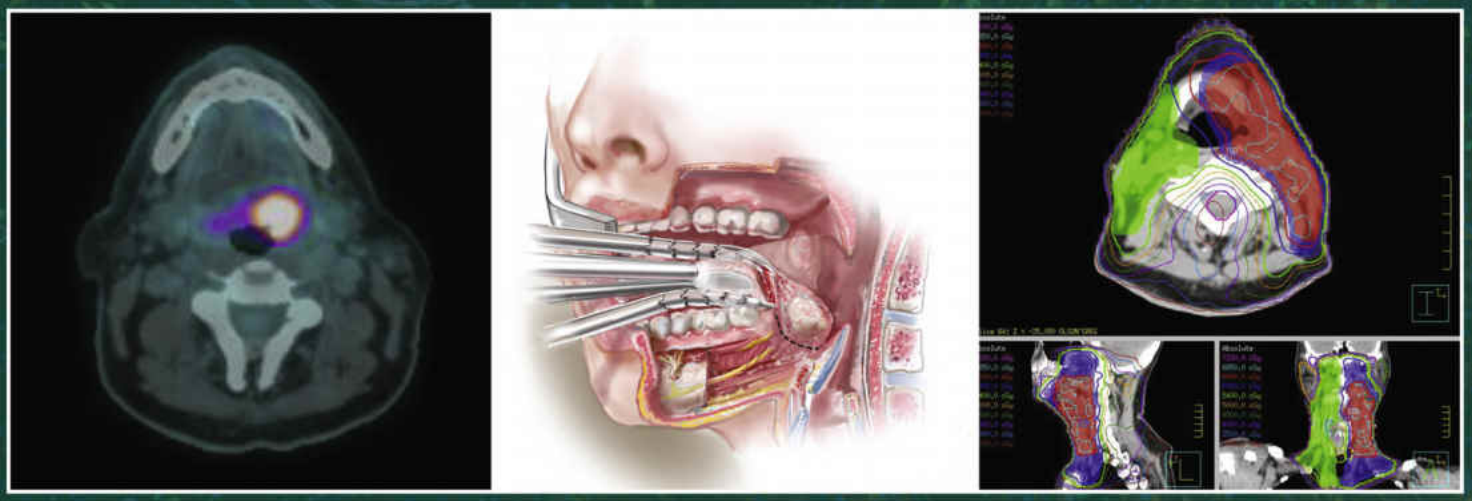
ORAL, HEAD AND NECK ONCOLOGY AND RECONSTRUCTIVE SURGERY

R. Bryan Bell | Rui P. Fernandes | Peter E. Andersen



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Oral, Head and Neck Oncology and Reconstructive Surgery

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To all whose lives are inexorably touched by
the capriciousness of head and neck cancer:
your grace and tenacity inspire us to do better.

RBB

RPF

PEA

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Foreword

In the past several decades, we have witnessed major advances in our understanding of cancer pathogenesis with corresponding improvements in treatments. This ranges from an understanding of intrinsic molecular drivers of cancer, micro-environmental changes that facilitate the development of cancer, a more complete recognition of how cancers evade immunological control, and, in the case of head and neck tumors, the critical contribution of human papillomavirus to disease pathogenesis. This knowledge has translated into numerous therapies targeting specific molecular features of cancer along with highly effective immune-targeted therapies. At the same time, there have been remarkable improvements in surgical and radiation technologies that allow for improved patient outcomes. All of these new advances are rapidly being incorporated into new standards of care that require multi-disciplinary teams to most effectively manage patients with cancer. Against this backdrop, R. Bryan Bell and his colleagues provide a comprehensive textbook for managing the most common adult head and neck cancers, with an emphasis on technological innovations in oncologic and reconstructive surgery, rehabilitation, as well as the emerging therapeutics, such as immunotherapy and molecularly targeted therapy. This textbook will serve as an important point of reference for continued improvements in treatment paradigms that will lead to even better outcomes for patients with head and neck cancers, and we all look forward to these future advancements.

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1 Epidemiology

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PART 1: GLOBAL PERSPECTIVE

Newell W. Johnson, Hemantha K. Amarasinghe

Introduction and Scope

The term *head and neck cancer* is generally used to describe the range of malignant neoplasms of soft tissue origin that develop in the oral cavity including the lips, nasal cavity, paranasal sinuses, pharynx, larynx, and salivary glands. The skin is included in many descriptions, but not usually ocular and intracranial neoplasms, nor those of endocrine or lymphatic origin—thus excluding thyroid and parathyroid cancers, lymphomas, and sarcomas.

Approximately 90% of head and neck cancers are squamous cell carcinomas (SCCs), which originate from the epithelium of the mucosal lining of the upper aerodigestive tract (UADT), and adenocarcinomas from associated secretory glands. Head and neck squamous cell carcinoma (HNSCC) is strongly associated with environmental and lifestyle risk factors, particularly tobacco use, both smoked and "smokeless"; the chewing of areca nut (i.e., betel nut); regular alcohol consumption, diets poor in antioxidant vitamins and minerals; ultraviolet (UV) light from the sun; indoor and outdoor air pollution; occupational exposures to radiation or chemical carcinogens; and, increasingly, certain viruses, perhaps sexually transmitted—notably "high-risk" genotypes of the human papillomavirus (HPV) family (particularly HPV16 and HPV18, especially when originating in the tonsil, base of tongue, and elsewhere in the oropharynx), and some human herpesviruses (HHVs; Epstein-Barr virus [EBV] with nasopharyngeal carcinoma). There is a modest inherited susceptibility. Chronic trauma and chronic inflammation are reemerging as significant cofactors. Around the world, with the exception of HPV-related cancers, HNSCC is predominantly a disease of the poor; inequalities and contributing factors have been analyzed by Johnson and colleagues.[1]

HNSCC is known for its capricious biologic behavior and is characterized by local tissue destruction, early and frequent metastasis to the cervical lymph nodes, and a relatively high rate of distant metastases. A large proportion of patients have recurrence of the primary lesion and/or develop a second primary neoplasm, even after effective local therapy. Respiratory and cardiovascular comorbidities are common, usually resulting from tobacco and alcohol abuse and/or poor nutrition.

HPV-associated HNSCC is a distinct clinical and biologic entity that responds much better than HPV-negative carcinomas to conventional therapies. However, HPV-related disease is much less frequent in oral cavity and larynx cancers (<5%) than it is in cancers of the oropharynx (40–80%).[2] The prevalence of HPV in oropharyngeal cancers significantly increased in recent years, and the annual number of HPV-positive oropharyngeal cancers will be likely higher than the number of cervical cancers by the year 2020.[3,4] Whereas the incidence and survival rates of oropharyngeal cancer are greatly increased because of HPV infection, the majority of patients with oral cavity and laryngeal cancer develop locoregional relapse (56%), and as many as a third (34%) will also develop distant metastases despite technologic improvements in local therapies.[5] Indeed, only two biotherapies have been approved by the U.S. Food and Drug Administration (FDA) for HNSCC in the past 10 years: monoclonal antibodies directed at blocking the family of epidermal growth factor receptors (cetuximab) on the surface of malignant keratinocytes, in neoplasms with overexpression of these molecules; and, more recently, an immunotherapy targeting programmed cell death receptor 1 (PD-1), pembrolizumab. New therapeutic strategies for recurrent/metastatic (R/M) oral squamous cell carcinoma (OSCC) are thus urgently needed, particularly in the HPV-negative patient.

The first part of this chapter focuses primarily on the epidemiology of non–HPV-related head and neck cancer, which comprises the greatest burden to society worldwide. Data come from a variety of sources, and certainly cancer registries play a vital role in monitoring the incidence of and mortality from cancers. However, the quality of data available across the globe is highly variable. Many parts of the world produce no data at all, and in others (often among the most populous), the data may come from localized, atypical regions. Hospital-based cancer registries naturally gather biased information—only from patients who are seen in the hospital; in many developing countries, patients may not come to attention at all, either because of fear or because of the inability of poor people to access hospital services. Data may be even more unreliable

because, in many resource-poor countries, follow-up, even of treated patients, is impossible. Death certification is not always compulsory, and there is limited international standardization in the categories for cause of death, let alone calibration of those signing death certificates.

Fortunately, many nations have high-quality population-based cancer registries, with compulsory reporting of all malignancies. These are guided by, and quality assured by, both national authorities and the positive influence of the World Health Organization (WHO), mostly through its constituent body, the International Agency for Research on Cancer (IARC), headquartered in Lyon, France. Increasingly, hospital records contain information on lifestyle and other known or suspected risk factors. The growth of biologic "tumor banks" or "tissue banks" from which molecular markers and mechanisms can be researched is encouraging, and there are several large, international consortia using such banks to unravel the genome of all cancers—notably the International Cancer Genome Project, which has several collaborating centers dealing with head and neck cancers (https://icgc.org); the Cancer Genome Atlas in the United States (www.genome.gov/17516564), and the Wellcome Trust Sanger Institute Cancer Genome Project in the United Kingdom (www.sanger.ac.uk/research/projects/cancergenome).

Data from all over the world are collated and are available from the websites of all of these bodies; this includes free access to programs that allow online interrogation of the databases. Many of the tables and graphs in this chapter have been generated in this way. Within the United States, the website of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute provides similar sophisticated opportunities to registered users. It is based on data from, currently, 20 population-based registries, and although these by no means cover the whole nation, they provide insight into evolving epidemiologic trends (http://seer.cancer.gov/registries/list.html).

History

Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumor is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years. Some historians speculate that a high incidence of nasal cancer may have been present in some ancient populations because of the inhalation of wood smoke in poorly ventilated huts. In approximately 400 BC, Hippocrates described a common chronic ulcer at the edge of the tongue that he attributed to the presence of sharp teeth rubbing against the tongue: a challenge to differential diagnosis that is still real today! Even earlier, in the sixth century BC, the classical Sanskrit text on surgery, the *Sushruta Samhita,* described the removal of tumors from the head and neck. Modern Western medicine received its foundation from early Roman medical writings. Nevertheless, real advances in the management of head and neck cancers had to wait until the advent of comparatively safe and effective anesthesia and surgical excision in the 18th century.

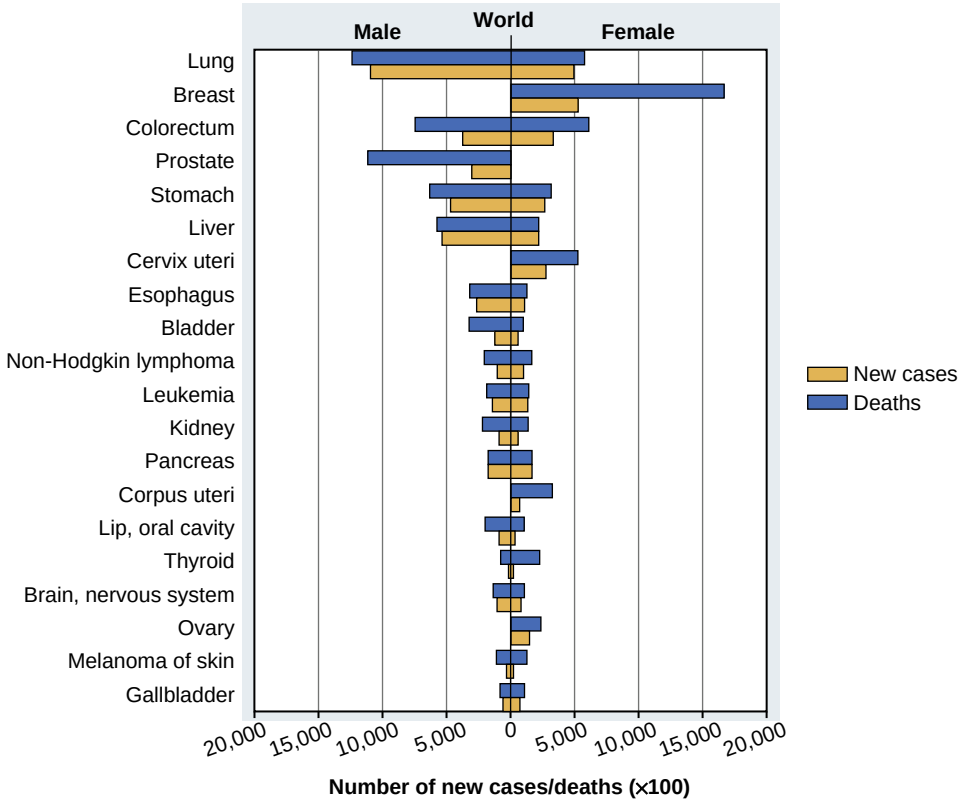
Global Prevalence of Head and Neck Cancer

Depending on the number of anatomic sites and subsites included, head and neck cancer (*International Statistical Classification of Diseases and Related Health Problems,* 10th revision [ICD-10]: C00–C14) is the seventh most common type of cancer, representing about 4.3% of all cases and accounting for an estimated 599,637 new cases and 224,834 cancer deaths worldwide every year. Fig. 1.1 compares several head and neck cancers with cancers affecting other body sites. Numbers of new cases and of deaths attributed to cancer at these anatomic sites are given for males and females; males predominate in all head and neck sites.

Data extracted from the Cancer Incidence in Five Continents database for the period 2003–2007 also facilitate a global overview.[6] When oral and pharyngeal cancers are considered, the annual estimated incidence is around 300,373 cases for cancers of the lip and oral cavity (ICD-10: C00–C08) and 142,378 for other pharyngeal cancers (C09–C10, C12–C14) excluding the nasopharynx; two thirds of these cases occurred in developing countries.[2] There is wide geographic variation in the incidence rates of oral cancer, nasopharyngeal cancer, "other pharynx" cancer, cancer of the larynx, and cancer of the esophagus (Table 1.1). Furthermore, there are marked differences among countries in the same geographic region. For example, oral cancer has the highest crude rates in the world in Melanesia, the Maldives, Sri Lanka, Bangladesh, France, and Hungary.[2] The extremely high rates in the relatively small populations of the Melanesian Islands have not been comprehensively researched, but data from Papua New Guinea (see later) define the importance of areca nut (betel) chewing (called *buai* in Papua New Guinea) and smoking habits as the major risk factors.

The majority of HNSCCs continue to be related to tobacco in various forms, betel quid chewing, heavy alcohol drinking, and dietary micronutrient deficiency.[7] There is a clear dose-response relationship (Fig. 1.2). Worldwide, four times more men than women smoke. In 2002 there were 941 million male smokers, which was 43% of all men older than 15 years. The largest population of male smokers lives in China, where men are more likely to smoke than not to smoke. Even Puerto Rico and Sweden, with the lowest percentages of men who smoke, still have 17% who are smokers.

