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Chapter **5**

Oral Cancer: Prevention, Early Detection, and Treatment

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INTRODUCTION

Oral cancer is the 11th most common cancer in the world, accounting for an estimated 300,000 new cases and 145,000 deaths in 2012 and 702,000 prevalent cases over a period of five years (old and new cases) (tables 5.1 and 5.2) (Bray and others 2013; Ferlay and others 2013). For this chapter, oral cancers include cancers of the mucosal lip, tongue, gum, floor of the mouth, palate, and mouth, corresponding to the International Classification of Diseases, 10th revision [ICD-10], codes C00, C02, C03, C04, C05, and C06, respectively. Two-thirds of the global incidence of oral cancer occurs in low- and middle-income countries (LMICs); half of those cases are in South Asia. India alone accounts for one-fifth of all oral cancer cases and one-fourth of all oral cancer deaths (Ferlay and others 2013).

Tobacco use, in any form, and excessive 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 India, East Asia, Eastern Europe, and parts of South America (Forman and others 2013), 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[1]

Oral cancer incidence and mortality are high in India; Papua New Guinea; and Taiwan, China, where chewing of betel quids with tobacco or without tobacco or areca nut chewing is common, as well as in Eastern Europe, France, and parts of South America (Brazil and Uruguay), where tobacco smoking and alcohol consumption are high. The age-standardized incidence rates for men are, on average, twice as high as those for women (tables 5.1 and 5.2). Incidence rates do not follow a particular pattern from low- to high-income countries (HICs), 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 men and women.

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Table 5.1 Oral Cancer in Men (All Ages): Global Incidence, Mortality, and Prevalence, World Health Organization Geographic Classification, 2012

Population	Incidence		Mortality		Prevalence	
	Number	ASR (W)	Number	ASR (W)	Number	Five-year
World	198,975	5.5	97,919	2.7	198,267	467,157
More developed regions	68,042	7	23,380	2.3	67,978	195,233
Less developed regions	130,933	5	74,539	2.8	130,289	271,924
WHO Africa region	8,009	3.4	5,026	2.2	7,763	18,446
WHO Americas region	31,898	5.9	8,532	1.5	31,805	94,953
WHO East Mediterranean region	11,601	5.1	6,185	2.8	11,533	27,236
WHO Europe region	45,567	7.1	18,621	2.8	45,499	118,151
WHO South-East Asia region	70,816	8.9	45,247	5.7	70,667	122,976
WHO Western Pacific region	31,013	2.7	14,292	1.2	30,929	85,233
Africa	10,230	3.3	6,083	2.1	9,961	23,560
Latin America and Caribbean	12,988	4.6	5,244	1.9	12,918	32,424
Asia	111,994	5.2	65,045	3	111,683	230,389
Europe	42,573	7.5	17,598	3	42,539	111,347
Oceania	2,280	9.6	661	2.7	2,279	6,908

Source: Incidence/mortality data: Ferlay and others 2013. Prevalence data: Bray and others 2013.
Note: ASR (W) = age-standardized incidence rate per 100,000 population, for the world population structure; WHO = World Health Organization.

Table 5.2 Oral Cancer in Women (All Ages): Global Incidence, Mortality, and Prevalence, World Health Organization Geographic Classification, 2012

Population	Incidence		Mortality		Prevalence	
	Number	ASR (W)	Number	ASR (W)	Number	Five-year
World	101,398	2.5	47,409	1.2	100,784	234,992
More developed regions	32,781	2.6	9,908	0.6	32,683	93,180
Less developed regions	68,617	2.5	37,501	1.4	68,101	141,812
WHO Africa region	5,475	2	3,504	1.4	5,349	12,766
WHO Americas region	17,302	2.6	4,271	0.6	17,204	48,526
WHO East Mediterranean region	9,080	4.1	4,812	2.2	8,993	21,570
WHO Europe region	20,366	2.4	6,556	0.7	20,305	51,933
WHO South-East Asia region	32,648	3.9	20,487	2.5	32,482	58,034
WHO Western Pacific region	16,511	1.3	7,776	0.6	16,435	42,123
Africa	7,046	2	4,258	1.3	6,892	16,409
Latin America and Caribbean	7,645	2.2	2,381	0.7	7,586	17,813
Asia	56,856	2.5	32,363	1.4	56,549	117,362
Europe	18,843	2.5	6,033	0.7	18,789	48,653
Oceania	1,351	5.3	484	1.9	1,350	4,042

Sources: Incidence/mortality data: Ferlay and others 2013. Prevalence data: Bray and others 2013.
Note: ASR (W) = age-standardized incidence rate per 100,000 population, for the world population structure; WHO = World Health Organization.

