Chapter 5. Prevention, Early Detection, and Treatment of Oral Cancer

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Abstract

The major causes of oral cancer include tobacco use, areca nut chewing and heavy alcohol drinking; avoiding these can prevent the disease. Preceded by precancerous lesions, early oral cancers present as small painless ulcers or growths that can be detected, by careful physical examination, and effectively treated. Prevention, early detection and treatment are effective interventions to reduce the worldwide burden of oral cancer.

Introduction

Oral cancer is the eleventh most common cancer in the world, accounting for an estimated 263,000 new cases; 610,600 prevalent (old and new) cases; and 127,700 deaths annually in 2008 tables 5.1 and 5.2) (Ferlay and others 2010). For this chapter, oral cancers include cancers of the lip, tongue, gum, floor of the mouth, palate, and mouth, corresponding to International Classification of Diseases,10th revision [ICD-10] codes C00, , C02, C03, C04, C05, and C06. Two-thirds of the global incidence of oral cancer occurs in developing countries; half of those cases are in South Asia. India alone accounts for one-fifth of all oral cancer cases and a one-fourth of all oral cancer deaths (Ferlay and others 2010).

Tobacco use, in any form, and alcohol use are the major risk factors for oral cancer. With dietary deficiencies, these factors cause more than 90 percent of oral cancers. Preventing tobacco and alcohol use and increasing the consumption of fruits and vegetables can potentially prevent the vast majority of oral cancers (Sankaranarayanan and others 2013). When primary prevention fails, early detection through screening and relatively inexpensive treatment can avert most deaths. However, oral cancer continues to be a major cancer in the Indian subcontinent, East Asia, eastern Europe, and parts of south America (Curado and others 2007), where organized prevention and early detection efforts are lacking. This chapter discusses the epidemiology, prevention, early detection, and treatment of oral cancers, as well as the cost-effectiveness of interventions.

Oral Cancer: Incidence, Mortality, and Survival

Incidence and Mortality

Oral cancer incidence and mortality are high in the Indian subcontinent; Papua New Guinea; and Taiwan, China, where tobacco chewing is common, as well as in Eastern Europe, France, and parts of South America (Brazil and Uruguay), where alcohol consumption is high. The age-standardized incidence rates for men are, on average, twice as high as the incidence rates for women (tables 5.1 and 5.2). Incidence rates do not follow a particular pattern from low- to high-income countries, when countries are grouped into wealth strata (figure 5.1). In selected countries where some reliable cancer registries exist, India is highest and Belarus is lowest, with incidence rates varying by more than five times in both men and women (figures 5.2 and 5.3). Estimated age-standardized incidence rates of oral cancer also vary among countries in different regions (maps 5.1 and 5.2).

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Figure 5.1 Age-Standardized Incidence Rates of Oral Cancers in Countries by Income Level

Source: Bray and others 2013.

Figure 5.2 Age-Standardized Incidence Rates for Oral Cancer in Men in Selected Countries

Source: Bray and others 2013.

Figure 5.3 Age-Standardized Incidence Rates for Oral Cancer in Women in Selected Countries

Source: Bray and others 2013.

Table 5.1 Oral Cancer in Men: Global Incidence, Mortality, and Prevalence, World Health Organization Geographic Classification

	Incidence		Mortality		Prevalence	
Population	**Number**	**ASR (W)**	**Number**	**ASR (W)**	**Number**	**Five-year**
World	170,496	5.2	83,109	2.6	169,815	401,075
More developed regions	62,757	6.8	21,878	2.3	62,688	178,779
Less developed regions	107,739	4.6	61,231	2.7	107,127	222,296
WHO Africa region (AFRO)	6,704	3.2	2,997	1.6	6,563	15,525
WHO Americas region (PAHO)	28,770	5.8	7,565	1.5	28,696	85,948
WHO East Mediterranean region (EMRO)	9,843	4.9	4,295	2.3	9,784	23,088
WHO Europe region (EURO)	42,108	6.9	17,819	2.9	42,068	108,621
WHO Southeast Asia region (SEARO)	59,001	8.4	39,345	5.7	58,717	101,378
WHO Western Pacific region (WPRO)	23,999	2.3	11,063	1	23,914	66,342
Africa	8,361	3	3,716	1.5	8,203	19,327
Latin America and the Caribbean	11,569	4.6	4,776	1.9	11,521	29,072
Asia	91,327	4.7	54,518	2.9	90,918	185,843
Europe	40,026	7.4	16,768	3.1	39,990	103,895
Oceania	2,012	9.5	542	2.4	2,008	6,062

Sources: Incidence/mortality data: Ferlay and others 2010. Prevalence data: Bray and others 2013.

Table 5.2 Oral Cancer in Women: Global Incidence, Mortality, and Prevalence, World Health Organization Geographic Classification

	Incidence		Mortality		Prevalence	
Population	**Number**	**ASR (W)**	**Number**	**ASR (W)**	**Number**	**Five-year**
World	92,524	2.5	44,545	1.2	92,048	209,581
More developed regions	28,391	2.3	8,811	0.6	28,318	80,194
Less developed regions	64,133	2.6	35,734	1.5	63,730	129,387
WHO Africa region (AFRO)	4,970	2	2,233	1	4,855	11,571
WHO Americas region (PAHO)	14,175	2.3	3,744	0.6	14,119	40,046
WHO East Mediterranean region (EMRO)	7,301	3.7	3,200	1.8	7,241	17,381
WHO Europe region (EURO)	17,943	2.1	6,099	0.7	17,896	45,756
WHO South-East Asia region (SEARO)	36,399	5	23,608	3.3	36,264	64,600
WHO Western Pacific region (WPRO)	11,725	1	5,657	0.5	11,664	30,200
Africa	6,253	2	2,796	1	6,132	14,546
Latin America and the Caribbean	5,911	1.9	2,107	0.7	5,888	13,760
Asia	54,059	2.7	32,141	1.6	53,798	108,022
Europe	16,908	2.2	5,563	0.7	16,871	43,514
Oceania	1,129	4.8	301	1.2	1,128	3,453

Sources: Incidence/mortality data: Ferlay and others 2010. Prevalence data: Bray and others 2013.

Note: ASR = Age-standardized incidence rate per 100,000 population

The buccal (cheek) mucosa is the most common site for oral cancer in South and Southeast Asia; in all other regions, the tongue is the most common site (Curado and others 2007). Regional variations in incidence and the site of occurrence relate to the major causes, which are alcohol and smoking in Western countries, and betel quid and tobacco chewing in South and Southeast Asia (Lambert and others 2011). Oral cancer mortality rates range between 1 and 15 per 100,000 persons in different regions; mortality rates exceed 10 per 100,000 in Eastern European countries, such as the Czech Republic, Hungary, and Slovakia (Ferlay and others 2010). Oral cancer mortality rates are influenced by trends in oral cancer incidence, access to treatment, and variations in site distribution.

The observed trends in incidence and mortality among men and women are closely correlated with the patterns and trends in tobacco and alcohol use (figures 5.4 and 5.5). A slowly decreasing

trend in the incidence of oral cancers has been observed among men and women in India over the past two decades, although concern is growing that increasing use of commercial smokeless tobacco/areca nut products in sachets may lead to future increases in incidence (Satyanarayana and Asthana 2008); an increasing incidence has been reported from Pakistan. An increasing trend in incidence has been reported from Karachi in Pakistan (Bhurgri and others 2006) and in Taiwan (Tseng 2013) due to increases in chewing and alcohol drinking. Oral cancer incidence and mortality rates have been steadily declining over the past two decades due to declining smoking prevalence and alcohol consumption in the United States populations covered by the Surveillance, Epidemiology, and End Results (SEER) program (Brown, Check, and Devesa 2011). However, a recent increase in base tongue cancers, possibly driven by the human papillomavirus (HPV), has been observed in white men in this population (Saba and others 2011).

Oral cancer incidence and mortality rates have been declining steadily in most European countries over the past two decades; until recently, rates had been increasing in some Central European countries, including Hungary and Slovakia, reflecting changes in alcohol and tobacco consumption (Bonifazi and others 2011). Oral cancer mortality has declined steadily in France since reaching a peak in the early 1990s, and the decline correlates with the reduction in per capita alcohol consumption. Incidence and mortality have been stable in England and Scotland, the Nordic countries, and the Russian Federation. Mortality rates have been steadily declining in Australia and Hong Kong, China, but increasing in Japan and the Republic of Korea (Yako-Suketomo and Matsuda 2010).

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Figure 5.4 Trends in Oral Cancer Incidence and Mortality in Men by Income Level, Selected Countries

Source: Bray and others 2013.