The Global Adult Tobacco Survey (GATS) is the global standard for systematic monitoring of adult tobacco use (smoking and smokeless) in the world. In India alone, the GATS survey, conducted in 2009–10 by the International Institute for Population Sciences (IIPS) Mumbai, covered about 99.9% of the total population of India. The survey revealed that more than one third (35%) of adults in India used tobacco in some form or another—48% of males and 20% of females; 21% of adults used only smokeless tobacco, 9% only smoked, and 5% smoked and used smokeless tobacco. Thus, in India there were approximately 275 million tobacco users, 164 million users of only smokeless tobacco, 70 million smokers only, and more than 42 million users of both smoking and smokeless tobacco. The distribution of tobacco use in India has been well mapped by Gupta.[8,9]



• **Fig. 1.1** Global scenario of the burden of cancer: new cases and deaths per annum, in 2012, for the top 20 cancers. (Data from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012.* Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

TABLE 1.1 World Standardized Incidence Rates for Upper Aerodigestive Tract Cancers per 100,000 per Year

	Mouth (ICD-10: C00–08)		Nasopharynx (ICD-10: C11)		Remainder of Pharynx (ICD-10: C09–10 Plus C12–14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
	Lip, all of tongue, all of mouth, and major salivary glands		Data for C30, Malignant neoplasm of nasal cavity and middle ear; and for C31, Malignant neoplasm of accessory sinuses; and for C32, Malignant neoplasm of larynx, are not included here		Tonsil, remainder of oropharynx, pyriform fossa, hypopharynx, and sites not otherwise specified among C00–C13				This code excludes cancers arising at the gastroesophageal junction which are included in stomach cancers, the majority of which are adenocarcinomas; included here, therefore, are mostly SCCs sharing common risk factors with the mouth	
Country	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
World	5.5	2.5	1.7	0.7	3.2	0.7	3.9	0.5	9.0	3.1
More developed	7.0	2.6	0.6	0.2	4.7	0.8	5.1	0.6	6.4	1.2
Less developed	5.0	2.5	2.0	0.8	2.8	0.7	3.5	0.4	10.1	4.1
Africa	3.3	2.0	1.5	0.8	1.1	0.6	2.7	0.3	5.6	3.5
Eastern Africa	4.5	2.8	1.9	1.1	1.0	0.6	2.3	0.3	11.9	7.8
Middle Africa	3.5	1.8	1.3	0.6	1.7	0.6	1.4	0.2	4.2	2.0
Northern Africa	2.8	1.8	2.3	1.0	0.8	0.7	4.2	0.4	2.4	1.5

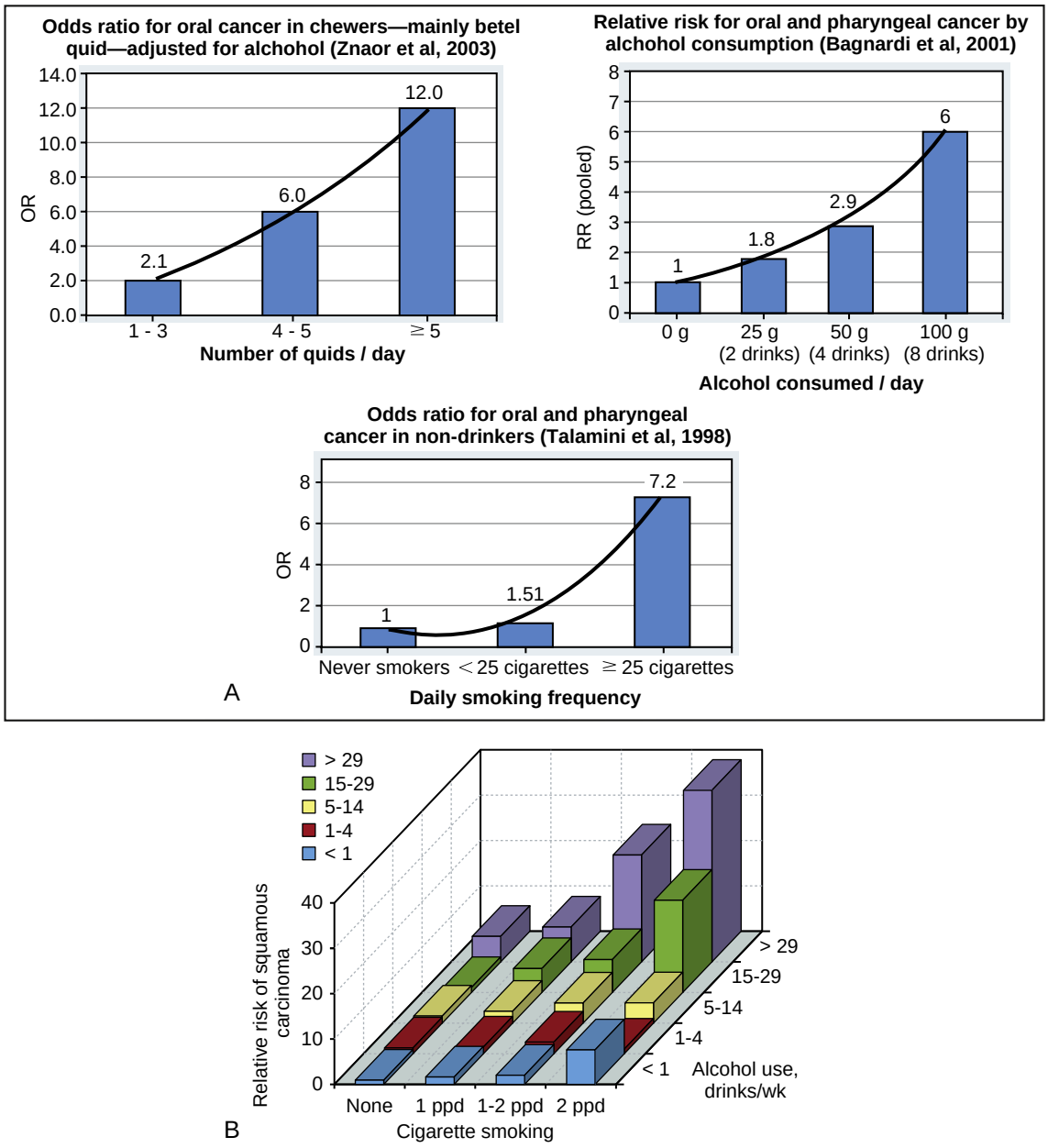
TABLE 1.1 World Standardized Incidence Rates for Upper Aerodigestive Tract Cancers per 100,000 per Year—cont'd

	Mouth (ICD-10: C00–08)		Nasopharynx (ICD-10: C11)		Remainder of Pharynx (ICD-10: C09–10 Plus C12–14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
Country	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Southern Africa	6.3	2.3	0.4	0.2	3.9	1.5	5.0	0.9	13.7	6.7
Western Africa	1.7	1.4	0.7	0.4	0.6	0.1	1.4	0.1	0.8	0.4
Caribbean	4.8	1.8	0.4	0.2	3.6	0.9	7.9	0.9	4.6	1.2
Central America	2.6	1.7	0.2	0.1	1.0	0.3	4.0	0.6	1.7	0.6
South America	5.3	2.4	0.5	0.2	3.0	0.5	5.2	0.7	7.0	2.0
Northern America	7.2	3.2	0.7	0.3	4.2	1.0	4.0	0.9	5.4	1.1
Asia	5.2	2.5	2.3	0.9	3.1	0.7	3.3	0.4	11.4	4.3
Eastern Asia	2.4	1.1	2.5	1.0	1.3	0.2	2.2	0.2	16.9	5.4
Southeastern Asia	4.0	2.5	6.4	2.4	2.6	0.7	2.7	0.5	3.6	1.0
South Central Asia	9.9	4.7	0.6	0.2	6.2	1.4	4.6	0.6	6.5	3.9
Western Asia	2.7	1.6	1.3	0.5	0.8	0.4	6.5	0.9	2.9	2.1
Europe	7.5	2.5	0.6	0.2	5.2	0.9	6.2	0.6	5.8	1.2
Central and Eastern Europe	9.1	2.0	0.6	0.2	5.3	0.5	7.9	0.4	5.6	0.8
Northern Europe	5.9	3.1	0.4	0.2	3.4	1.0	3.4	0.6	8.1	2.7
Southern Europe	5.8	2.1	0.7	0.3	3.4	0.5	7.2	0.6	3.2	0.6
Western Europe	7.9	3.2	0.5	0.2	7.5	1.6	4.9	0.7	6.8	1.6
Australia	8.8	3.9	0.6	0.3	3.3	0.7	3.1	0.3	5.4	1.7
New Zealand	5.5	2.7	0.9	0.3	2.4	0.4	2.3	0.4	5.6	1.8
Melanesia	22.9	16.0	0.4	0.1	3.4	0.4	2.7	0.6	3.6	1.4
Micronesia	4.9	0.0	3.3	2.0	0.0	0.0	0.0	0.0	3.3	0.0
Polynesia	4.1	1.8	2.0	0.8	3.8	0.0	3.2	0.4	3.0	0.3

Adapted from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.
SCC, squamous cell carcinoma.

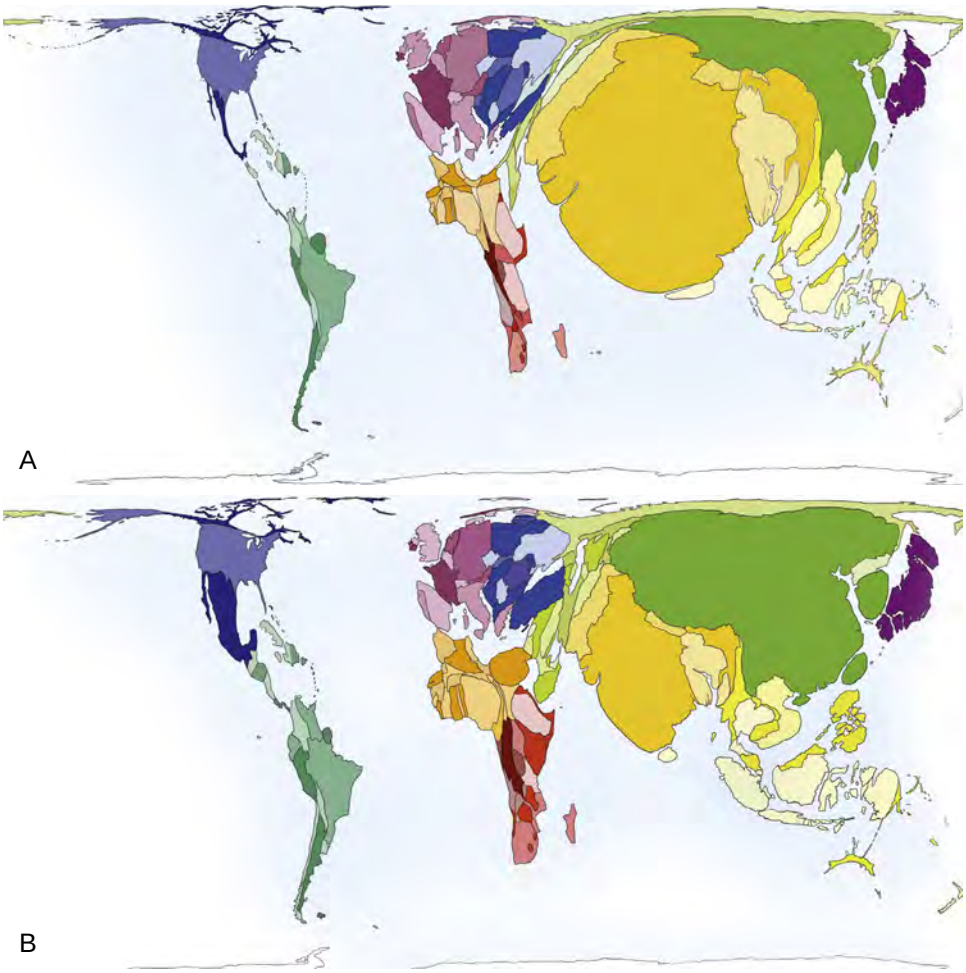
With the data taken as a whole, it is apparent that the public health burden of HNSCC is predominantly a result of smoking and is borne by Eastern Europe, Central and Eastern Asia, and South Asia (Fig. 1.3). China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia, Mongolia, Armenia, and Kenya are the five top-ranked countries for smoking prevalence, at 77%, 69%, 69%, 68%, and 67%, respectively.