The estimated age-standardized incidence rates of oral cancer also vary among countries in different regions (maps 5.1 and 5.2).

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 (Forman and others 2013). 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 the Slovak Republic (Ferlay and others 2013). Oral cancer mortality rates are influenced by 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. An increasing trend in incidence has been reported in Karachi, Pakistan (Bhurgri and others 2006), and in Taiwan, China (Tseng 2013), caused by increases in tobacco and areca nut chewing and alcohol drinking. Oral cancer incidence and mortality rates have been steadily declining over the past two decades because of declining smoking prevalence and alcohol consumption in the United States (Brown, Check, and Devesa 2011).

However, a recent increase in cancers at the base of the tongue, possibly driven by the human papillomavirus (HPV), has been observed in white men in the United States (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

Figure 5.1 Age-Standardized Incidence and Mortality Rates of Oral Cancer, by World Bank Income Classification, 2012
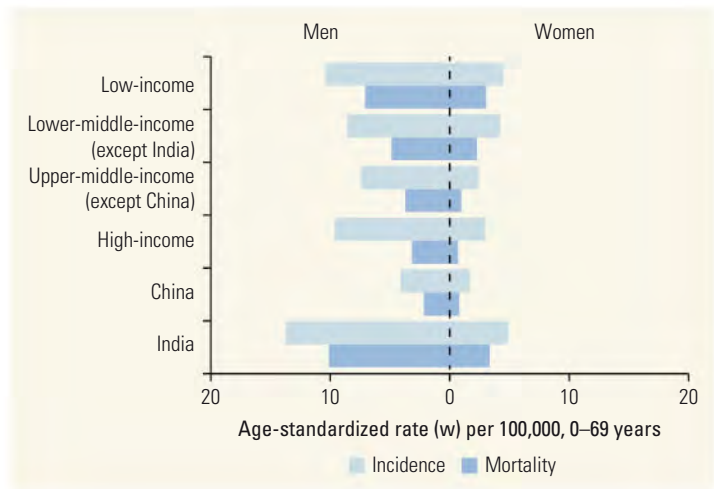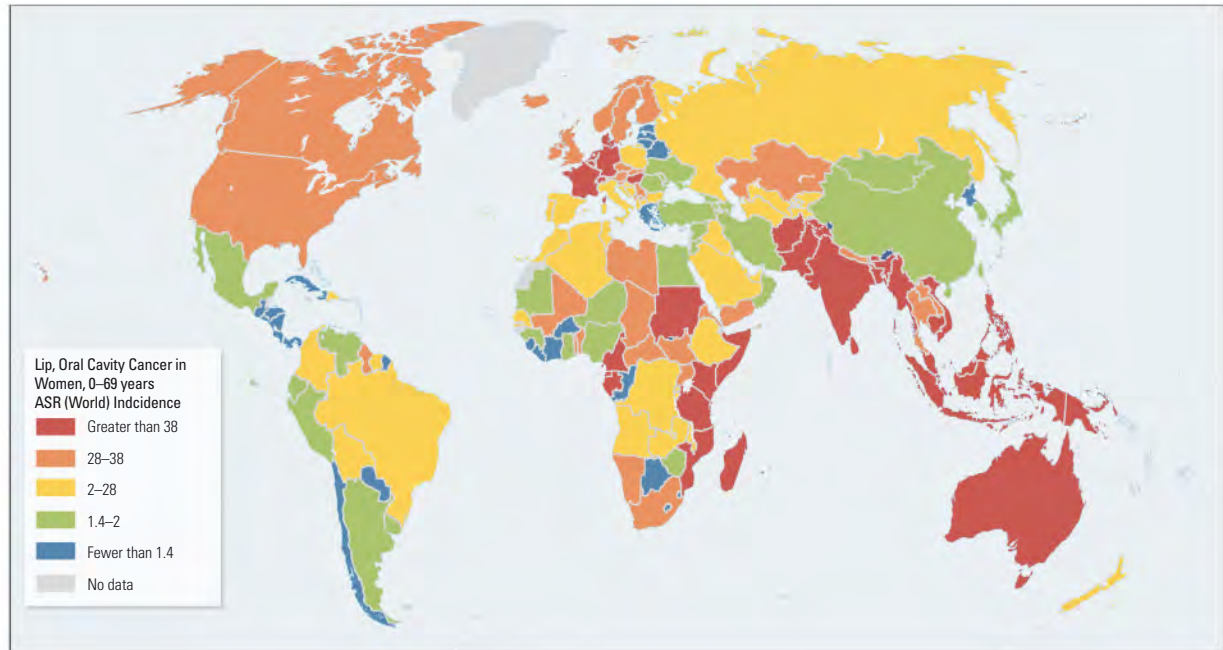

Source: Ferlay and others 2013.