Figure 5.5 Trends in Oral Cancer Incidence and Mortality in Women by Income Level, Selected Countries

Source: Bray and others 2013.

Survival

In the United States, 5-year survival]improved by more than 11 percentage points between 1992 and 2006 **(Pulte and Brenner 2010); five-year survival is now approximately 65 percent (Howlader and others 2010; Ries and others 2008). In Europe, it is approximately 50 percent (Sant and others 2009). In India, five-year survival is less than 35 percent; in China, the Republic of Korea, Pakistan, Singapore, and Thailand,** it ranges between 32 and 54 percent (Sankaranarayanan and others 2010; Sankaranarayanan and Swaminathan 2011). Overall, the five-year survival for early, localized cancers exceeds 80 percent and falls to less than 20 percent when regional lymph nodes are involved.

Oral Cancer: Risk Factors and Prevention

The major causes of oral cancer worldwide remain tobacco in its many different forms, heavy consumption of alcohol and, increasingly, infection with certain types of HPV; the effects of these factors is exacerbated in malnourished individuals. The relative contribution of risk factors varies from population to population, but oral cancer is, everywhere, predominantly a disease of poor people (Johnson and others 2011). Prevention of this devastating disease can come from fundamental changes in socioeconomic status and from actions to reduce the demand, production, marketing, and use of tobacco products and alcohol. A healthy diet, good oral and sexual hygiene, and awareness of the signs and symptoms of disease are also important. Success depends on political will, intersectoral action, and culturally sensitive public health messages disseminated through educational campaigns and mass media initiatives.

Smokeless and Smoking Tobacco Use

Smokeless tobacco in the form of betel quid, oral snuff, and betel quid substitutes such as guktha, nass, naswar, khaini, mawa, mishri, and gudakhu increases the risk of oral precancerous lesions and oral cancer two- to fifteen-fold (IARC 2004b; IARC 2007; Javed and others 2010; Johnson and others 2011; Gupta and others 2011; Gupta, Ariyawardana, and Johnson 2013; Somatunga and others 2012). In most areas, betel quid consists of tobacco, areca nut, slaked lime, catechu, and several condiments, wrapped in a betel leaf. In recent years, small, attractive, and inexpensive sachets of betel quid substitutes containing a flavored and sweetened dry mixture of areca nut, catechu, and slaked lime with tobacco (gutkha) or without tobacco (pan masala), often claiming to be safer products, have become widely available and are increasingly used by young people, particularly in the Indian subcontinent. These products have been strongly implicated in oral submucous fibrosis (OSMF), which places individuals at high risk for malignancy.

More than 50 percent of all oral cancers in the Indian subcontinent and Sudan and South Sudan and about 4 percent of oral cancers in the United States, are attributable to smokeless tobacco products. Smokeless tobacco use among young people is increasing in South Asia, with the marketing of the products made from areca nut and tobacco and convenient packaging; as a consequence, oral precancerous conditions in young adults have increased significantly (Gupta and others 2011; Sinha and others 2011).

Consistent evidence from many studies indicates that tobacco smoking in any form increases the risk of oral cancer by two- to 10-fold in both men and women (IARC 2004a). Risk increases substantially with duration and frequency of tobacco use; risk among former smokers is consistently lower than among current smokers, and there is a trend of decreasing risk with increasing number of years since quitting. Use of smokeless tobacco and/or alcohol in combination with tobacco smoking greatly increases the risk of oral cancer. The biological plausibility is provided by the identification of several carcinogens in tobacco, the most abundant and strongest being tobacco-specific N-nitrosamines, such as N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (IARC 2007). These are formed by N-nitrosation of nicotine, the major alkaloid responsible for addiction to tobacco.

Controversy continues over the dangers of snuss, the form of oral smokeless tobacco commonly used in Scandinavia. These products use non-flue-cured tobaccos; decades of use does produce

oral cancer at the site where the quid is commonly held—between the cheek and gingiva (Hirsch and others 2012).

The fact that more than 80 percent of oral cancers can be attributed to tobacco and/or alcohol consumption justifies regular oral examinations targeting tobacco and alcohol users, as well as prevention efforts focusing on tobacco and alcohol control (Radoi and others 2013). The World Health Organization Framework Convention on Tobacco Control (WHO FCTC), an evidence-based international treaty, aims to reduce the demand for tobacco globally both by price, tax, and non-price measures (see chapter 10 for a full discussion of tobacco control.)

Areca Nut Chewing

Areca nut or betel nut, now regarded as a type 1 carcinogen (IARC 2004b; IARC 2007), is chewed raw, dried, or roasted, or as part of betel quid by millions of people in Asia; its use is spreading across the Pacific, as well as in emigrant Asian communities worldwide. Cheap, prepackaged areca nut products, such as pan masala, are of recent concern, especially among youth. The inclusion of tobacco in the betel quid adds considerably to the carcinogenicity (Amarasinghe and others 2010; Johnson and others 2011).

Alcohol Use

Epidemiological studies indicate that drinking alcoholic beverages increases the risk of oral cancer two to six-fold and is an independent risk factor (IARC 2010), with risk increasing with quantity consumed. The risk varies by population and individual and subsite within the oral cavity (Radoi and others 2013). The combined use of alcohol and tobacco has a multiplicative effect on oral cancer risk. The various pathways by which alcohol may exert carcinogenic influence include topical exposure leading to a direct effect on cell membranes, altered cell permeability, variation in enzymes that metabolize alcohol, and/or systemic effects, such as nutritional deficiency, immunological deficiency, and disturbed liver function. A recent review failed to identify an association between the use of mouthwash containing alcohol and oral cancer risk, or any significant trend in risk with increasing daily use of mouthwash (Gandini and others 2012).

Poor Nutrition and Compromised Defenses

High consumption of fruits and vegetables is associated with a reduction of 40 to 50 percent in the risk of oral cancer (Lucenteforte and others 2009; Pavia and others 2006; World Cancer Research Fund/American Institute for Cancer Research 2007). In developed countries, selected aspects of diet may account for 20 to 25 percent of oral cancers, and this proportion is likely to be higher in developing countries. Chemoprevention studies have not established a preventive effect of retinoid and carotenoid dietary supplements (Chainani-Wu, Epstein, and Touger-Decker 2011; Wrangle and Khuri 2007).

Other Risk Factors

Polymorphisms

Most carcinogens are metabolized through the cytochrome p450 system in the liver. If this system is defective by virtue of inheriting a particular form of the gene, the risk of many cancers

is enhanced. Polymorphisms in CYP2E1 appear to be particularly important with oral and other head and neck cancers, the relative risks being 1.5 or less (Lu, Yu, and Du 2011).

Polymorphisms in alcohol-metabolizing enzymes also contribute to the risk. Individuals with the fast-metabolizing allele of alcohol dehydrogenase (ADH3[1-1]) have a greater risk of developing oral cancer in the presence of alcoholic beverage consumption than those with the slow-metabolizing forms; this higher risk re-enforces the role of acetaldehyde as the carcinogen involved (Heck and others 2010).

Mate Drinking

Mate, a leaf infusion that is commonly drunk many times a day in parts of South America—usually very hot—appears to enhance the risk of oral cancer by a small amount (Deneo-Pellegrini and others 2012).

Viruses

Recent evidence suggests that HPV infection may be an independent risk factor for cancer of the base of tongue, tonsils, and elsewhere in the oropharynx. HPV may modulate the process of carcinogenesis in some tobacco- and alcohol-induced oral and oropharyngeal cancers, and it may act as the primary oncogenic agent for inducing carcinogenesis among nonsmokers (Johnson and others 2011; Prabhu and Wilson 2013). Growing evidence suggests that such oropharyngeal infections can be sexually transmitted (Heck and others 2010).

Chronic Trauma

It now seems clear that chronic trauma, from sharp teeth, restorations, or dentures, contributes to oral cancer risk, although this higher risk commonly occurs only in the presence of the other local risk factors (Piemonte, Lazos, and Brunotto 2010).

Oral Cancer: Natural History

Oral cancer has a long preclinical phase that consists of well-documented, potentially malignant disorders (PMD). The PMD include homogeneous leukoplakia, non-homogeneous leukoplakia, verrucous leukoplakia, erythroplakia, OSMF, lichen planus and chronic traumatic ulcers. The estimated annual frequency of malignant transformation of oral potentially malignant disorder (OPMD) ranges from 0.13 percent to 2.2 percent (Amagasa, Yamashiro, and Uzawa 2011; Napier and Speight 2008).