In the developing world, tobacco and areca nut, used either alone or in combination, account for the vast majority of HNSCCs and oral potentially malignant disorders (OPMDs).[10] WHO has classified areca nut, a common component of many different chewing habits, as carcinogenic to humans.[10–13] UV radiation is relevant to lip cancer. Despite the significance of tobacco and alcohol as risk factors, in the West there are distinct subgroups of patients without these traditional risk factors: younger males who never smoked yet



• **Fig. 1.2** **A** and **B,** The dose-response relation for the major risk factors for oral and pharyngeal cancers. *OR,* odds ratio; *ppd,* packs per day; *RR,* relative risk. (**A** from 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* 23:237–246, 2011. Sources: Znaor A, Brennan P, Gajalakshmi V, Mathew A, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer*. 2003;105[5]:681–686. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer*. 2001;85[11]:1700–1705. Talamini R, La Vecchia C, Levi F, et al. Cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers who smoke tobacco. *J Natl Cancer Inst*. 1998;90[24]:1901–1903. **B** from Schottenfeld D, Fraumeni JF, editors: *Cancer epidemiology and prevention,* ed 2, New York, 1996, Oxford University Press.)

develop oropharyngeal cancer; elderly women in whom etiologic factors are not clear[14]; and younger females in whom it has been suggested that estrogen deficiency may influence susceptibility to oral cancer. In the case of young nonsmoker males, it has become apparent that oncoviruses are an important cause of HNSCC, especially in Western Europe and North America, where "high-risk" genotypes of the HPV family cause cancer in the tonsil, base of tongue, and other oropharyngeal sites. In Asia, EBV is a major cause of nasopharyngeal carcinoma. Significantly, younger mean age at menopause and higher rates of hysterectomy may influence the higher rates of oral cancer seen among younger women.[15] Data presented in this chapter are, whenever possible, separated by sex. In addition, one of the major limitations of the existing databases is the "lumping"



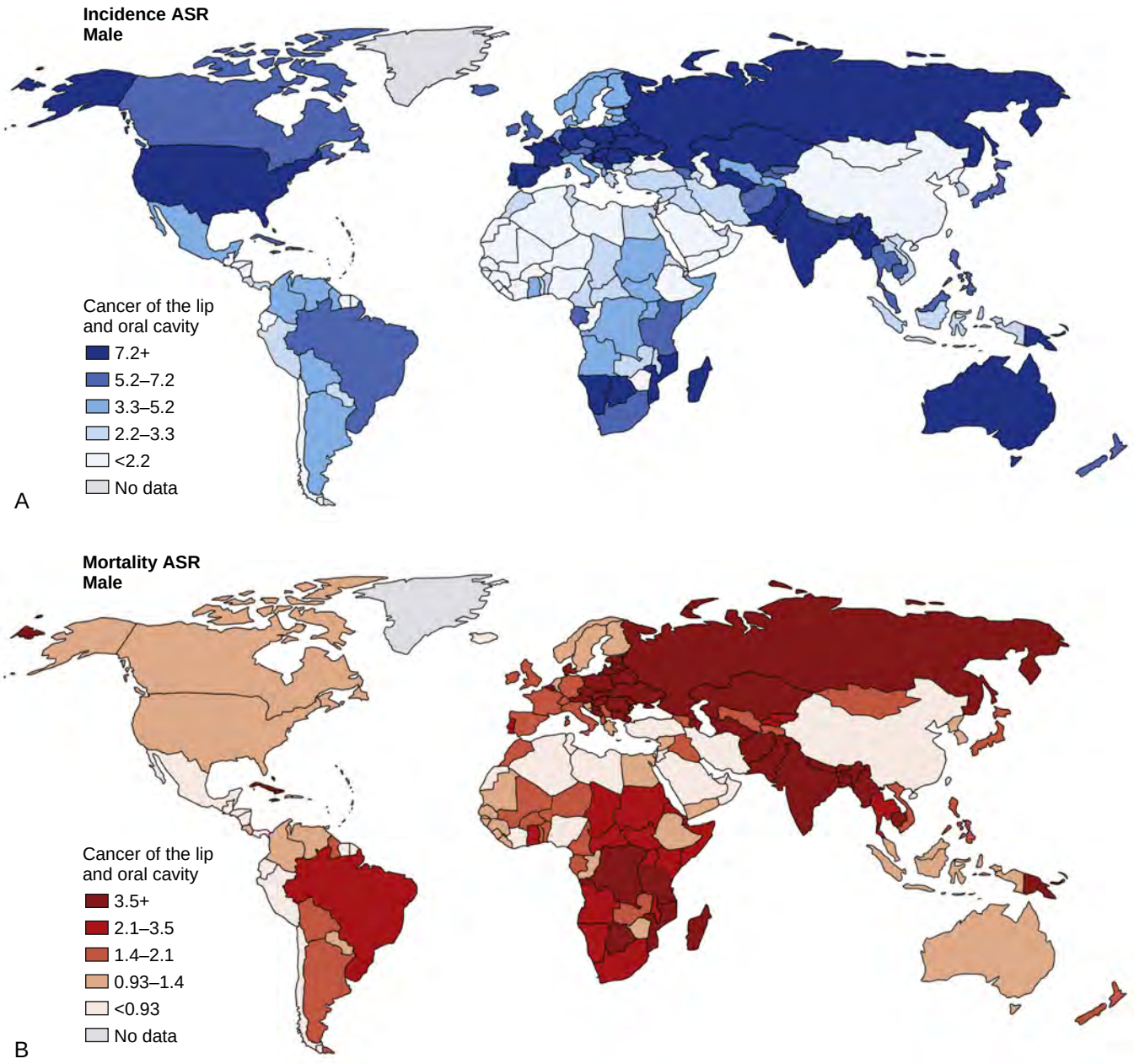
• **Fig. 1.3** These two maps (shown only for males here) distort countries on the basis of the number of deaths by mouth and pharynx cancer **(A),** and the number of male smokers **(B).** They show that the public health burden is borne by Eastern Europe, Central and Eastern Asia, and South Asia. China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia, Mongolia, Armenia, and Kenya are the five top-ranked countries for smoking prevalence, at 77%, 69%, 69% 68%, and 67%, respectively. Territory size shows the proportion of men who smoke who live there. (From www.worldmapper.org/display_extra.php?selected=419. Used with permission.)

of oral cavity cancers with cancers of the pharynx. With the evolving role of HPV in the Western world, it is clear that these are biologically distinct and should, in fact, be separated epidemiologically. We have attempted to do this whenever possible, and HPV-related oropharyngeal cancer, a disease that is clinically and biologically distinct from its non-HPV counterpart, will be covered in the second part of this chapter.

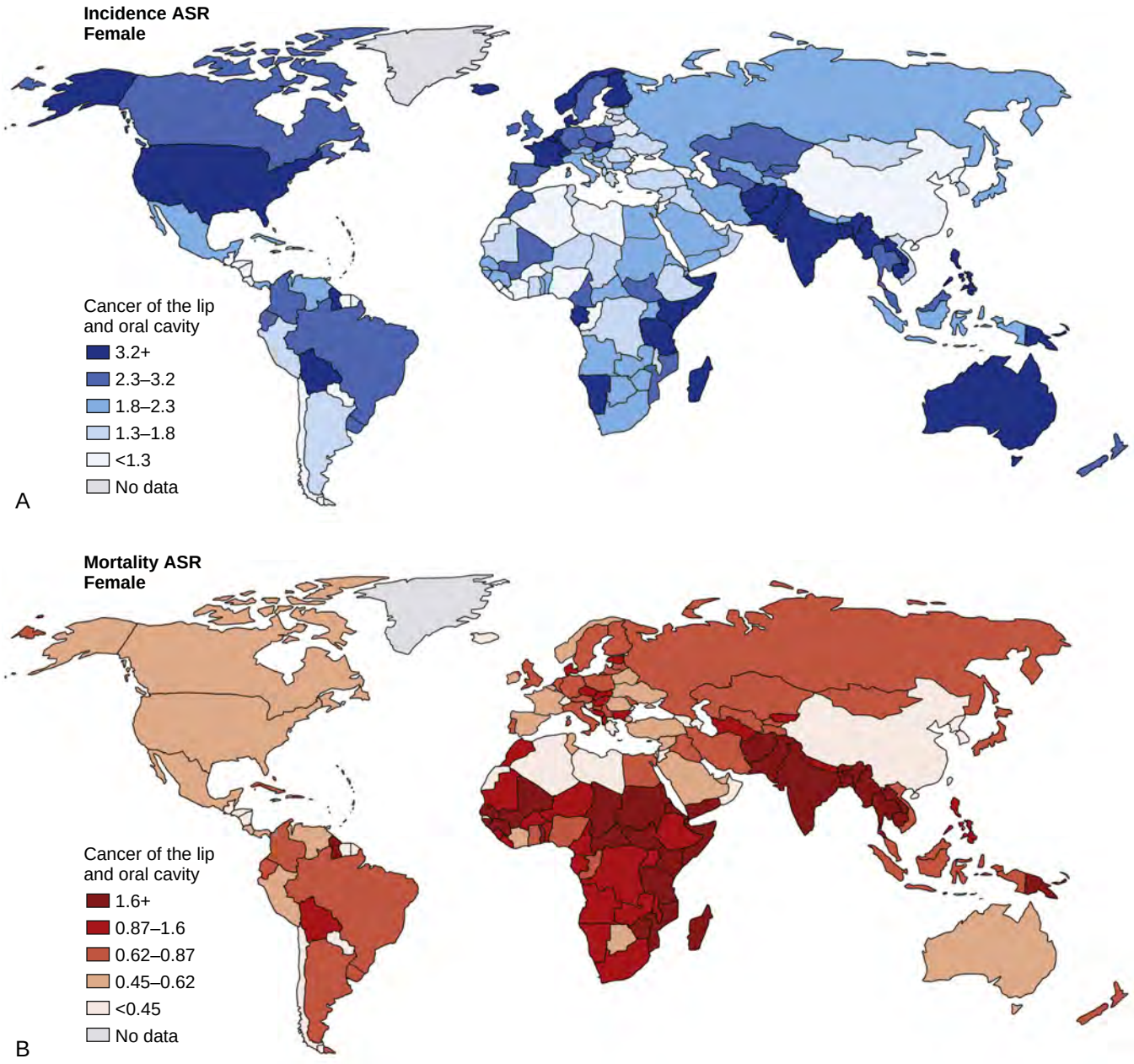
Geographic Differences

The world maps reproduced in this chapter (Figs. 1.4 to 1.9), although simplifying data by aggregation to national averages, contain important information. As with the tables, maps are shown for each of the important head and neck sites. It has been apparent for decades that the global picture for head and neck cancer is dominated by the incidence of oral cancer in southern Asia and of oral cavity plus nasopharyngeal cancer in East Asia. In the 1980s, in India, Bangladesh, Pakistan, and Sri Lanka, oral cancer was the most common site and accounted for about one third of all cancers: it is still the most common cancer among men in Sri Lanka.[16–18] The proportion is falling, partly owing to increased detection of other cancers by more extensive screening programs and improved techniques.[9] Even within the subcontinent there are striking differences in incidence rates. The highest rate for tongue and mouth cancer is reported for men living in South Karachi, Pakistan; the second highest is for those in Trivandrum city in Kerala, India. Extremely high rates for women are seen in the Tamil community in Malaysia—higher even than in Tamil Nadu itself; upper aerodigestive tract sites in Indian females in Peninsular Malaysia are the second most common cancers, behind cancers of the breast and before cancers of the uterine cervix.[19]

According to GLOBOCAN 2012, the highest incidence of oral cancers (ICD-10: C00–C08) is found in Melanesia (astounding rates of 22.9 per 100,000 men and 16.0 per 100,000 women, although there are caveats regarding the



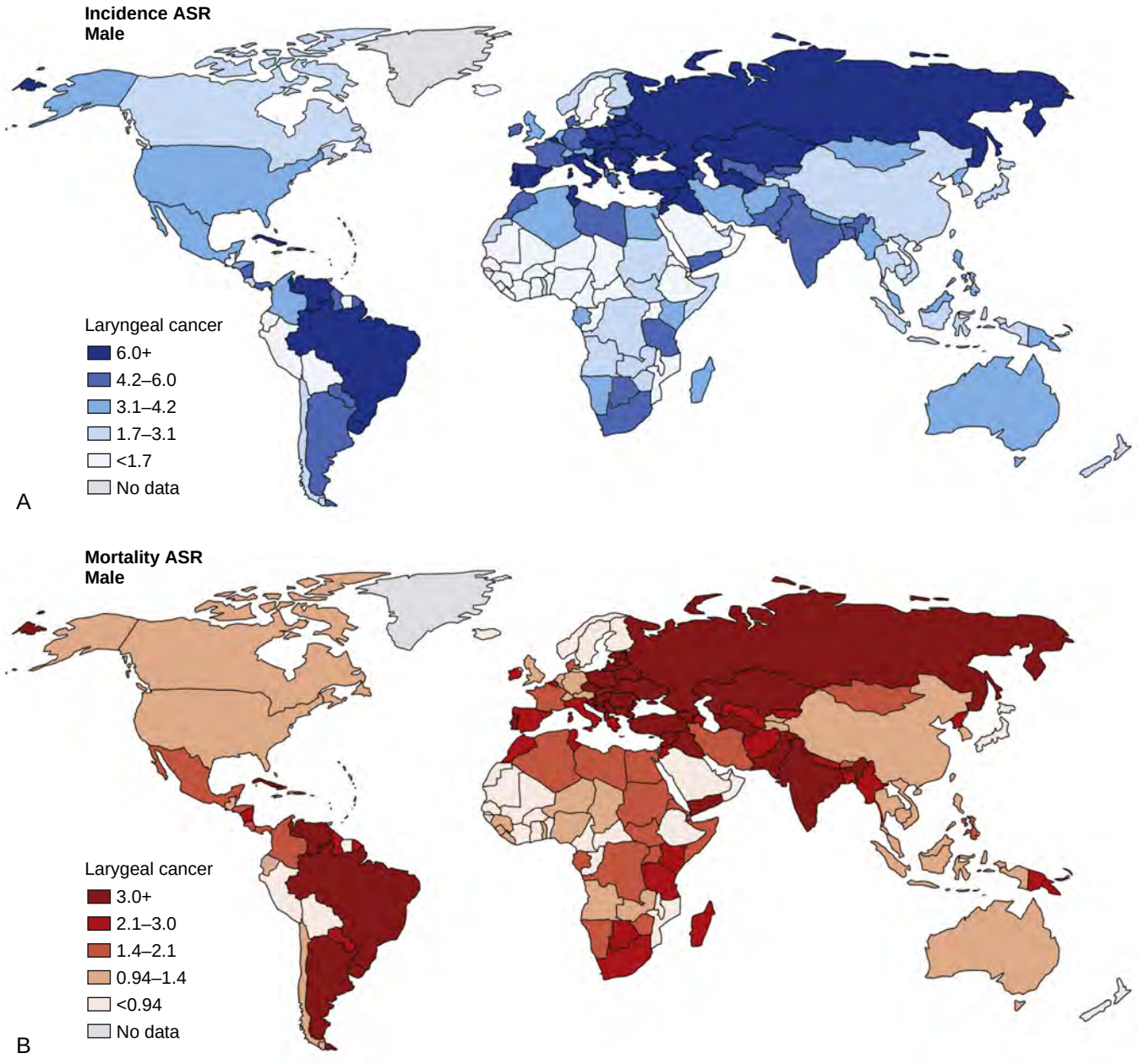
• **Fig. 1.4** **A,** Incidence and **B,** mortality age-standardized rates (ASR) for lip and oral cavity cancer in males, in quintiles, by country. A quick comparison of these maps makes a number of points. The "traditional" high-incidence areas of central Asia and the Indian subcontinent stand out; much of this is a result of betel quid use, with or without smokeless tobacco, plus smoking, sometimes alcohol abuse, and poor diet. Note that parts of both Western and Eastern Europe remain in the top quintile (see text). The African data are not particularly robust. Australia shows a high incidence owing to ultraviolet light–induced lip cancer in a fair-skinned population; mortality rates are not comparably high because lip cancer is comparatively easily treated. Eastern Europe and the former Soviet Republics have high mortality, partly related to low socioeconomic status, limited treatment facilities, and the fact that many patients have substantial comorbidities. As already mentioned, Papua New Guinea and surrounding Melanesian islands of the Western Pacific are in the top quintile both in incidence and mortality; indeed, Melanesia had the highest recorded rates in the world at the beginning of this millennium—associated with chewing of areca nut and tobacco use. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)



• **Fig. 1.5** **A,** Incidence, age-standardized rates (ASR), in females—lip and oral cancers. **B,** Mortality rate, ASR, in females—lip and oral cancers. Note the serious situation in the Indian Subcontinent, much of northern Asia, South America, and parts of the Middle East including the southern provinces of Saudi Arabia and Yemen. In parts of India, oral cancer is the leading cancer among women, because of heavy use of betel quids. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

quality of these data).[2] In India alone, over 100,000 cases of oral cancer are registered every year, and the numbers are rising. Although men predominate overall, among women a very high incidence is found throughout South Central Asia (4.7 per 100,000). In terms of countries, the Maldives and Sri Lanka have the highest incidence of oral cancer in the South Asian region. Poor access to health services contributes to high mortality.

