oral cavity, and pharyngeal cancers by subsite, this study supports the development and allocation of country-specific preventative, screening, and treatment resources to reduce the global burden of lip, oral cavity, and pharyngeal cancers in the near future.127

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