Very early preclinical invasive cancers present as painless, small ulcers, nodular lesions, or growths. These changes can be easily seen and are clinically detectable through careful visual inspection and palpation of the oral mucosa. Early, localized oral cancers (less than four centimeters) with no spread to the regional lymph nodes can be effectively treated and cured with surgery or radiotherapy alone, with no functional or cosmetic defects, resulting in five-year survival rates exceeding 80 percent.

Leukoplakia is a white plaque that may be categorized clinically as *homogeneous* or *non-homogeneous*. Homogeneous lesions are thin, flat, uniform, smooth, and white. Various types of non-homogeneous leukoplakia are ulcerated leukoplakia with a white and red appearance; nodular leukoplakia with tiny, white, pinhead-size raised nodules on an erythematous

background; or verrucous leukoplakia, with a proliferative, warty appearance. Erythroplakia presents as a red patch with smooth or granular surface that cannot be characterized clinically or pathologically as any other definable disease (Warnakulasuriya, Johnson, and Waal 2007). Histologically, erythroplakia has a higher probability than leukoplakia to harbor dysplasia or underlying occult invasive cancer and a higher probability of malignant transformation.

Oral lichen planus may present as interlacing white keratotic lines (known as *Wickham's striae*) with an erythematous border, or as a mix of erythematous and ulcerated areas surrounded by finely radiating keratoticstriae. Oral lichen planus migrate over time, tend to be multifocal, and often present with symptoms ranging from episodic pain to severe discomfort.

Oral submucous fibrosis (OSMF), restricted to people of Indian subcontinent origin, presents with a burning sensation, blanching of the oral mucosa, and intolerance to spicy food. Loss of papillae in the tongue, stiffening and atrophy of the oral and pharyngeal mucosa, and distorted uvula develop as the disease progresses, leading to reduced mouth opening, and difficulty in swallowing and speaking. Histologically, fibrosis and hyalinization occur in the lamina propria, followed by atrophy of the overlying epithelium, which is susceptible to oral cancer when exposed to carcinogens.

Palatal lesions are specific to populations who smoke with the lighted end of tobacco product inside the mouth (known as *reverse smoking*), resulting in white or mixed reddish-white lesions of the palate. Actinic keratosis is clinically characterized by ulcerative, crust-forming lesions on the labial mucosa along the vermillion border; histological examination may show hyperkeratosis with or without epithelial dysplasia.

A higher risk of malignant transformation may be associated with the following factors: female gender, lesions of long duration, large OPMDs, OPMDs in nonusers of tobacco, tongue and floor of mouth lesions, non-homogeneous lesions, and lesions showing epithelial dysplasia (Hsue and others 2007; Napier and Speight 2008). However, it is currently impossible to predict with certainty which OPMD will become malignant during follow-up in patients. The malignant transformation of OPMD can be prevented by interventions, such as avoiding exposure to tobacco use and alcohol drinking and, in selected instances, by excision of the lesions.

Oral Cancer Screening: Accuracy and Efficacy

Although an affordable, acceptable, easy to use, accurate and effective screening test for oral cancer is available in high-risk countries, a decision to introduce population-based screening should take into account the level of health service development and available resources to meet the increased demand that screening entails. The target population for oral cancer screening consists of those aged 30 years and older who use tobacco and/or alcohol.

Visual screening of the oral cavity has been widely evaluated for its feasibility, safety, acceptability, accuracy to detect oral precancerous lesions and cancer, and its efficacy and cost-effectiveness in reducing oral cancer mortality (Johnson and others 2011; Sankaranarayanan and others 2005; Sankaranarayanan and others 2013). It involves systematic visual and physical examination of the intraoral mucosa under bright light for signs of OPMDs, as well as early oral cancer, followed by careful inspection and digital palpation of the neck for any enlarged lymph nodes. It is a provider-dependent, subjective test; accordingly, its performance in detecting

lesions varies among providers. Comprehensive knowledge of the oral anatomy, the natural history of oral carcinogenesis, and the clinico-pathological features of the OPMDs and preclinical cancers are important prerequisites for efficient providers of oral visual screening.

Visual Screening by Health Care Personnel

A variety of health care personnel—including dentists, general practitioners, oncologists, surgeons, nurses, and auxiliary health workers—may provide oral visual screening after training, for which resources are available (Ramadas and others 2008). Sensitivity ranges from 40 percent to 93 percent, and specificity ranges from 50 percent to 99 percent for detecting PMDs and early asymptomatic oral cancers (Downer and others 2004; Mathew and others 1997; Mehta and others 1986; Warnakulasuriya and others 1984; Warnakulasuriya and Nanayakkara 1991). The potential harms of oral visual screening may include additional diagnostic investigations, such as incisional or excisional biopsy; anxiety associated with false-positive screening tests; detection and treatment of biologically insignificant, non-progressive OPMDs that may have no impact on oral cancer mortality; and false reassurance from false-negative tests.

A significant reduction of 34 percent in oral cancer mortality among a high-risk group of tobacco or alcohol users following three rounds of oral visual screening has been demonstrated in a cluster-randomized controlled trial in India (Sankaranarayanan and others 2005; Sankaranarayanan and others 2013). A 15-year follow-up found sustained reduction in oral cancer mortality, with larger reductions in those adhering to repeated screening rounds; there was a 38 percent reduction in oral cancer incidence (95 percent confidence interval [CI] 8 percent to 59 percent), and an 81 percent reduction in oral cancer mortality (95 percent CI 69 percent to 89 percent) in tobacco and/or alcohol users who were screened four times (Sankaranarayanan and others 2013). This study was the basis for an American Dental Association expert panel that recommended that clinicians look for signs of PMDs or early-stage cancers while performing routine visual and tactile screening in all subjects, particularly in those who use tobacco or alcohol, or both. The panel also concluded that the life-saving benefits for subjects with treatable lesions was more important than the potential harms incurred by those with benign or non-progressive lesions.

Self-Examination and Other Screening

Although mouth self-examination using a mirror has been evaluated as a screening test in some studies (Elango and Others 2011; Mathew and others 1995; Scott and others 2010), whether it could lead to reductions in oral cancer mortality is not known. There is insufficient evidence to recommend the routine use of other oral screening tests, such as toluidine blue staining, chemiluminescence, tissue fluorescence imaging, tissue fluorescent spectroscopy, and salivary analysis and cytology for primary screening of oral cancer (Johnson and others 2011; Patton, Epstein, and Kerr 2008; Richards 2010; Su and others 2010).

Despite the high risk of oral cancer in the Indian subcontinent, no national or regional screening programs exist in the region. The only large-scale ongoing national oral cancer screening programs are in Cuba and Taiwan, China. The Cuban program has been in existence since 1984. An evaluation conducted in 1994 indicated that 12 percent to 26 percent of the target population has been screened annually, but less than 30 percent of screen-positive individuals complied with referrals (Fernandez and others 1995). Consequently, the program was reorganized in 1996, with the target age raised from 15 years to 35 years, screening intervals increased from one to three

years, and the referral system revamped. No further formal evaluation has been carried out since, but there has been no reduction in oral cancer incidence or mortality rates in Cuba over the past three decades. The outcomes from the Cuban program emphasize that screening programs without efficient organization and resources are not an effective use of limited resources.

The impact of visual screening on oral cancer incidence and mortality rates in Taiwan, China, is not yet evident.

Oral Cancer: Early Clinical Diagnosis and Staging

Primary care dental and general practitioners should play a major role in referring patients to cancer treatment facilities for early diagnosis and treatment. Improving the skills of these primary care doctors is essential to improving prospects for early diagnosis, particularly among patients who use tobacco or alcohol in any form. Routine biopsy in those clinically presenting with features of oral precancerous lesions may lead to early diagnosis of underlying preclinical invasive oral cancer. In addition to history, physical examination, and biopsy, a simultaneous assessment of the upper aerodigestive tract is necessary because patients with oral cancer have a high risk of cancers developing in other head and neck sites and in the lungs.

Once a diagnosis of oral cancer is confirmed, staging assessment is completed and treatment is planned. The Union for International Cancer Control (UICC) Tumor, Nodes, Metastasis (TNM) staging system is widely used for staging oral cancer (Patel and Shah 2005; Sobin and Wittekind 2002) (table 5.3), in which **T** indicates the size and extent of spread of the primary tumor, **N** indicates the extent spread to the regional lymph nodes in the neck, and **M** indicates the spread to distant organs. The TNM categorization is further grouped into stages 0 through 4, which denote increasing severity of disease and decreasing survival.