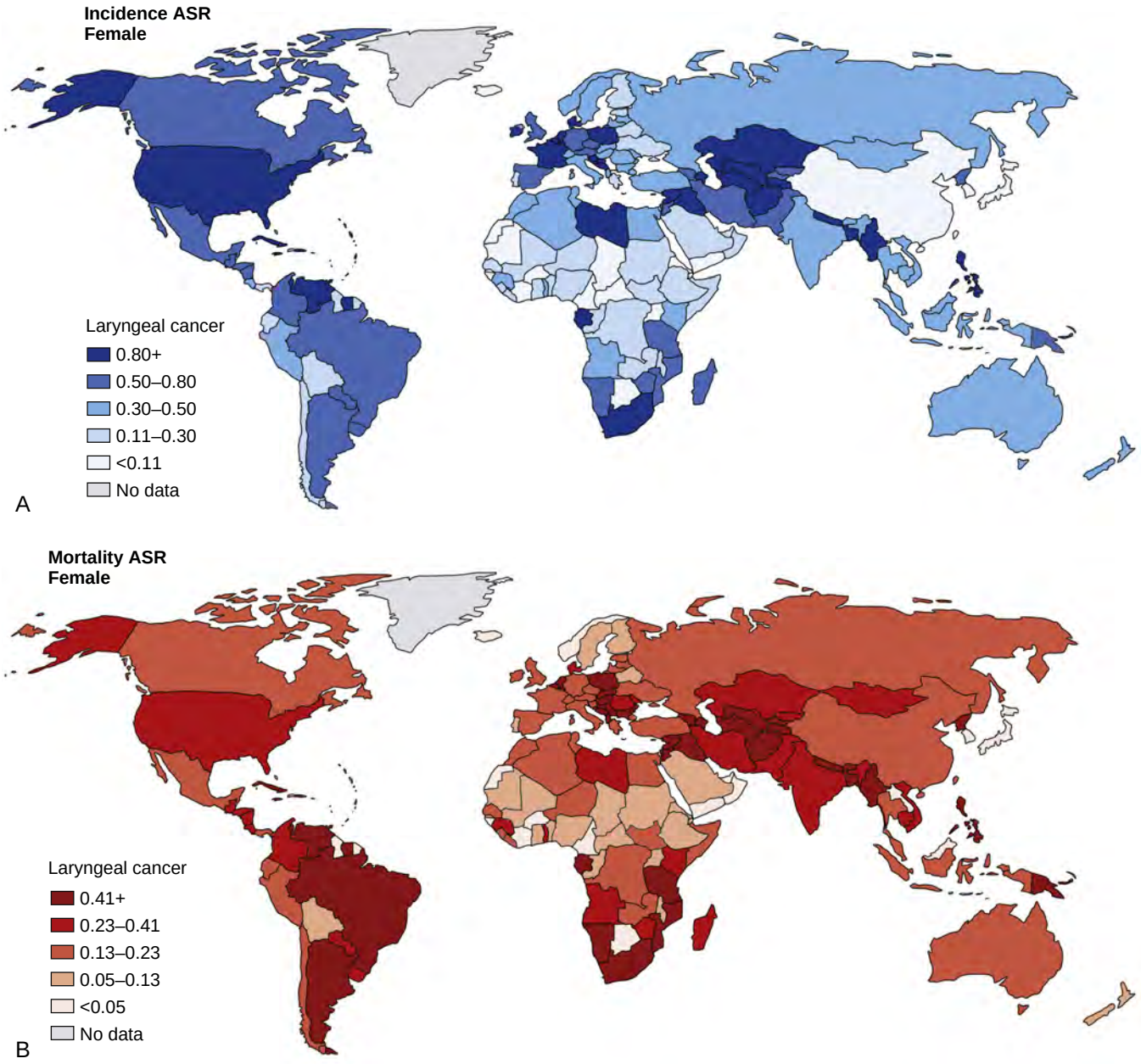
More than 126,000 cases of oral cancer (ICD-10: C00-C08) occur every year in South and Southeast Asia alone, with poor prospects for survival. About 90% of these cases are attributable to smoking and chewing habits. It is encouraging that overall rates in India are showing a decreasing trend in successive birth cohorts; declining trends were observed for mouth (ICD-10: C03–C06) and tongue (C01–C02) cancers among females and tongue cancers among males between 1982 and 2000,[11] and this has continued. However, population growth in the subcontinent means that the disease burden continues to rise. Better primary prevention is essential[12] (Fig. 1.10). There is growing concern that commercial areca nut and tobacco



• **Fig. 1.6** **A,** Incidence, age-standardized rates (ASR), in males—laryngeal cancer. **B,** Mortality, ASR, in males—laryngeal cancer. Rates of laryngeal cancer largely reflect smoking rates in men around the globe, with the surprising exceptions of China and Japan, where incidence **(A)** and mortality **(B)** among men are comparatively low, despite prevalence rates of smoking in males of 50% or higher; however, as noted earlier, Japanese rates are on the rise. The proportionately higher death rate in Eastern Europe, Russia, and the former Soviet Republics is again related to late stage at diagnosis and high rates of comorbidities associated with low socioeconomic status and difficulties with access to care. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

products will contribute to future rises in the incidence of oral submucous fibrosis (OSF) and of subsequent oral cancer.[13]

The overall incidence of smoking-related cancers appears to be decreasing in many parts of the world (Figs. 1.11 to 1.16). For cancers of the oropharynx and tonsils, as well as the hypopharynx, the highest combined incidence rate is currently seen in France, and this is increasing. For women, the highest age-standardized rate (ASR) for mouth and tongue cancer specifically was in India.[6] Data from Japan show a dramatic increase in oral and pharyngeal cancer incidence (ICD-10: C01–C14) for both sexes; there was a 4.4-fold increase for males and 3.8-fold increase for females in the total numbers between 1965 and 1999—noted from data retrieved from the Osaka Cancer Registry.[20] There is also an upward trend for

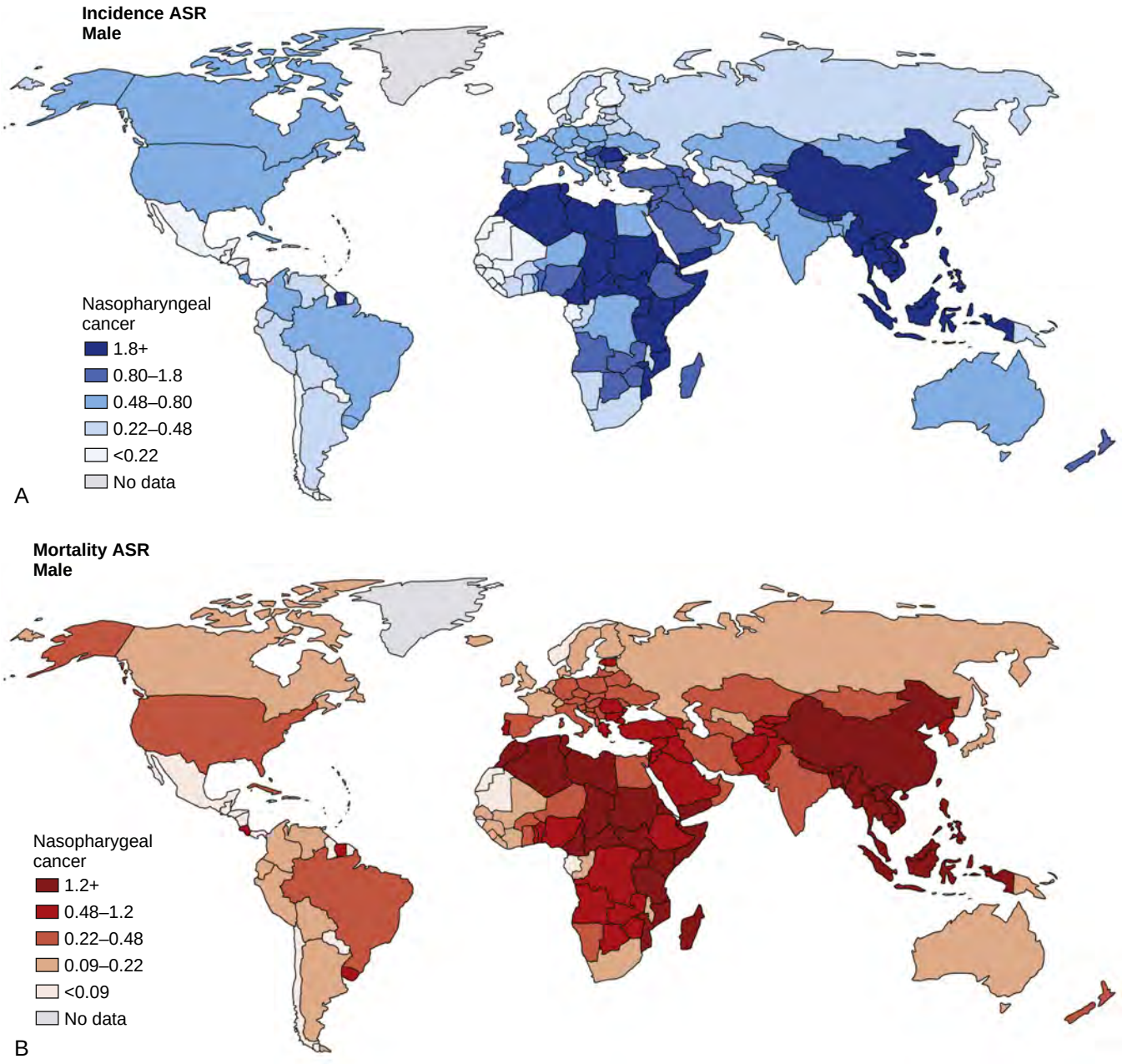


• **Fig. 1.7** **A,** Incidence, age-standardized rates (ASR), in females—laryngeal cancer. **B,** Mortality, ASR, in females—laryngeal cancer. Because smoking is far less prevalent in women than in men in most societies, the laryngeal cancer rates are low worldwide, and less can be read into this aspect of "geographic pathology." Nevertheless, there are clear challenges to be met in much of the continent of South America, in Central Europe, and in the United States. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

both males and females in Australia and among the non-Maori population in New Zealand. Lip cancer in fair-skinned populations, particularly due to UV light, is a growing problem.[21]

A study in Mumbai, India, indicated a decreasing trend in oral cancer incidence among Indian men, which, it was suggested could have been due to a decrease in the use of betel quid or pan and associated oral smokeless tobaccos over this period.[22] However, there continues to be a high prevalence of smokeless tobacco use among young adult men and women, especially in the form of Pan Parag/Gutka-type products, and cigarette smoking is increasing.

In the United States, the estimated numbers of incident cases for tongue, mouth, and other oral cavity cancers in 2008 were 15,250 cases for men and 7650 for women; for the pharynx, the number of incident cases for men was 10,060, and 2350 for women (3% of all cancer cases in men). For cancer of the larynx, 12,250 incident cases were estimated, of which 9680 were in men. The incidence rates for cancers of the oral cavity and pharynx or throat were stable or declining for men and women in most age groups during the period 1973–2003 in the United States, probably related to changes in tobacco

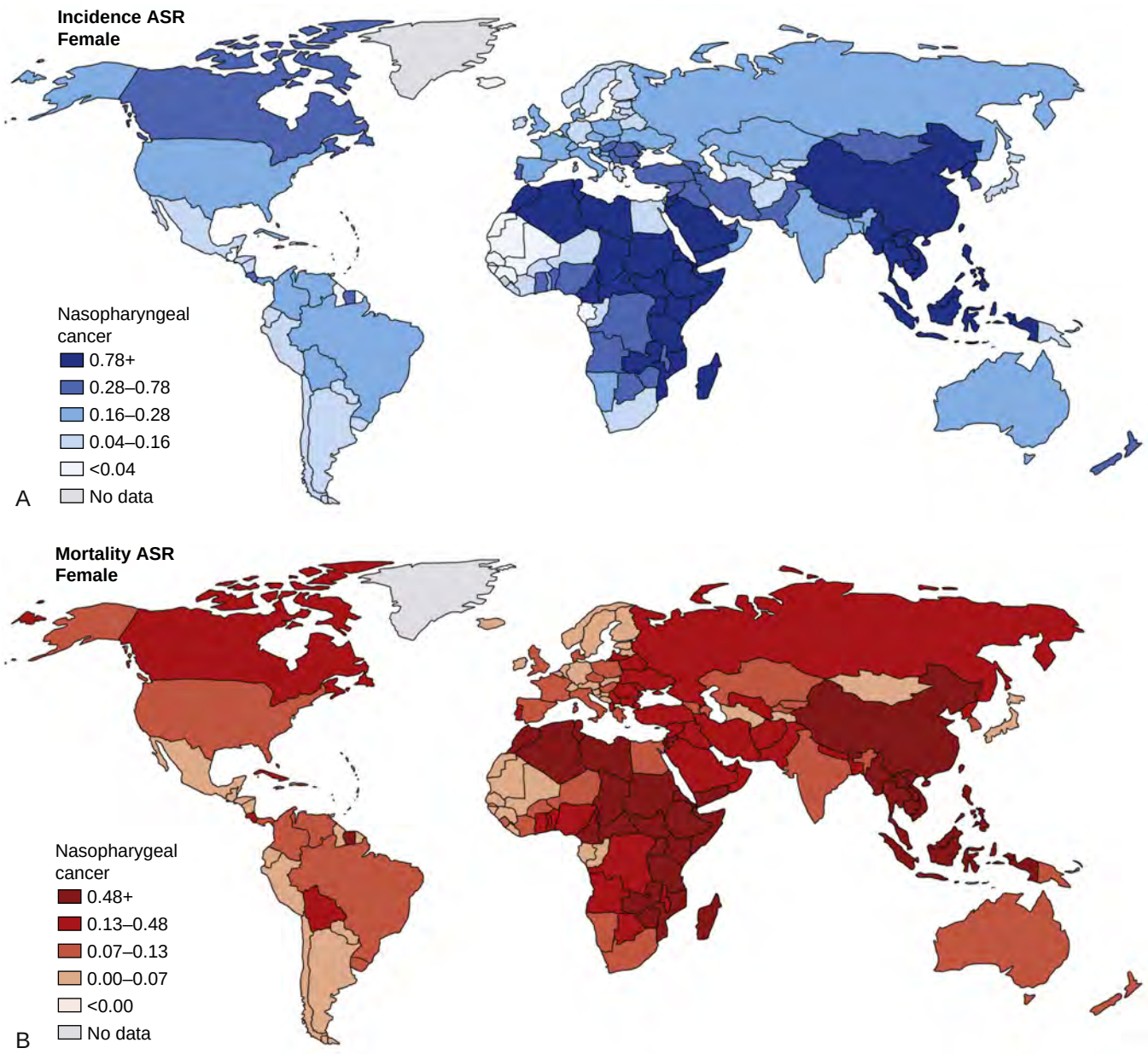


• **Fig. 1.8 A,** Incidence, age-standardized rates (ASR), in males—nasopharyngeal cancer. **B,** Mortality, ASR, in males—nasopharyngeal cancer. Risk factors for nasopharyngeal cancer are comparatively well understood. It is a biologically distinct disease, driven by Epstein-Barr virus, in subjects with genetic susceptibility, compounded by toxins in particular cultural dietary practices. Both incidence **(A)** and mortality rates **(B)** are historically high in North, Central, and East Africa, in Indonesia, and in China—particularly Guangdong Province, Hong Kong, and emigrant communities from these areas. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