Oral cancer staging involves assessing the clinical extent of disease through physical examination, biopsies, and imaging investigations, including x-rays of mandible, maxillary sinuses, chest, computerized tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) imaging, depending upon what is available. Advanced imaging techniques such as CT, MRI, and PET may be useful in more accurately evaluating local spread, such as invasion of muscles, bone, and cartilage, and lymph node metastases, as well as in planning treatment, but these investigations are seldom feasible in low- and middle-income [countries (LMICs).

Table 5.3 Clinical Staging of Oral Cancer, Treatment Modalities, and Prognosis by Clinical Stage

Composite Stage	Extent of Disease	TNM Category	Treatment Options	Five-Year Survival (percent)
0	Cancer is limited to the epithelium (carcinoma in-situ) (Tis) and has not spread to deeper layers and nearby organs, regional (neck) lymph nodes (N0), or distant organs (M0)	TisN0M0	Limited surgical excision	~100
I	Primary tumor measures 2 centimeters or less (T1)and has not spread to regional organs, regional (neck) lymph nodes (N0), or distant organs (M0)	T1N0M0	Radical surgery only, or radical radiotherapy only	>90
II	Primary tumor is larger than 2 centimeters and lesser than 4 centimeters (T2) and has not spread to regional organs, regional (neck) lymph nodes (N0), or distant organs (M0)	T2N0M0	Radical surgery only, or radical radiotherapy only; in selected cases, combination therapy	>70
III	Primary tumor measures >4 centimeters (T3) and has not spread to neck nodes (N0) and distant organs (M0); or the tumor is any size (T1 to T3) and has spread to one lymph node measuring 3 centimeters or less on the same side of the of the neck (N1) as the primary tumor and the cancer has not spread to distant organs (M0)	T3N0M0 T1 to T3, N1, M0	Combined modality treatment with surgery and/or radiotherapy and/or chemotherapy	30-40 20-25
IV	The tumor involves nearby structures (including the mandible, tongue muscles, maxillary sinus, and skin (T4); or the tumor is any size but involves one lymph node measuring 3 to 6 centimeters on the same side of neck (N2a) or one lymph node measuring no more than 6 centimeters on the opposite neck (N2b), or two or more lymph nodes no more than 6 centimeters on any side of the neck (N2c); or lymph node involvement measuring >6 centimeters (N3); or distant metastases (M1)	T4, N0 or N1, M0 Any T, N2, or N3 M0 Any T, any N, M1	Multimodality management treatment with surgery and/or radiotherapy and/or chemotherapy for cancers without distant metastases; palliative radiotherapy and/or chemotherapy and pain/symptom relief measures	5-10 <5

Source: Sobin L. H., and Ch. Wittekind. 2002. *UICC TNM classification of malignant tumours*. Geneva: UICC.

Note: TNM = tumor, mode, metastasis.

Oral Cancer: Management

Oral cancer is predominantly a loco-regional disease that tends to infiltrate adjacent bone and soft tissues and spreads to the regional lymph nodes in the neck. Distant metastasis is uncommon at the time of diagnosis. A thorough inspection and palpation of the oral cavity and examination of the neck is mandatory. CT and MRI imaging are widely used to assess the extent of involvement of adjacent structures, such as bones and soft tissues. Surgery and radiotherapy are the main treatment modalities for oral cancer. Given the skills, expertise, and infrastructure required for staging and treatment with minimal physical, functional, and cosmetic morbidity, oral cancer treatment is usually carried out in specialized cancer hospitals such as comprehensive cancer centers or in hospitals at the highest level of health services (tertiary care centers).

Treatment of Early-Stage Oral Cancer (Stages I and II)

Surgery and radiotherapy are widely used for the treatment of early oral cancer, either as single modalities or in combination. The choice of modality depends on the location of the tumor, cosmetic and functional outcomes, age of the patient, associated illnesses, patient's preference, and the availability of expertise.

Most early-stage oral cancers can be locally excised or treated with radiotherapy, with no or minimal functional and physical morbidity. Elective neck dissection to remove lymph nodes may be considered in selected cases, such as patients with Stage I tongue cancer and stage II oral cancers at other oral sites, who may be at high risk of microscopic but not clinically evident involvement of the neck nodes (N0) (El-Naaj and others 2011; Hicks, Jr., and others 1997; Vijayakumar and others 2011; Woolgar 2006; Zwetyenga and others 2003). Postoperative radiotherapy is indicated in patients with positive or involved resected margins who are not candidates for re-excision.

External beam radiotherapy and brachytherapy, either alone or in combination, is an alternative to surgery for early stage oral cancers. Excellent outcomes have been demonstrated following brachytherapy alone or in combination with external beam radiotherapy for small tumors (Fujita and others 1999; Marsiglia and others 2002; Wendt and others 1990). Deep infiltrative cancers have a high propensity to spread to regional lymph nodes; therefore, brachytherapy alone, which does not treat regional nodes adequately, is not recommended. Newer techniques, such as three-dimensional conformal radiotherapy and intensity modulated radiotherapy (IMRT), can minimize the side effects of radiotherapy by delivering the radiation dose to the tumor more precisely and accurately while avoiding healthy surrounding tissues. However, these treatments require advanced equipment and are more expensive than conventional radiotherapy.

Treatment of Locally Advanced Tumors of the Oral Cavity (Stages III and IVA)

Locally advanced tumors are aggressive, and loco-regional treatment failure rates are high. Combined modality approach integrating surgery, radiotherapy with or without chemotherapy, planned and executed by a multidisciplinary team is always preferred. Due importance should be given to factors such as functional and cosmetic outcome and the available expertise. Surgery followed by postoperative radiotherapy is the preferred modality for patients with deep infiltrative tumors and those with bone infiltration (Lundahl and others 1998). Postoperative concurrent chemo radiation has been found to be superior in those with surgical margins showing

cancerous changes indicating incomplete excision of the tumor compared to radiotherapy alone (Bernier and others 2004; Cooper and others 2004). The use of chemotherapy prior to surgery may eliminate the need to remove the mandible—a major benefit—although it does not confer a survival benefit (Licitra and others 2003).

Primary radiotherapy, with or without chemotherapy, is a reasonable option for locally advanced tumors without bone involvement, especially for those patients with inoperable disease, who are medically unfit for surgery, or who are likely to have unacceptable functional and cosmetic outcomes with surgery. Incorporating chemotherapy with surgery or radiotherapy is useful in younger patients with good general conditions increasing survival by about 5 percentage points at five years (Blanchard and others 2011).

Side Effects of Radiotherapy

Side effects may occur during or immediately following radiotherapy—acute reactions—or months to years after treatment. Acute reactions are self-limiting and generally resolve within two to three weeks. These reactions are due to the inflammation of tissues within the radiotherapy treatment field. Alteration of taste, pain, difficulty in eating, mucosal ulceration of the oral cavity, bacterial and fungal infections, increased thickness of saliva, discoloration of the overlying skin and desquamation, epilation within the field of treatment, and edema of the skin are the major side effects. Maintenance of good oral hygiene, frequent cleaning of the oral cavity with soda-saline solution, analgesics, and control of infection are recommended for conservative management of these side effects. Good hydration, a high-calorie diet, and avoidance of spicy and hot food are recommended.

Late effects of radiation are related to dose per fraction, total dose, and the type and volume of the tissue irradiated. Late effects include loss of hair within the irradiated area, dry mouth (xerostomia), thickening of the skin, dental caries and, rarely, necrosis of the mandible or maxillary bone.

Complications of Surgery

The common complications of surgery are infection, collection of blood (hematoma), skin necrosis, flap failure, and wound breakdown. Resorption of bone, osteomyelitis, and salivary fistula can also occur. Complications are more frequent when neck dissection is part of the surgery. Fatal hemorrhage can occur if the carotid artery is exposed in the wound; hence proper covering of the artery with a muscle flap is advisable during the neck dissection. Resection of the structures can interfere with cosmetic appearance and functions such as speech, swallowing, and airway. These complications can be minimized through reconstructive surgery and by good prosthetic rehabilitation.

Posttreatment Follow-Up

Patients with oral cancer are at risk for developing loco-regional recurrences and second malignancies. After completion of the treatment, patients should be followed up at regular intervals to detect any signs of recurrences. Patients should be encouraged to give up tobacco and alcohol and be educated about the signs and symptoms of recurrence.

Prognosis

Lymph node involvement and tumor size are the most important prognostic factors. Data for the United States for 1975-2007 reports a year-year survival for all stages of oral cancer of 60.9 percent, 82.5 percent for early stage disease, and 54.7 percent for locally advanced oral cavity cancer (Ries and others 2008). The reported five-year overall for oral cancer (for all stages combined) from populations in LMICs such as China, Cuba, India, Pakistan, and Thailand ranged from 26 percent to 45 percent; for Stages I and II, the survival rates ranged from 36 percent to 83 percent. The inferior survival rates in LMICs versus high-income countries (HICs) reflect disparities in the availability, accessibility, and affordability of diagnostic and treatment services (Sankaranarayanan and others 2010; Sankaranarayanan and Swaminathan 2011).

Economics of Preventing and Screening for Oral Cancers in Low- and Middle-Income Countries

Cost-Effectiveness Assessments

Only a few cost-effectiveness studies of oral cancer screening focus on LMICs; therefore, we include a broader range of studies, including some from HICs. Although these studies may not be directly relevant to the resource-limited setting, they provide valuable insights into the potential cost-effectiveness of interventions.

Primary Prevention

Interventions targeted at reducing or eliminating tobacco and alcohol use should be considered for implementation when shown to be cost-effective. All the interventions presented are cost-effective even for LMICs**,** but the most cost-effective interventions are generally also quite affordable. In the case of tobacco cessation, increasing the price of tobacco products is the most cost-effective approach, with incremental cost-effectiveness ratios ranging from US$4 to US$34 per disability-adjusted life-year (DALY). Alcohol control interventions tend to have higher cost-effectiveness ratios; advertising bans and reduced access range from US$367 to US$1,307; combination strategies (including price increases, reduced access, and advertisement bans) range from US$601 to US$1,704. (Interventions to decrease tobacco use are covered in more detail in chapter 10.)

Screening

Table 5.4 summarizes findings from the relevant cost-effectiveness studies. Among the four studies of the cost-effectiveness of oral cancer screening, three—all set in HICs—used decision analytic modeling and the other; the only one from a resource-constrained environment used data from the randomized clinical trial in India. Only the Indian study (Subramanian and others 2009) directly reflects the costs and effectiveness likely to be experienced in LMICs. In general, the age at screening was 35 or 40 years and older; three of the four studies included both high-risk and average-risk individuals. All of the studies presented incremental cost-effectiveness compared to the scenario of no screening. A variety of interventions were assessed, using both invitation and opportunistic screening; visual inspection was performed by specialists (oral cancer surgeons), dentists, or trained health care workers.

The results indicate that screening is cost-effective even in low- and middle-income settings. The study from India provides evidence that oral cancer screening by visual inspection costs less than US$6 per person in a screening program; this has an incremental cost-effectiveness ratio of US$835 per life-year saved. The most cost-effective and affordable option in the limited resource setting is to offer oral cancer screening to high-risk individuals, for example, tobacco and alcohol users. The incremental cost-effectiveness ratio for screening high-risk individuals in southern India is US$156 per life-year saved. There is wide variation in the incremental cost-effectiveness reported across the studies, probably due to factors such as the underlying prevalence of disease and the local cost of cancer treatment. The cost of care related to screening, diagnosis, and treatment can differ substantially, even among countries classified as LMICs. Accordingly, it is essential to systematically assess costs at the country or even local level to analyze the cost-effectiveness and resources required to implement oral cancer screening

Table 5.4 Oral Cancer Screening Cost-Effectiveness Studies

Study	Country	Setting/Population	Methodology/Cost data	Interventions/tests compared	Cost-Effectiveness assessment
Van der Meij and others 2002	Netherlands	Individuals with OLP	Decision analytic model; all relevant clinical costs	Screening by oral specialist or dentist versus no screening	$53,430 per ELS or $2,137 per QALY for screening by specialist compared with no screening: lower cost-effectiveness ratio for screening by dentists
Speight and others 2006	United Kingdom	Screening programs for individuals 40 years and older in the primary care setting	Decision analytic model: all relevant invitation and clinical costs	No screening compared to invitation and opportunistic screening	Opportunistic screening of high risk individuals aged 40-60 most cost-effective: about $19,000 per QALY.
Subramanian and others 2009	India	13 clusters randomized in Kerala; those 35 years or older were eligible for the study	Cost-effectiveness assessment, including both program and clinical costs	Visual inspection by trained health care workers compared to usual care	US$835 per LYS for all individuals; US$156 per LYS for high-risk individuals.
Dedhia and others 2011	United States	Community-based screening for high-risk males (40 years or older, tobacco and/or alcohol users)	Markov model: clinical costs included but no program costs	Oral exam (visual inspection and manual palpation) by trained health care workers compared to no screening	A budget of $3,363 per person over a 40 year cycle for screening is cost-effective

Note: ELS = Equivalent Life Saved; LYS = Life Years Saved; OLP = oral lichen planus; QALY = Quality adjusted life years.

Future Research Needs

Primary prevention, especially smoking cessation, and secondary prevention, focused on high-risk individuals, is likely to be both cost-effective and affordable in LMICs. Additional studies are required to assess the cost-effectiveness and budget implications of visual screening for oral cancers in LMICs. These studies should focus on the screening delivery structure to identify the most cost-effective approach to provide oral cancer screening to high-risk individuals.

When cancer screening policies are implemented, the success of the program will depend on participation by the target population. Even when screening and follow-up care is free of charge, patients may not be able to afford to lose a day's wage to attend screening clinics or travel to health centers to receive follow-up diagnostic testing or treatments. The indirect costs borne by the patients may be particularly challenging among those in the lower socioeconomic strata. These are the very individuals likely to be at higher risk for developing oral cancers; it is, therefore, vital that identifying approaches to encourage and sustain participation among this potentially hard-to-reach high-risk population be given high priority.

Conclusion

A multifaceted approach that integrates health education, tobacco and alcohol control, early detection, and early treatment is needed to reduce the burden of this eminently preventable cancer. How to accomplish this is known; astonishingly, it has not been applied in most countries, and not at all in the high-burden countries. Improving awareness among the general public and primary care practitioners, investing in health services to provide screening and early diagnosis services for tobacco and alcohol users, and providing adequate treatment for those diagnosed with invasive cancer are critically important oral cancer control measures. Imaging, histopathology, cancer surgery and radiotherapy infrastructure and services, trained professionals, and the availability of chemotherapeutic agents are inadequate in many LMICs, seriously compromising early detection and optimum treatment. As this chapter has demonstrated, however, these are affordable and cost-effective.

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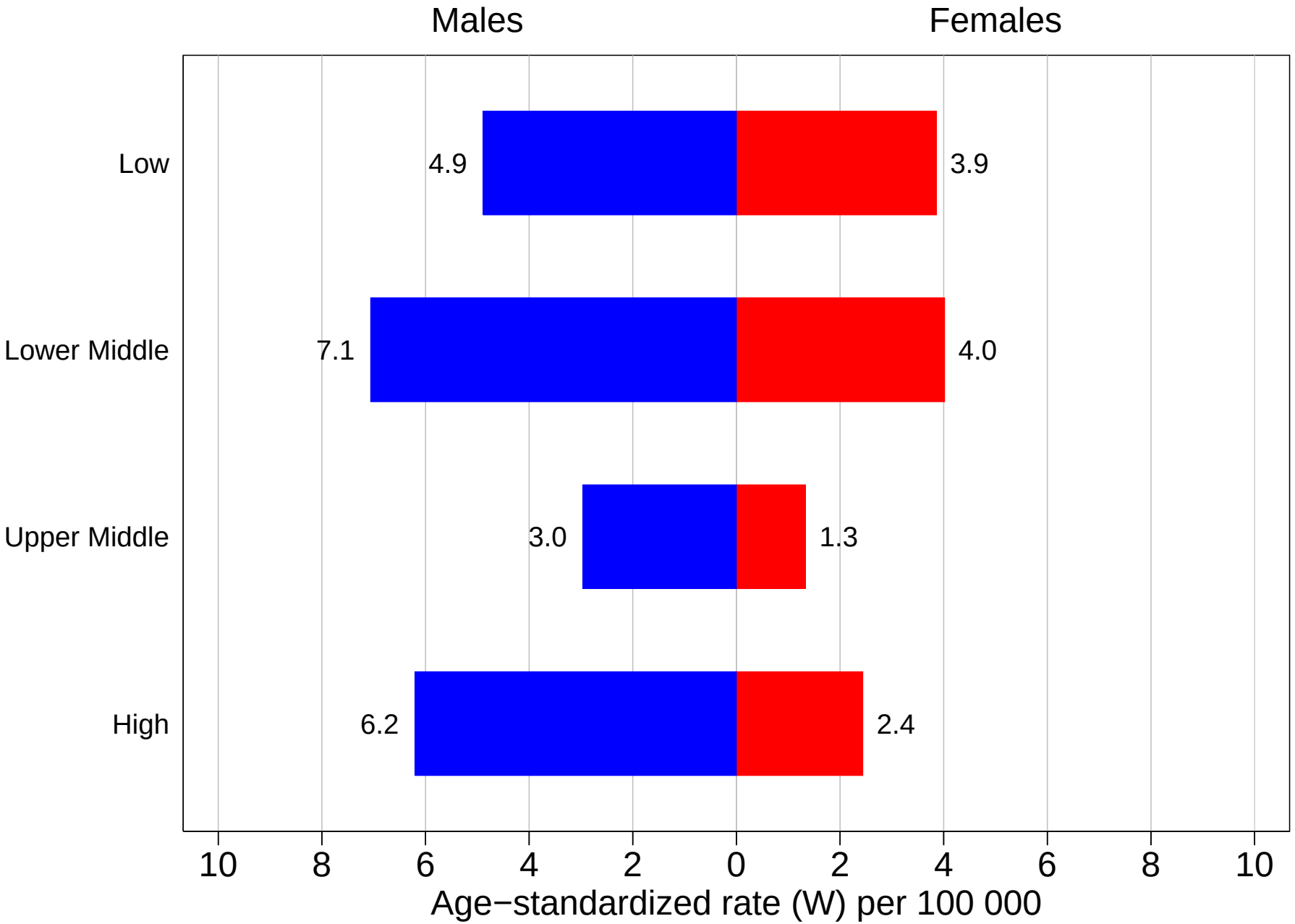