and alcohol consumption. This is a highly pleasing situation, common to many countries with advanced care facilities but not reflected in most of the high incidence countries elsewhere in the world. Cancer of the larynx has always been a serious public health problem in nations with high smoking prevalence, and this remains problematic in China and Eastern Europe and the former Soviet Union. Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (see Fig. 1.13).

Sex Differences

Worldwide, the incidence of head and neck cancers overall is higher for males than females. According to the IARC,[2] the age-specific incidences of "oral cavity," "nasopharynx," and "other pharynx" cancers were 5.5, 1.7, and 3.2 per 100,000 population for males in 2012 and 2.5, 0.7, and 0.7 for females, respectively (see Table 1.1). The higher rates in males may result from their greater exposure to the most important risk factors, such as heavy



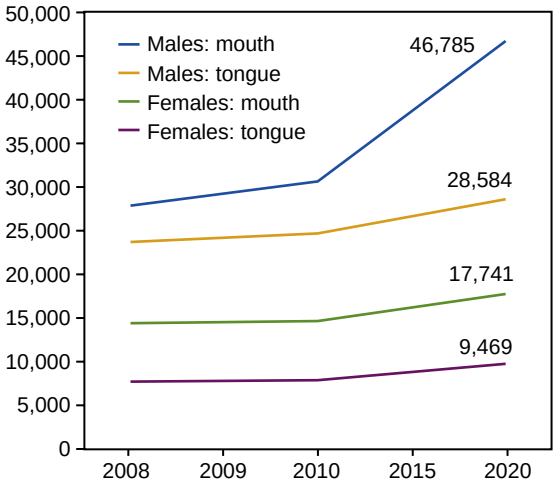
• **Fig. 1.9** **A,** Incidence, age-standardized rates (ASR), in females—nasopharyngeal cancer. **B,** Mortality, ASR, in females—nasopharyngeal cancer. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

alcohol and tobacco consumption for intraoral cancer and sunlight for lip cancer in those who work outdoors. However, oral cancer in females is increasing in some parts of the world. For instance, a study from Argentina showed the male/female ratio to be 1.24:1 for the period 1992–2000 compared with 7.1:1 for the 1950–1970 period.[23] The incidence of tongue and other intraoral cancers for women can be greater than or equal to that for men in high-incidence areas such as India, where betel quid/areca nut chewing (and sometimes smoking) are common among women—although this varies considerably from region to region.

Early this century in Europe, the incidence of oral cavity and pharyngeal cancers (ICD-10: C00–C14) among males varied substantially between 5.9 (Finland) and 32 (France) per 100,000 per annum.[24] Incidence rates among females were highest in Northern and Western Europe but were consistently lower than those for males. The male-to-female ratio decreased during the past 10 years and recently varied from 1.5 to 2.5 in Northern Europe to 7.7 in Lithuania. Between 1990 and 1999, the incidence rates for oral cancers in the United Kingdom rose in males of all ages from 6.5 to 8.3 per 100,000 (an increase of 18%) and in females from 2.6 to 3.6 per 100,000 (an increase of 30%) and continues to be a concern.[25]

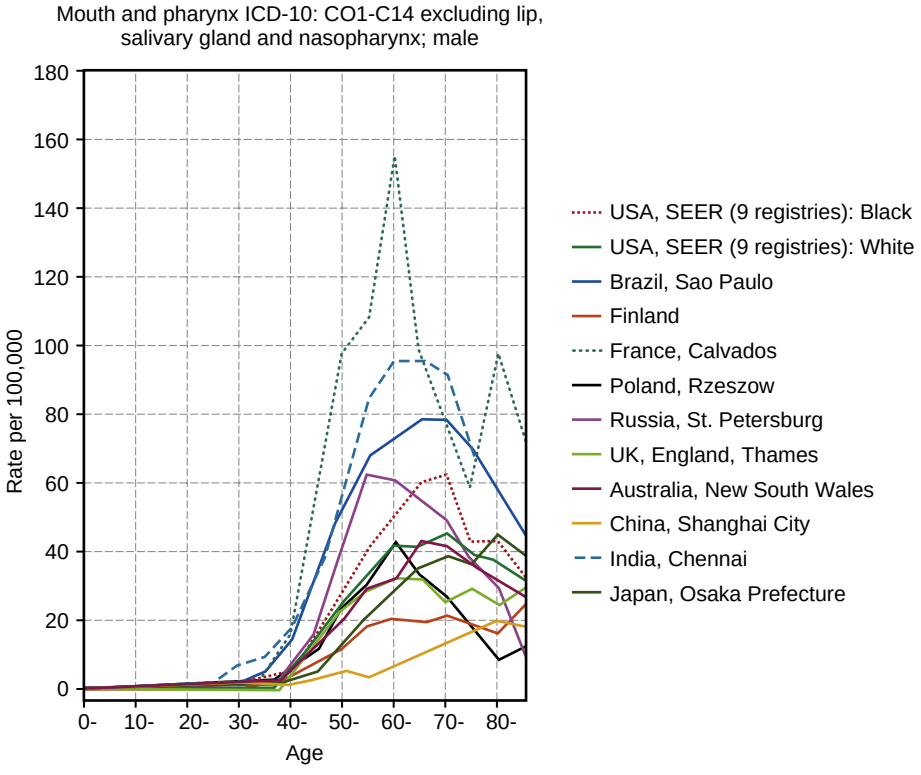
Ethnic Differences

Variations by ethnicity are largely due to social and cultural practices and the influence of dietary and genetic factors, although the latter are less well quantified. Variations in

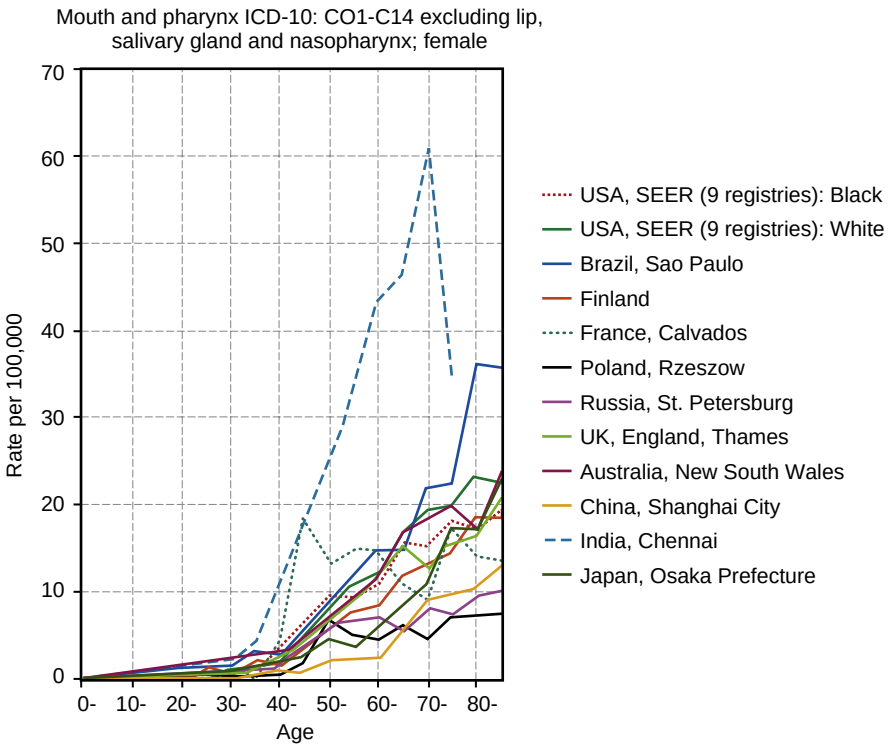


• **Fig. 1.10** Projected increases in the burden of mouth and tongue cancer in India in the next decade. (From Gupta B, Ariyawardana A, Johnson NW: Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. *Int Dent J* 53:12–25, 2013.)

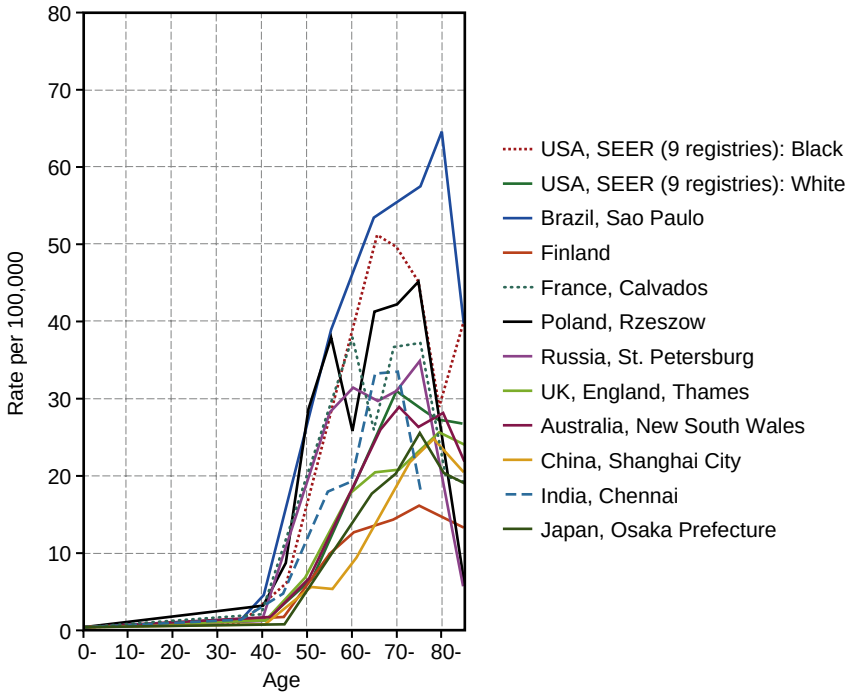
outcome are also affected by differences in access to health care. Where cultural practices represent risk factors, their continuation by emigrants from high-incidence regions to other parts of the world results in comparatively high cancer incidence in immigrant communities. This can also affect the subsites of oral cancer most commonly affected, as shown in a study from California.[26] The highest age-adjusted oral cancer rates in the United States are found among non-Hispanic men (17.5/100,000) followed by non-Hispanic women (6.6/100,000), with Asian and Hispanic populations showing lower incidence rates compared with white (Caucasian) ethnic groups. Tongue cancer was the most common type of oral cancer among every ethnicity. Asians were more likely to develop their malignancy in the buccal mucosa, a reflection of continuing areca and tobacco chewing habits. Another study showed that Native Americans and Alaskan Natives overall had significantly lower incidence rates than non-Hispanic whites.[27] Several studies from the United States have demonstrated that black patients with oral cancer have poorer overall and disease-specific survival than whites, mainly because of their comparatively poor access to health care.[28,29] This is especially concerning because the incidence of oral plus



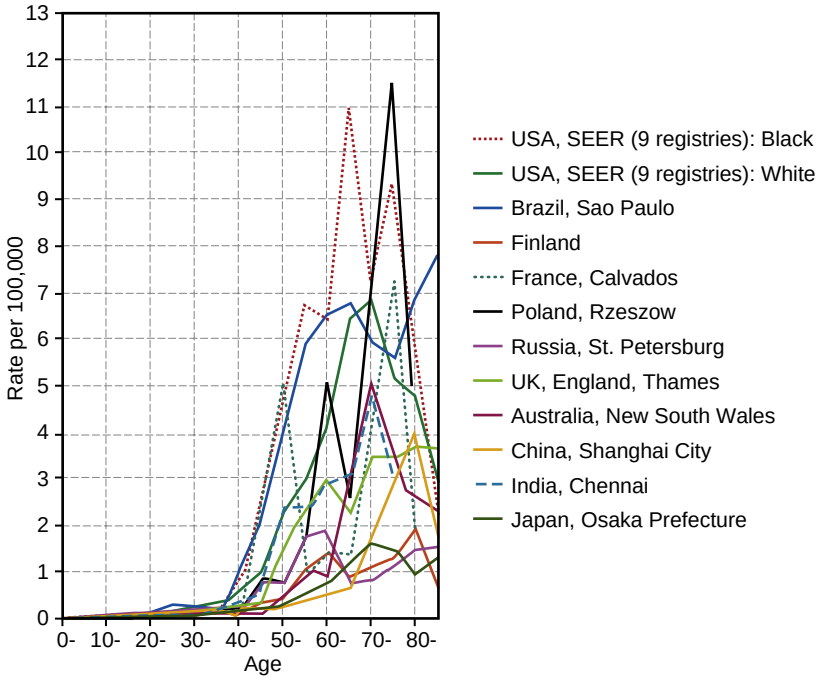
• **Fig. 1.11** Male age-specific incidence curves for oral and pharynx for selected countries. All upper aerodigestive tract cancers show a similar distribution. Most cases occur in the fifth to seventh decades of life, presumably because decades of exposure to tobacco, alcohol, and poor nutrition take time to synergize with other agents in triggering malignant transformation—or in allowing this to survive the host response. Nevertheless, a significant minority of cases appear in the third and fourth decades of life. These attract much interest; although associations with early commencement of smoking and with unsafe alcohol use can be demonstrated, a substantial minority of cases arise without exposure to traditional risk factors. Here, dietary inadequacies and human papillomavirus infection are likely to be important, and inherited predisposition may play a role. *SEER,* Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