Figure 5.1: Age-standardized incidence rates of oral cancer in countries by income level

SOURCE: Bray 2013 from Globocan 2008

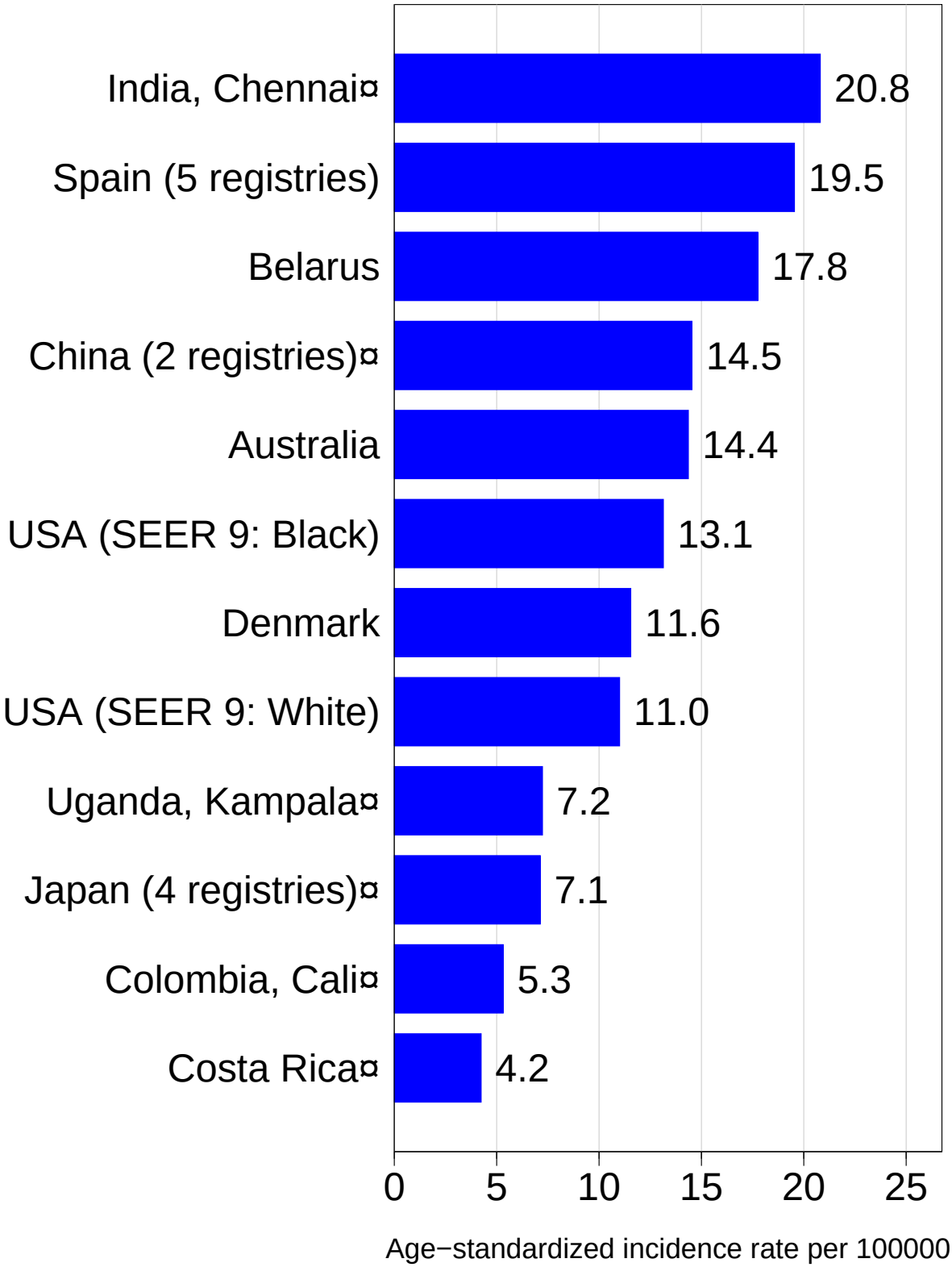


Figure 5.2: Age-standardized incidence rates of oral cancer in men in selected countries