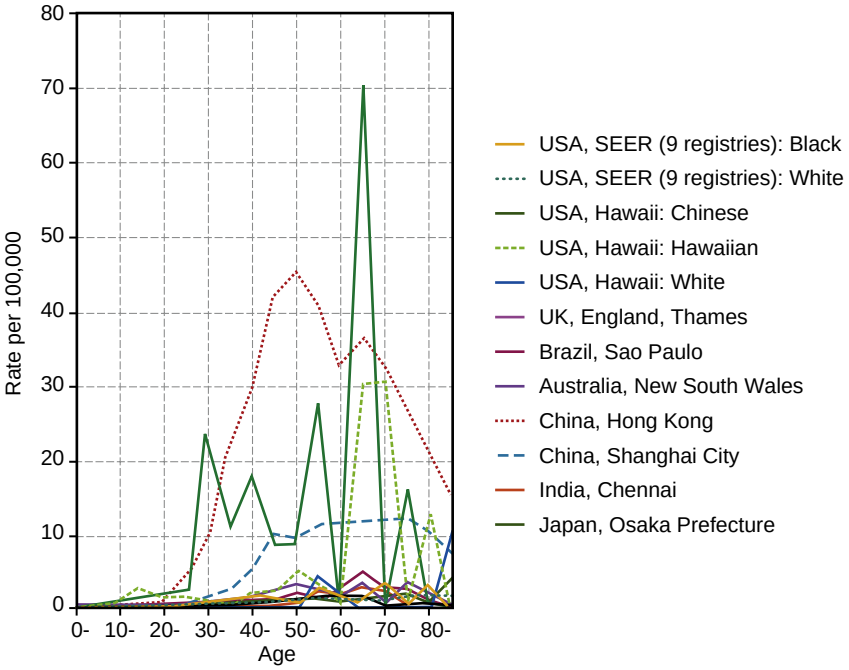
• **Fig. 1.12** Female age-specific incidence curves for oral and pharynx for selected countries. Rates for females are lower, and international differences are less marked. Rates in women in South India stand out; this is related to use of betel quid and tobacco, together with low socioeconomic status. *SEER*, Surveillance, Epidemiology, and End Results. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



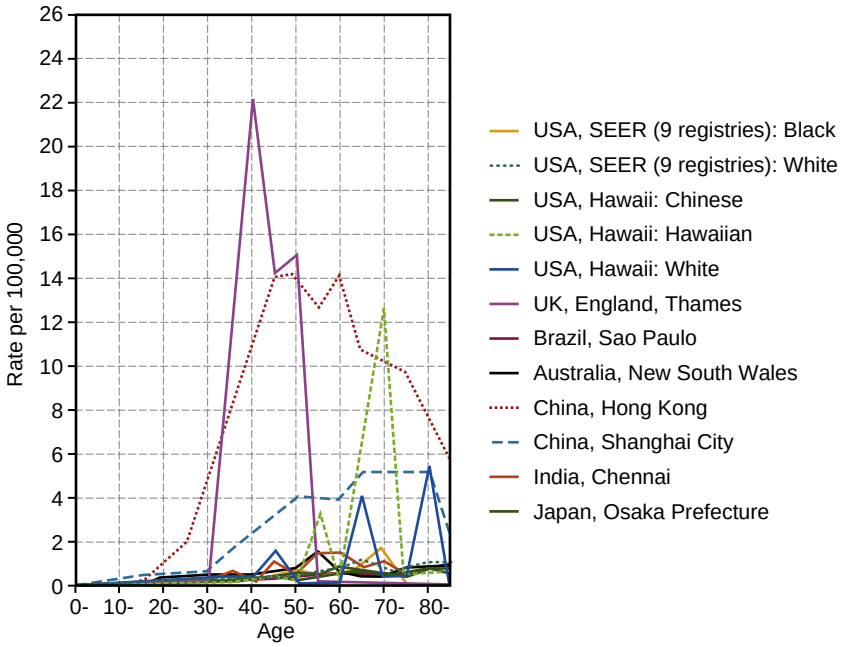
• **Fig. 1.13** Larynx—male. Many of the differences among populations are likely to be explained by smoking and other traditional risk factors. Serious public health challenges exist in the Brazilian example. Poland and the Russian example are consistent with the major concerns we have for Eastern Europe, Russia, and the former Soviet Republics as a whole. Blacks do poorly in the United States. Finland provides encouragement; indeed, this was the first country in the world to reach the World Health Organization target for the year 2000 of having less than 20% of the adult population smoking. Japan and China remain enigmas. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.14** Larynx—female. Although at first glance the spread for women looks larger, the rates are much lower than for men. Poland, as with much of Eastern Europe; American blacks; and Brazil again stand out. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.15** Nasopharynx—male. Nasopharyngeal cancer is a distinct disease. These countries have been chosen to reflect differences by population. Southern Chinese men are particularly susceptible—hence the alarming data from Hong Kong and to a lesser extent from Shanghai. Although the data are fragmentary, the markedly higher rates in Chinese Hawaiians compared with other racial groups are consistent with the ethnic bias. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.16** Nasopharynx—female. The highest rates of nasopharyngeal cancer in women are in Chinese women. *SEER,* Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

pharyngeal cancer for black men in the United States is so high, and the oropharynx is the sixth most common site for malignant disease in this group.[30]

In the Republic of South Africa, among Asian/Indian South Africans, oral and oropharyngeal cancer age-specific incidence rates (ASIR) were higher among females (ASIR, 4.60) than among males (ASIR, 3.80). Excluding those involving the lip, these cancers were highest among Coloureds (ASIR, 5.72) and lowest among blacks (ASIR, 3.16). Incidence rates increased significantly among Coloured South Africans over the period from 1992 to 2001 ($p < .05$), particularly for the oropharynx (available at http://repository.up.ac.za/bitstream/handle/2263/32412/AyoYusuf_Trends(2013).pdf?sequence=1).[30a] The age-adjusted incidence rate for oral and pharyngeal cancers is higher for South Asians than for other residents in England, particularly among females.[31] It is interesting to note that this study showed that British South Asian males have significantly better survival than their non–South Asian peers in the southeast of England, possibly a reflection of the more indolent progress of tobacco- and areca nut–induced lesions.[31]

Overall, there is an approximately 4- to 10-fold difference in HNSCC incidence among ethnicities, with disturbingly high rates in northwest France, Brazil, and South India. Note the much worse situation in American blacks compared with whites, explained by a mixture of risk-factor and socioeconomic reasons. Finland does comparatively well—not surprising in view of that nation's success in reducing the prevalence of smoking, though alcohol abuse remains a social problem. What is surprising are the low rates recorded for Shanghai, in spite of high smoking prevalence in this large city. China is currently developing a more comprehensive, nationwide cancer registry system, so more cogent data will soon be available.

Age Distributions

HNSCC is usually a disease that occurs in men after the fifth decade of life. The mean age at presentation is in the fifth and early sixth decades in Asian populations compared with the seventh and eighth decades in the North American population.[32–39] Statistics in the United States for 1975–2011 show that the median age at diagnosis for cancer of the oral cavity and pharynx was 62 years.[38]

Several studies have suggested that 4–6% of oral cancers now occur at ages younger than 40 years.[39] An alarming increase in incidence of oral cancers among younger people has been reported from many parts of the world,[40–43] a trend that appears to be continuing and is likely related to the increase in prevalence of HPV infection, which will be further explored in the second part of this chapter. There was a significant increase in the incidence of cancers in the tongue and tonsil among 20- to 40-year-olds in the United States between 1973 and 2001.[44] In Germany, Czechoslovakia, and Hungary, within one generation there has been an almost 10-fold rise in mortality from oral cancer in men aged 35–44.[45] Robinson and Macfarlane showed a dramatic increase in incidence rates for younger males in Scotland from the 1980s to the 1990s.[46] In the high prevalence areas of the world, in many cases patients are less than 40 years old, probably owing to heavy use of various forms of tobacco from an early age, although some recent data from India have not shown this.[47]

It is also clear that a number of cases of SCC occur in both young and old patients in the absence of traditional risk factors; in these patients the disease may pursue a particular aggressive course, more so in the elderly. A study conducted in southern England concluded that in a substantial proportion of cases of

younger people diagnosed with oral cancer, the disease occurs in the absence of known risk factors.[48] This, together with the relatively short duration of exposure in users, suggests that factors other than tobacco and alcohol are implicated in the development of oral cancer in a significant minority of cases. Diets poor in fresh fruits and vegetables were identified as conferring significant risk. There is now substantial evidence that HPV infections are driving this rise in younger adults; fortunately, HPV-related oropharyngeal cancers respond well to radiotherapy, permitting treatment deescalation and improved quality of life. It is also suggested that greater attention should be paid to familial antecedents of malignant neoplasms in younger patients with oral cancer.[49]

Mortality Trends

Current WHO mortality and trends of age-standardized (world population) mortality rates for the head and neck cancer sites of interest, within selected countries over the past three to six decades,[50] are presented in Table 1.2 and Figs. 1.17 to 1.22. Death rates for oral and pharyngeal cancer in males around the world are shown vividly in Fig. 1.17. There was a steady rise in oral cancer mortality in men from the 1950s to the late 1980s in most Western European countries[51]; rising rates have declined since that time in France, China, and Hong Kong, which had exceedingly high rates in the past. Unfortunately, in most countries in Central and Eastern Europe, oral cancer mortality in men continued to rise, reaching exceedingly high rates in Hungary, Slovakia, Slovenia, and the Russian Federation at the end of the past century. Hungary, Ukraine, Estonia, and Bulgaria showed more than a 100% increase in mortality rates for men during the 20-year period up to the turn of the millennium. Even though the rates of oral cancer are comparatively low among women (see Fig. 1.18), there was an increase in several countries in Europe (notably Hungary, Belgium, Denmark, and Slovakia) over this period. These disturbing rises are thought to have been related to high drinking and smoking patterns in these societies, together with poor diet in lower socioeconomic groups. Fortunately, improvements are now evident. Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (see Figs. 1.19 and 1.20). Trends for nasopharyngeal cancer, both good and bad, are shown for high-incidence countries (see Figs. 1.21 and 1.22).

In Europe, Hungary has the highest incidence and mortality of oral and pharyngeal cancer for both sexes.[52] Between 1984 and 1994, the Hungarian mortality rates for oral cancers rose by 83.5% and 72.3% in males and females, respectively, but this has now stabilized. Trends in the mortality rate among Italian and French males peaked in the 1980s, and rates decreased after 1990.[53] However, some persisting upward trends were registered for Belgium, Denmark, Greece, Portugal, and Scotland.[54] In the United States, the mortality rates per 100,000 population per annum for cancer of the oral cavity and pharynx for men were 5.61 in 1990 and 3.98 in 2004, the absolute decrease being 1.63 per 100,000, contributing to a 3% reduction in mortality for all sites. For women, the decrease across the same period was 0.56, contributing to a 2.5% reduction for all sites.[11]

In the United States, mortality from HNSCC appears to be declining. The death rates for cancer of the oral cavity and pharynx per 100,000 population in 2007–2011 were 3.8 for males and 1.4 for females,[12] down from 6.9 and 2.3, respectively, in 1975. This substantial improvement is not reflected in most of the rest of the world. The SEER Program in the United States reported an overall fall in the mortality from oral and pharyngeal cancer, between 1975 and 2004, of 1.87% per annum (Fig. 1.23). Table 1.3 shows a fall in all mortality rates for oral and pharyngeal cancer in the United States between 2002 and 2011. There was considerable fall in mortality among both black men and black women (annual percent change of −3.7 and −2.7, respectively). Furthermore, the SEER data show higher 5-year relative survival rates for whites (64.3%) and blacks (43.7%), who were diagnosed during the period 2004–2011 than for those who were diagnosed during the period 1974–1976 (when rates for whites and blacks were 55% and 36.3%, respectively).[13] The 5-year survival rates in the SEER registries range from a high of 72.1% for white women in Utah to a low of 24.8% for black men in metropolitan Atlanta. These striking differences are likely to be explained by a number of factors including socioeconomic condition, age, stage at diagnosis, continued presence or absence of environmental risk factors, and access to hospital services. African American patients have consistently poorer survival outcomes.[55]

What the SEER data do make clear is that there has been very little improvement in overall survival (OS) for patients with cancer of the oral cavity and larynx, whereas substantial improvement has been witnessed in cancer of the oropharynx (Fig. 1.24). Although this improvement was initially thought to be related to improved therapeutic modalities, it is now clear that it was the disease that changed and not the therapy. Non–HPV-related cancers continue to be associated with a poor prognosis, and better treatments are needed. The favorable response rates to conventional therapy associated with HPV-related oropharyngeal cancer have made de-escalation of treatment a high priority for clinicians.

Indeed, population-based survival rates around the world show little evidence of improvement over recent decades, despite vast improvements in treatment modalities. Cure rates and survival rates have improved with advances in surgical and other techniques in highly specialized, high-volume treatment institutions. Regrettably, such highly expert management is not yet uniformly available, and it may be decades before these results are reflected in population trends.

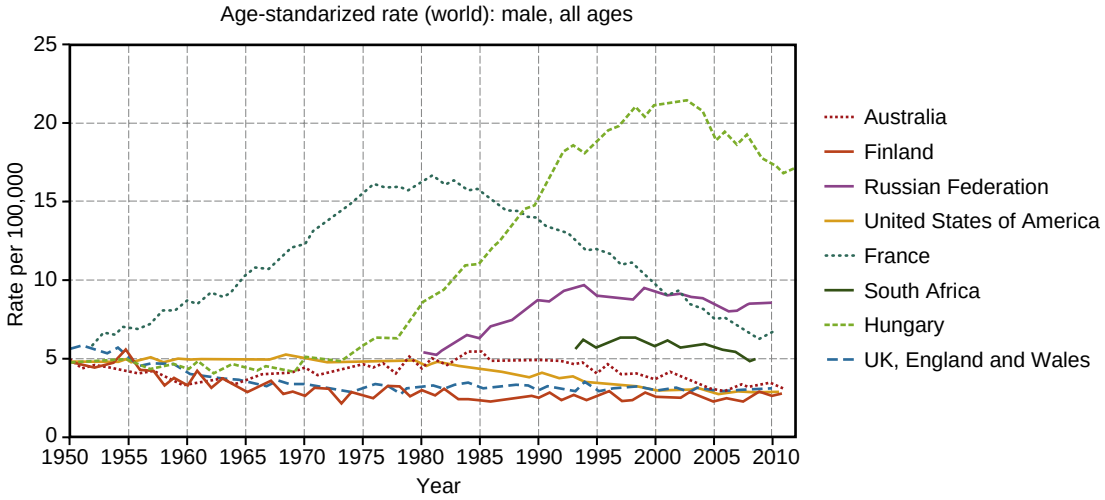
Mortality Trends by Birth Cohort and Forward Projections

Birth cohort statistics are a valuable way for interpreting time trends. Cases of particular cancers are transformed back, in 5-year age groups, to the date of birth of the affected individuals. Curves derived from the WHO mortality database for particularly instructive countries are given in Figs. 1.23 to 1.26.[51] In general, these show that for most UADT cancers in most

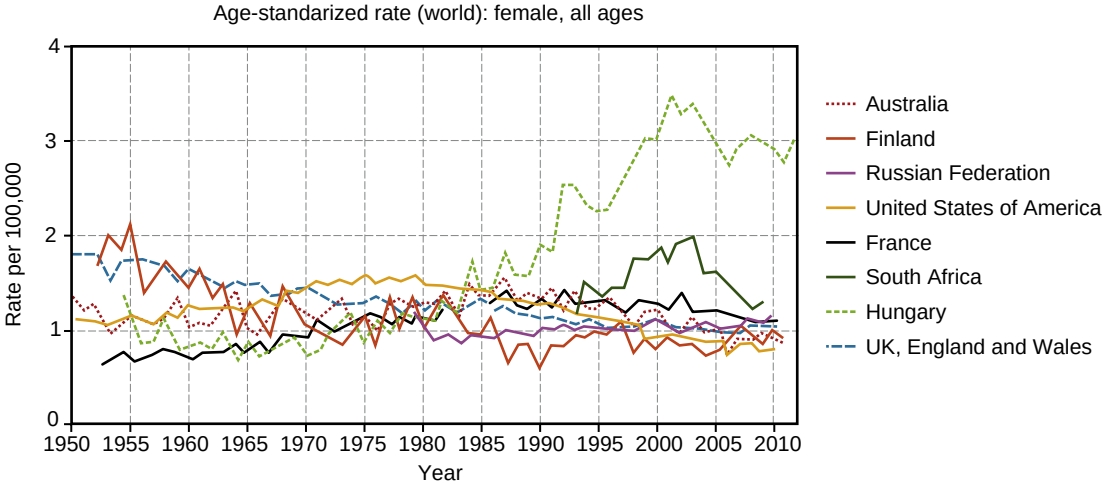
TABLE 1.2 Mortality Data Extracted from the GLOBOCAN 2012 Database, for Comparison with the Incidence Data in Table 1.1

Country	Mouth (ICD-10 : C00–C08)		Nasopharynx (ICD-10: C11)		Other Pharynx (ICD-10: C09–C10, C12–C14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
	Lip, all of tongue, all of mouth, and major salivary glands		Data for C30, Malignant neoplasm of nasal cavity and middle ear; and for C31, Malignant neoplasm of accessory sinuses; and for C32, Malignant neoplasm of larynx, are not included here		Tonsil, remainder of oropharynx, pyriform fossa, hypopharynx, and sites not otherwise specified among C00–C13		Cancer of the supraglottic, glottic, and subglottic larynx		This code excludes cancers arising at the gastroesophageal junction which are included in stomach cancers, the majority of which are adeno-carcinomas; included here, therefore, are mostly SCCs sharing common risk factors with the mouth	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
World	2.7	1.2	1.0	0.4	2.2	0.5	2.0	0.2	7.7	2.7
More developed	2.3	0.6	0.2	0.1	2.2	0.3	2.2	0.2	5.2	0.9
Less developed	2.8	1.4	1.3	0.5	2.2	0.5	2.0	0.3	9.0	3.6
Africa	2.1	1.3	1.1	0.6	0.9	0.4	1.5	0.2	5.3	3.3
Eastern Africa	3.2	1.9	1.4	0.9	0.9	0.5	1.5	0.2	11.2	7.3
Middle Africa	2.9	1.4	1.1	0.6	1.6	0.6	1.1	0.2	4.0	1.8
Northern Africa	1.3	0.8	1.4	0.6	0.6	0.6	2.0	0.2	2.3	1.4
Southern Africa	2.8	1.0	0.2	0.1	2.2	0.6	2.5	0.4	12.8	6.2
Western Africa	1.2	1.0	0.6	0.3	0.5	0.1	0.9	0.1	0.8	0.4
Caribbean	2.0	0.6	0.3	0.1	2.4	0.6	4.0	0.5	4.1	1.0
Central America	0.8	0.5	0.1	0.0	0.7	0.2	1.5	0.2	1.6	0.5
South America	2.2	0.7	0.2	0.1	2.2	0.4	3.3	0.4	5.6	1.5
Northern America	1.2	0.5	0.2	0.1	1.2	0.3	1.2	0.2	5.0	1.0
Asia	3.0	1.4	1.4	0.5	2.4	0.5	1.9	0.2	9.9	3.8
Eastern Asia	1.1	0.5	1.5	0.6	0.7	0.1	1.1	0.1	14.1	4.5
Southeastern Asia	1.9	1.2	3.8	1.4	2.1	0.5	1.3	0.2	3.3	0.9
South Central Asia	6.3	3.0	0.4	0.1	5.3	1.2	3.0	0.4	6.0	3.6
Western Asia	1.0	0.6	0.7	0.3	0.6	0.3	2.9	0.4	2.7	1.9
Europe	3.0	0.7	0.3	0.1	2.7	0.4	3.0	0.2	4.9	0.9
Central and Eastern Europe	5.1	0.7	0.3	0.2	3.8	0.3	4.9	0.2	5.0	0.6
Northern Europe	1.7	0.7	0.2	0.1	1.4	0.3	1.3	0.2	7.2	2.3
Southern Europe	1.9	0.6	0.3	0.1	1.8	0.3	2.9	0.2	2.8	0.5
Western Europe	2.0	0.6	0.2	0.1	2.7	0.5	1.5	0.2	5.0	1.2
Australia	1.3	0.6	0.2	0.1	1.2	0.3	1.0	0.1	4.7	1.3
New Zealand	1.4	0.7	0.3	0.1	1.0	0.2	0.8	0.1	4.4	1.6
Melanesia	14.4	10.2	0.3	0.1	2.8	0.4	1.9	0.4	3.4	1.4
Micronesia	2.0	0.0	1.3	1.0	0.0	0.0	1.1	0.0	3.3	0.0
Polynesia	1.4	0.0	0.6	0.0	2.0	0.3	2.0	0.7	3.0	0.3

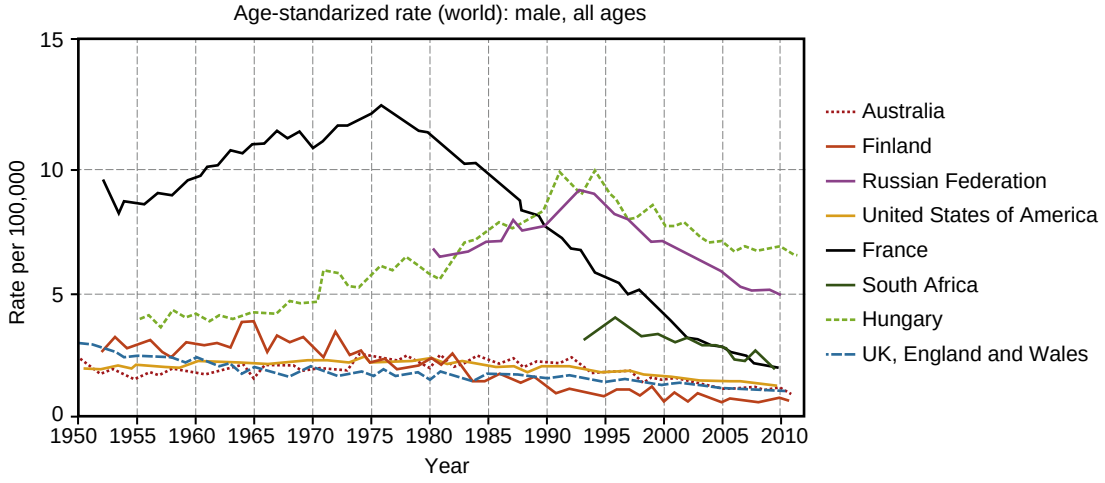
Adapted from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.
SCC, Squamous cell carcinoma.



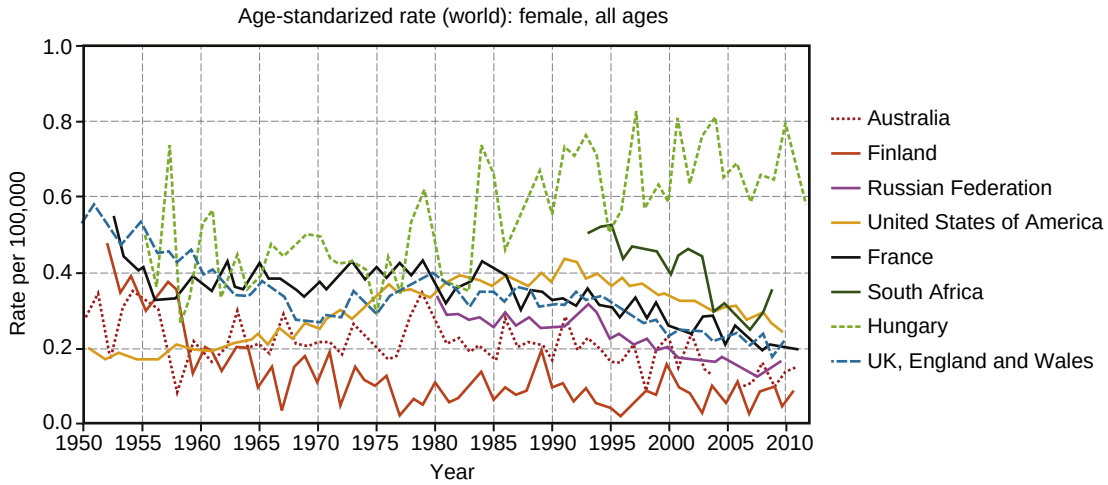
• **Fig. 1.17** Mortality from lip, oral cavity, and pharynx cancer—male. Trends in mortality over time are important to track and to understand. Mortality rates in Hungary are high, although a declining trend is evident from the year 2003. Russia remains a concern. France demonstrates what can be achieved. The overall modest downward trend in the other countries illustrated is encouraging. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



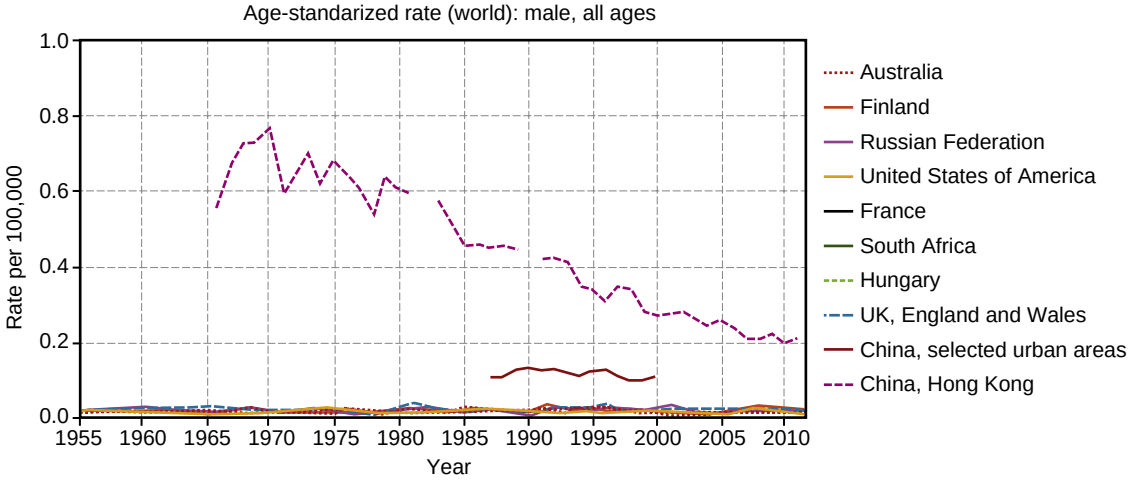
• **Fig. 1.18** Mortality from lip, oral cavity, and pharynx cancer—female. Although only approximately a tenth of the mortality rate in males, mortality rates in Hungarian females remain a challenge. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.19** Mortality from laryngeal cancer—male. Another success demonstrated for France, followed by healthy trends for the Russian Federation and Hungary. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.20** Mortality from laryngeal cancer—female. This is a "noisy" curve because of the comparatively low mortality rates in women. Worryingly, but not surprisingly, it suggests an upward trend in Hungary. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

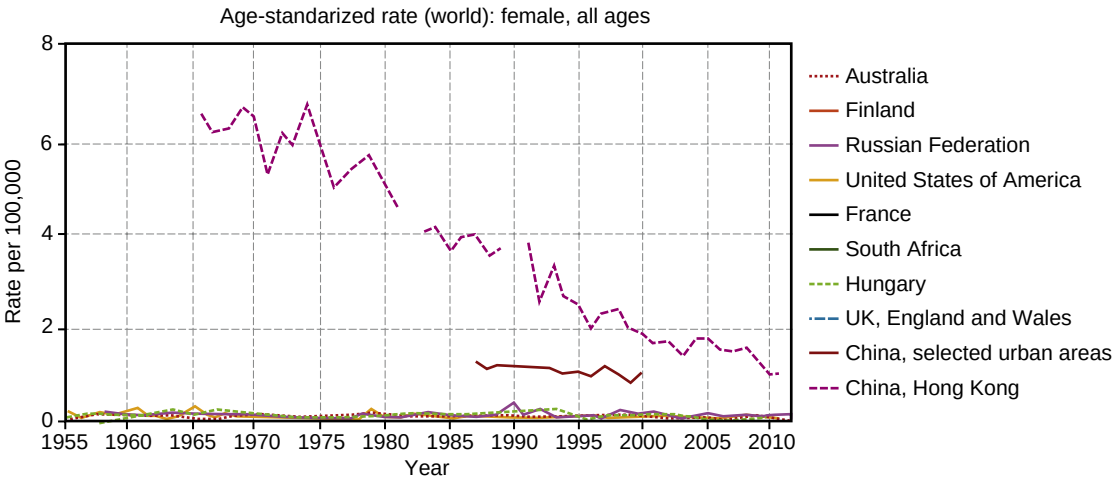


• **Fig. 1.21** Mortality from nasopharyngeal cancer—male. It is hoped that the successes in Hong Kong can be replicated in other high-risk groups. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

developed countries, rates fell in the later part of the 19th and early part of the 20th centuries. This trend has continued in, for example, the United States (see Fig. 1.23) and the United Kingdom (Fig. 1.25). However, in Hungary (Fig. 1.26) (and the same is true for most of Eastern Europe, Russia, and the former Soviet Republic), those born in the first half of the 20th century showed alarming rises in death rates. All members of these birth cohorts have now died, or they are in the highest-risk age groups; in these countries, we have thus seen a growing epidemic of UADT cancer. Indeed, the increasingly aging populations in many countries mean that crude rates, and thus disease burden, will continue to rise, as seen in the data from the United States and United Kingdom (see Fig. 1.23 to Fig. 1.25). It is encouraging to note that the curves now indicate that Hungary, for example, is showing control in younger people (see Fig. 1.26).