SOURCE: Bray 2013 from Cancer Incidence on Five Continents – IX

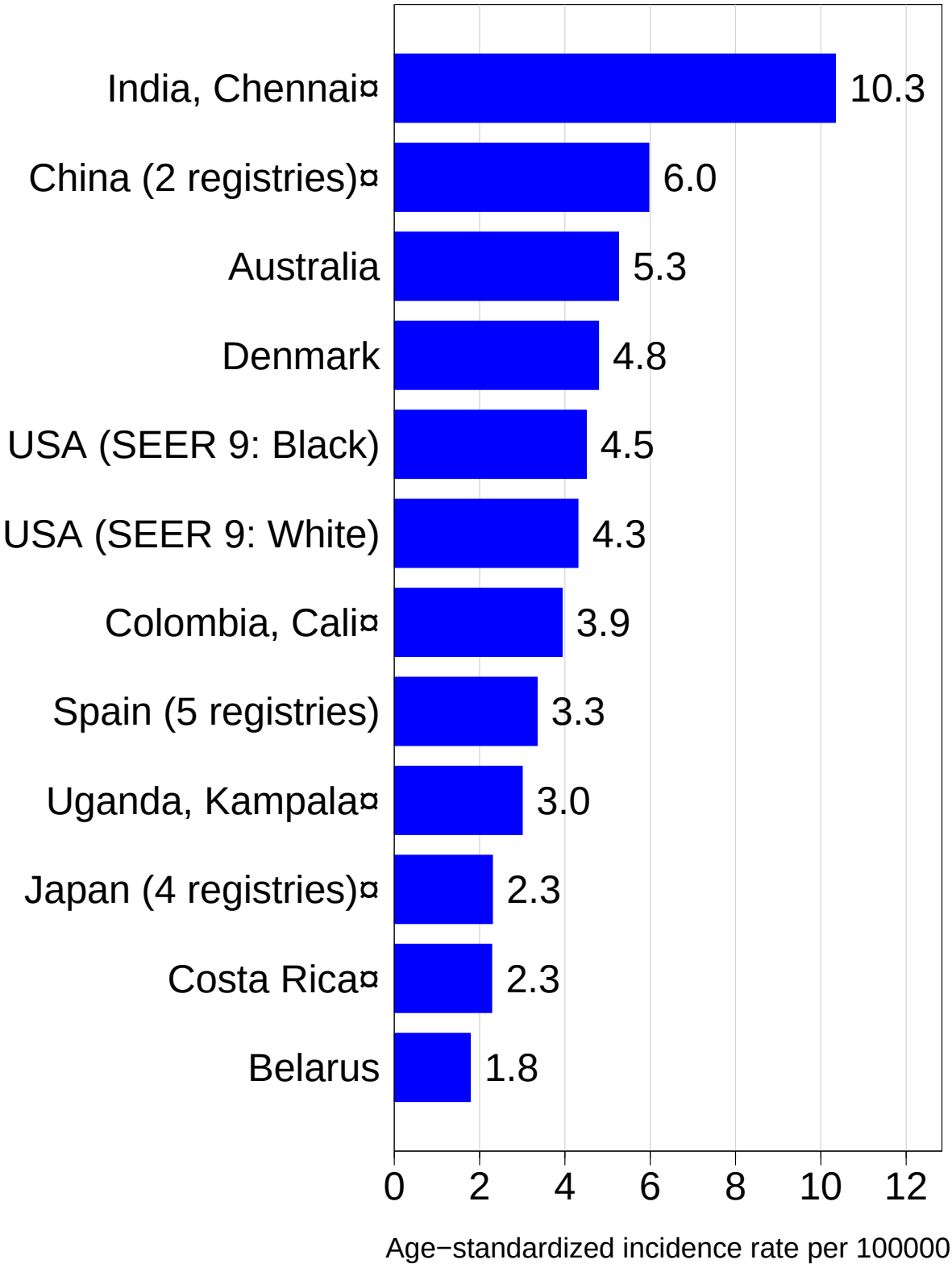
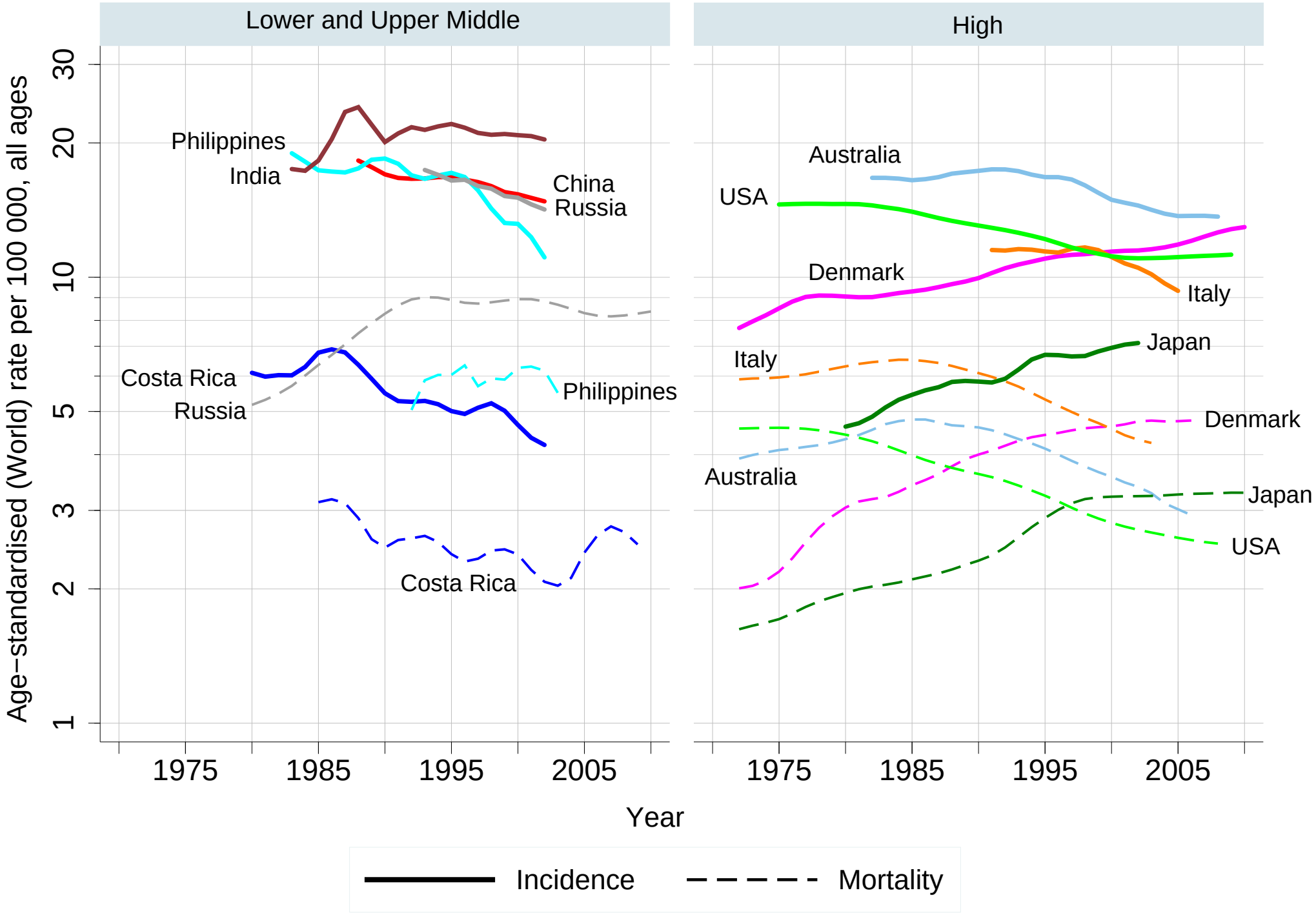


Figure 5.3: Age-standardized incidence rates of oral cancer in women in selected countries

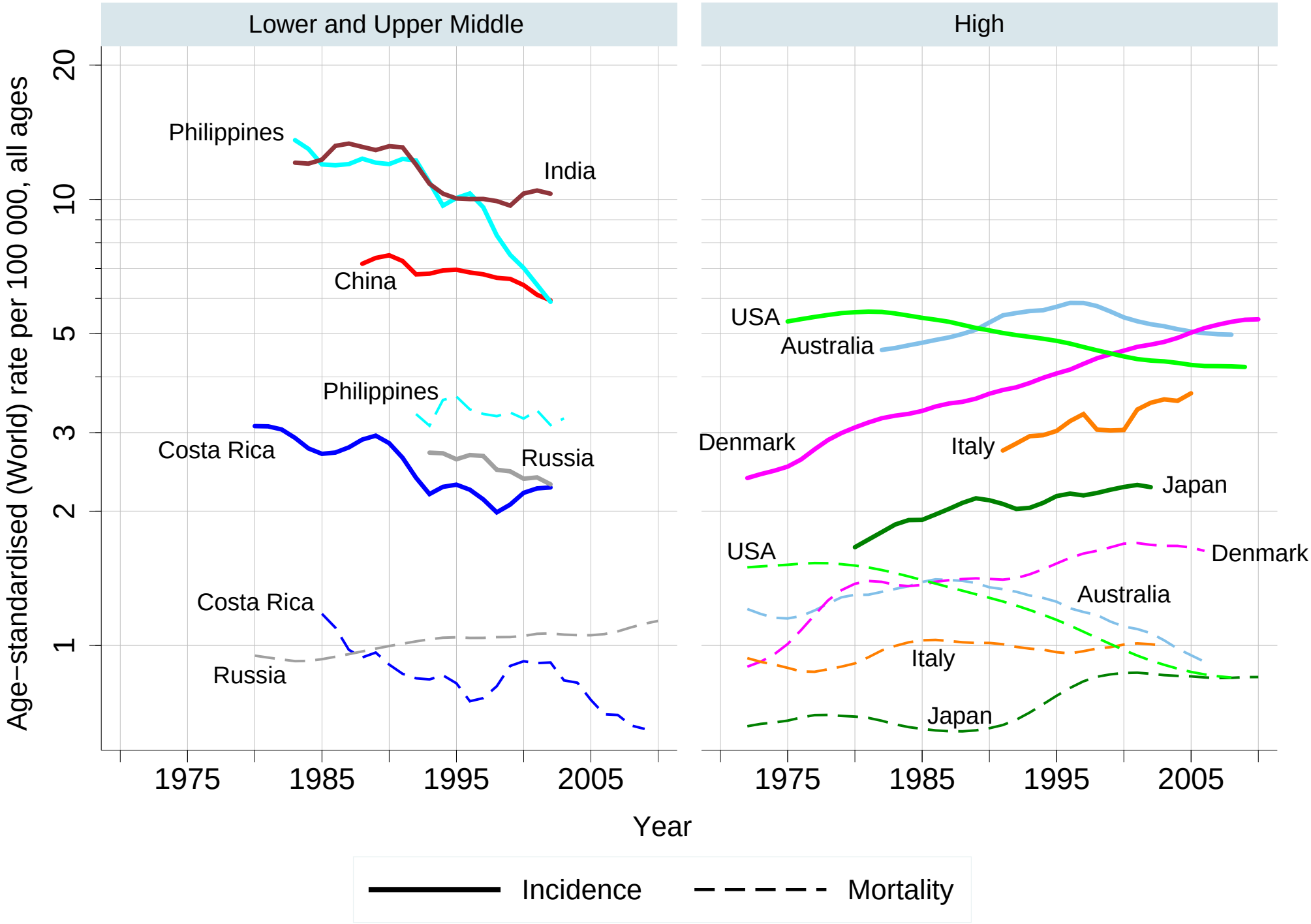
SOURCE: Bray 2013 from Cancer Incidence on Five Continents – IX

Figure 5.4: Trends in oral cancer incidence and mortality in men in selected countries by income level

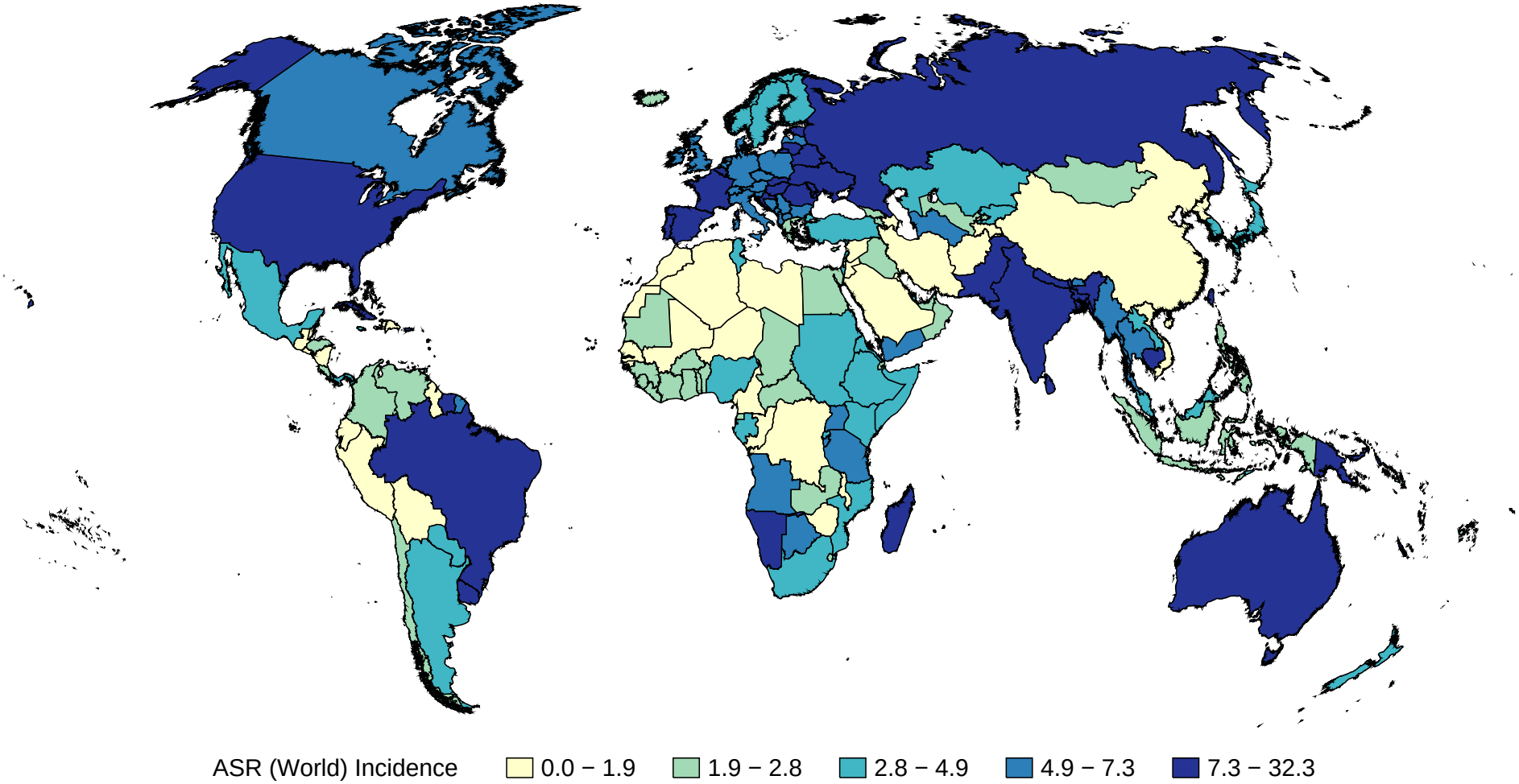


SOURCE: Bray 2013 from Cancer Incidence on Five Continents – IX

Figure 5.5: Trends in oral cancer incidence and mortality in women in selected countries by income level

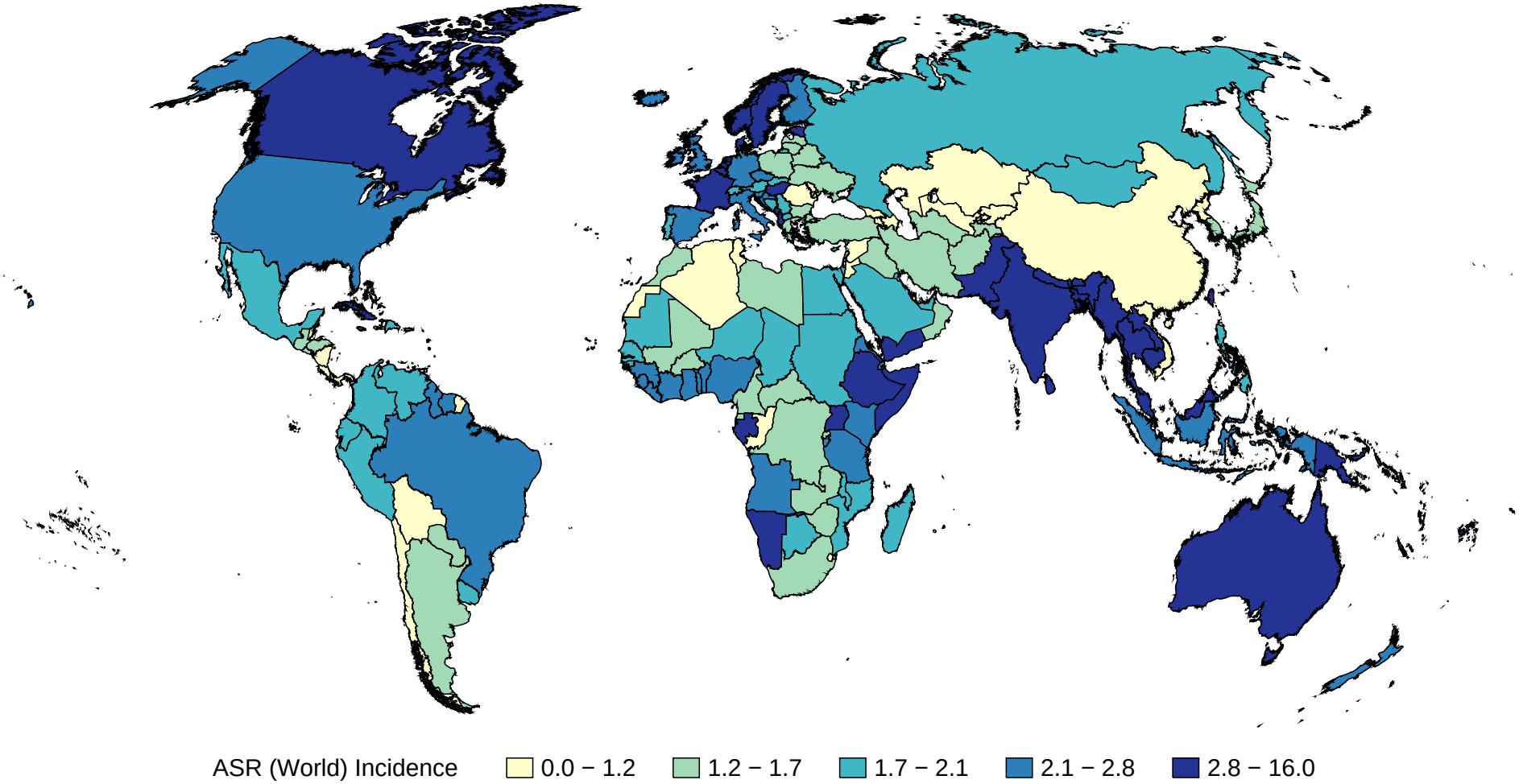


SOURCE: Bray 2013 from Cancer Incidence on Five Continents - IX



Map 5.1: Estimated age-standardized incidence rates of oral cancer in men by country

SOURCE: Bray 2013 from Globocan 2008



Map 5.2: Estimated age-standardized incidence rates of oral cancer in women by country

SOURCE: Bray 2013 from Globocan 2008