Etiology of Head and Neck Cancer

The majority of OSCCs are related to tobacco in various forms, betel quid chewing, heavy alcohol drinking, and dietary micronutrient deficiency. There is a clear dose-response relationship. Nevertheless, in the West, a distinct subgroup of patients without these traditional risk factors exists—predominantly elderly women in whom etiologic factors are not clear. In the developing world, use of tobacco and areca nut, either alone or in combination, accounts for the vast majority of oral cancers and OPMDs. WHO has classified areca nut, a common



• **Fig. 1.22** Mortality from nasopharyngeal cancer—female. From a lower initial base, Hong Kong women share this success story. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

component of many different chewing habits, as carcinogenic to humans. UV radiation is relevant to lip cancer, and there is increasing evidence regarding the role for "high-risk" genotypes of the HPV family, especially for cancer of the tonsil, base of tongue, and other oropharyngeal sites.

Betel Quid

A betel quid generally contains betel leaf, areca nut, and slaked lime, and may contain tobacco. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added according to local preference.[11]

Betel Leaf

The leaves of the *Piper betel* vine (a member of the pepper family) contain betel oil, a volatile liquid, which contains several phenols including hydroxychavicol, eugenol, betel phenol, and chavicol. These compounds may to some extent be protective, sharing some of the antioxidant properties of many plant polyphenols. Vitamin C, a large amount of carotene, and 36 trace elements have also been reported in the betel leaf—clearly beneficial micronutrients.[56]

Betel Inflorescence

Apart from the leaf, other parts of the vine such as the stem and inflorescence (the flowers or pods; catkins) are also consumed with areca nut. Consumption of the inflorescence is common in Melanesia and parts of Taiwan and in China, and it is mostly added to the quid for its aromatic flavor.[11] Betel inflorescence contains a high concentration of phenolic compounds including hydroxychavicol, eugenol, isoeugenol, eugenol methyl ester, and safrole. Safrole itself, a major phenolic compound, is classified as a weak carcinogen in rats and is banned as a food and cosmetic additive by the FDA in the United States, inter alia; however, there is no direct evidence for its carcinogenicity in humans.

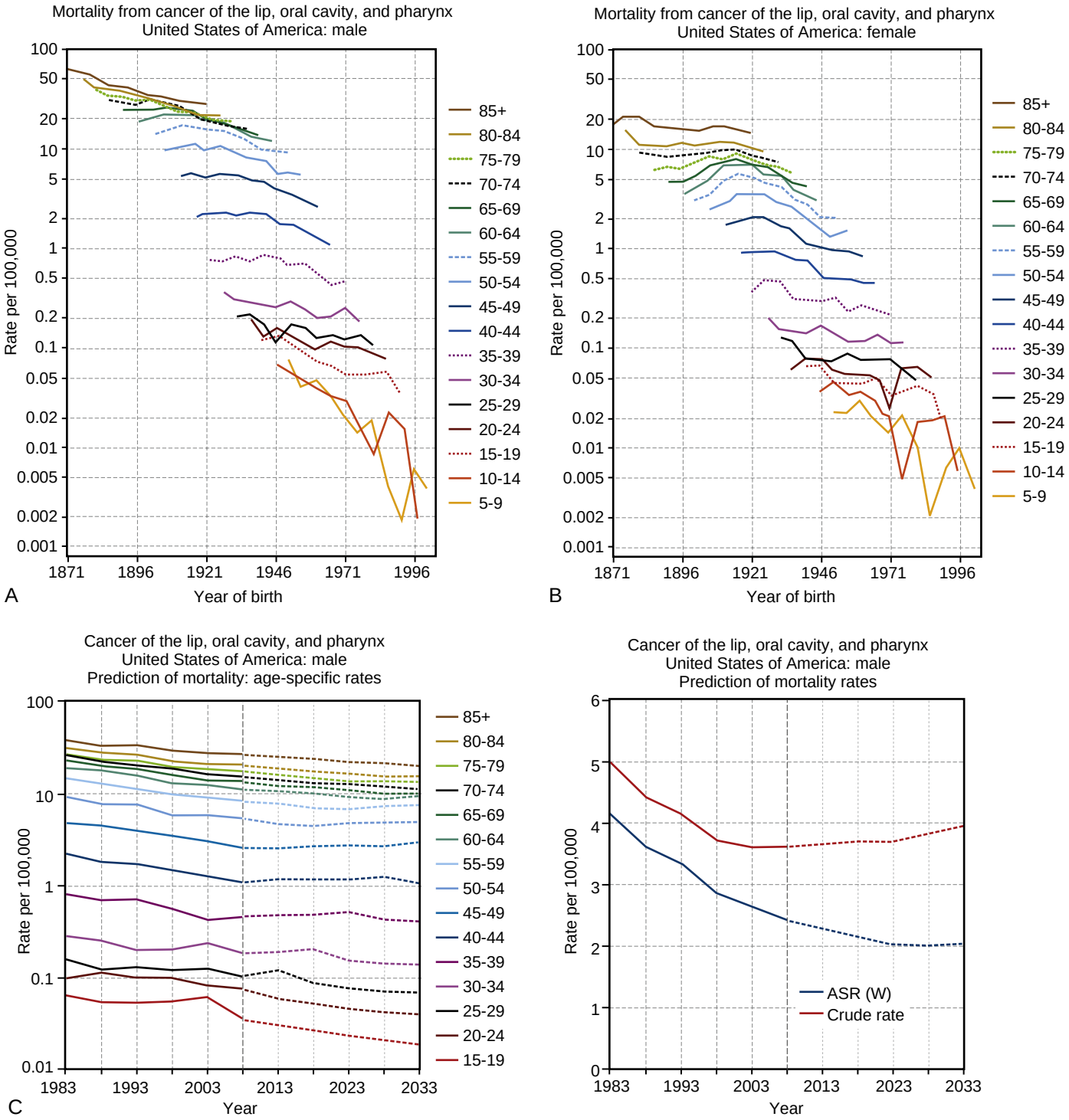
Areca Nut

Areca nut is the seed of the fruit of the oriental palm *Areca catechu.* It is the basic ingredient of a variety of widely used chewed products. The consumption of areca nut is indigenous to India, Sri Lanka, Bangladesh, Myanmar, Taiwan, and numerous islands in the South Pacific. It is also popular in parts of Thailand, Indonesia, Malaysia, Cambodia, Vietnam, Philippines, Laos, and China and in emigrant communities from these countries. It is believed that *A. catechu* may be native to Sri Lanka, West Malaysia, and Melanesia. Areca nut is used as a masticatory substance by approximately 600 million people worldwide. It is estimated that 10–20% of the world's people chew areca nut in some form, often mixed in betel quid (pan).[57] Patterns of use across South and Southeast Asia[58] and the growing public health problem across the Pacific Islands have been extensively documented.[59]

Screening in Saipan and Guam has shown a prevalence of OPMDs of almost 20% among users of betel when other ingredients were added.[60]

The major constituents of the nut are carbohydrates, fat, proteins, fiber, polyphenols (flavonols and tannins), alkaloids, and mineral matter. Among the chemical constituents, alkaloids are the most important chemical. The nut has been shown to contain at least six related alkaloids, of which four (arecoline, arecaidine, guvacine, and guvacoline) have been conclusively identified.[61]

Nitrosamine derivatives from each of the four major areca alkaloids are produced by nitrosation of the alkaloids in dried stored nuts, in the mouth, and especially in the acid conditions found in the stomach, in the presence of nitric oxide generated by bacterial action. Two of these derivatives are accepted as carcinogenic in animal studies, especially MNPN

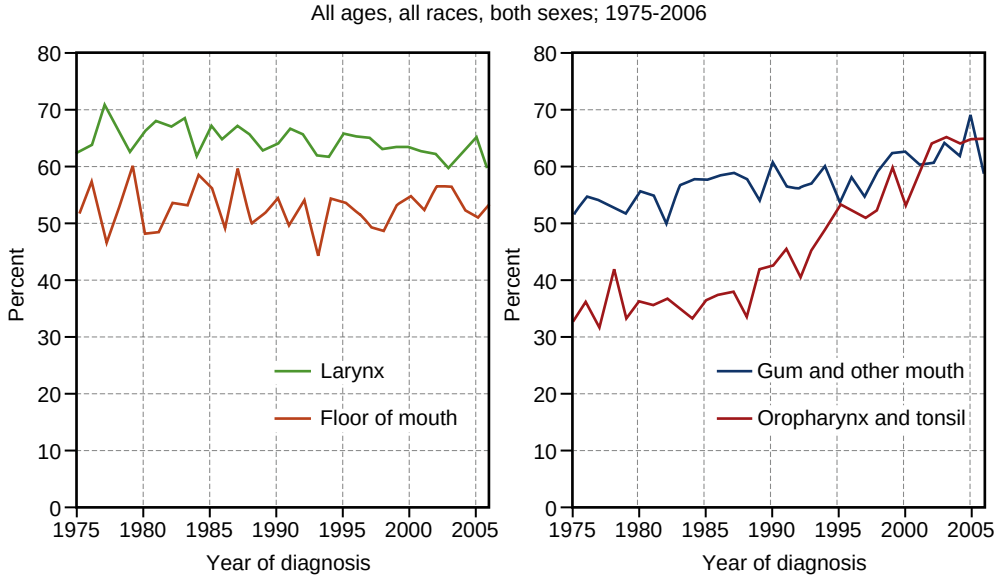


• **Fig. 1.23 A,** Mortality from oral cancer, United States—male. **B,** Mortality from oral cancer, United States—female. Trends in mortality rates for cancers of the lip, oral cavity, and pharynx combined in American women born between approximately 1870 and the turn of the 21st century. There has been a steady decline at all ages, most marked in the youngest cohorts. **C,** Age-specific mortality from oral cancer, United States—male. There has been a steady decline at all ages, most marked in the younger cohorts. This presentation of the age-specific mortality rates for lip, oral cavity, and pharyngeal cancers combined for U.S. males confirms the data above. Although there have been declines in all age groups, projections show rising disease burden in the decades ahead because of the aging of the population. *ASR(W),* Age-standardized incidence rate (world). (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

TABLE 1.3 Mortality Trends (Annual Percentage Change) for Oral and Pharyngeal Cancer in the United States Between 2002 and 2011, by Race and Sex

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	−1.0*	−0.9*	−1.5*	−0.6*	−0.4*	−1.3*	−3.4*	−3.7*	−2.7*

Data from Surveillance, Epidemiology, End Results (SEER) program. Cancer Statistics review, 1975–2011, published in 2014.
*Indicates that the annual percentage change in rate is statistically significantly different from zero ($p < .05$).



• **Fig. 1.24** Five-year relative survival comparison of primarily human papillomavirus (HPV)–unrelated cancers, floor of mouth, gum and other mouth, larynx vs. primarily HPV-related cancers (oropharynx). (From Surveillance, Epidemiology, and End Results (SEER) data, 1975–2010.)

(methylnitrosaminoproprionitrile). Endogenous nitrosation is significantly higher in subjects with poor oral hygiene as determined by volumes of dental plaque.[62] This implies that, on the basis of the availability of substrates from both areca nut and tobacco, there is a more extensive formation of nitrosamine in subjects with poor oral hygiene if they also chew tobacco.[63] Moreover, direct evidence that reactive oxygen species (ROS), such as the hydroxyl radical (HO), are generated in the oral cavity owing to auto-oxidation of polyphenols contained in areca nut and enhancement by the alkaline pH from slaked lime has been reported.[11,64]

Areca Nut–based Industrially Packaged Products. A variety of packaged areca products are now available. These are mostly manufactured in India and Pakistan, and exported worldwide where they are used by old and new habitués. The most common are *gutka* and *pan masala.* Gutka is a dry, relatively nonperishable commercial preparation containing areca nut, slaked lime, catechu, condiments, and powdered tobacco. The same mixture without tobacco is called *pan masala.*[65]

Systemic Effects of Areca Nut. Although largely beyond the scope of this chapter, it is important to realize that areca nut has widespread systemic ill effects.[66] These include psychological and behavioral disturbances due to inhibition of uptake of gamma-aminobutyric acid; neurotoxicity and addiction; cardiac arrhythmias and increased risk of myocardial infarction; hyperlipidemia and metabolic syndrome; hypothyroidism; and premature birth and infertility. Furthermore, the IARC monograph makes it clear that areca nut contributes not only to cancers of the mouth and oropharynx, but also to cancers of the esophagus, liver and biliary tract, lung, and uterus.

Damage to Oral Soft Tissues From the Chewing of Areca Nut and Related Products

Lichenoid Lesions. Areca-induced lichenoid lesions, mainly on buccal mucosa and tongue, are recognized. They are considered to be type IV contact hypersensitivity-type lesions that resemble oral lichen planus (OLP) clinically.[67]

Betel Chewer's Mucosa. Betel chewer's mucosa was first described by Mehta and colleagues (1971) and is characterized by a brownish-red discoloration of the oral mucosa. It is often