Map 5.1 Age-Standardized Incidence Rates of Oral Cancer in Men, 2012
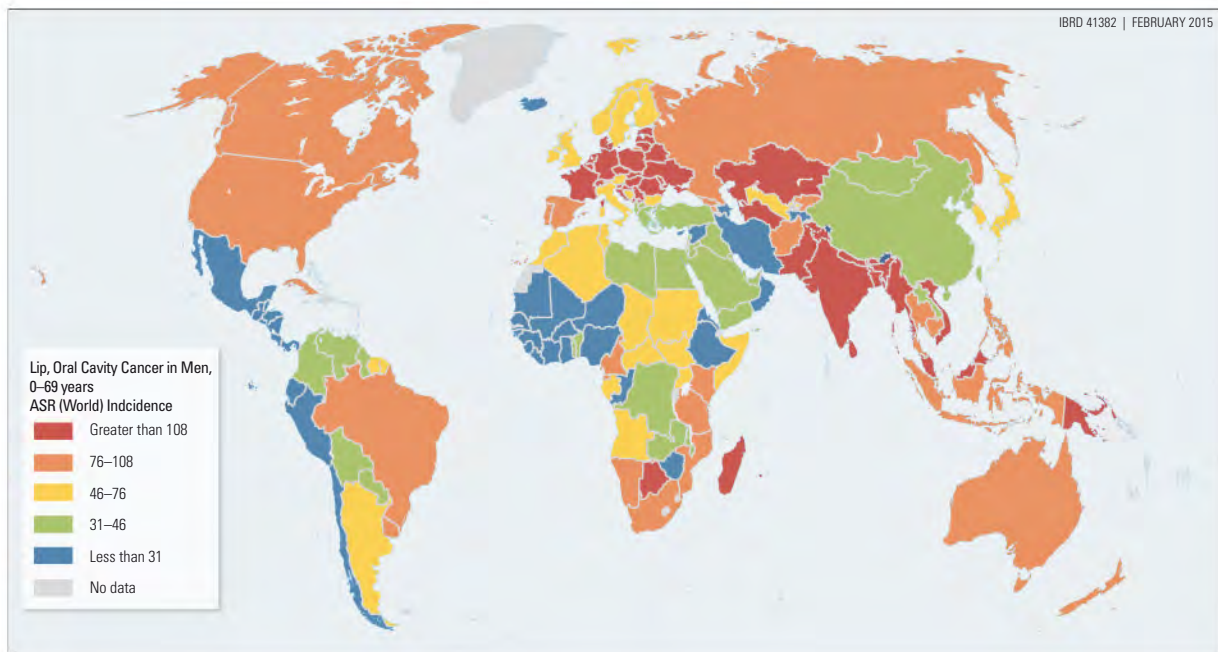
Source: Ferlay and others 2013.
Note: ASR = Age-Standardized Rate.

Map 5.2 Age-Standardized Incidence Rates of Oral Cancer in Women, 2012

Lip, Oral Cavity Cancer in
Women, 0–69 years
ASR (World) Indcidence

- Greater than 38
- 28–38
- 2–28
- 1.4–2
- Fewer than 1.4
- No data

Source: Ferlay and others 2013.
Note: ASR = Age-Standardized Rate.

increasing in some Central European countries, including Hungary and the Slovak Republic, 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 the Nordic countries, the Russian Federation, and the United Kingdom. Mortality rates have been steadily declining in Australia and Hong Kong SAR, China, but increasing in Japan and the Republic of Korea (Yako-Suketomo and Matsuda 2010).

Survival

In the United States, five-year survival improved by more than 11 percentage points between 1992 and 2006 (Pulte and Brenner 2010) and 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. Although the relative contribution of risk factors varies from population to population, oral cancer is predominantly a disease of poor people (Johnson and others 2011). Prevention of this devastating disease can come from fundamental changes in socioeconomic status, as well as from actions to reduce the demand, production, marketing, and use of tobacco products and alcohol (Johnson and others 2011). A healthy diet, good oral and sexual hygiene, and awareness of the signs and symptoms of disease are 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 (locally called guktha, nass, naswar, khaini, mawa, mishri, and gudakhu) increases the risk of oral precancerous lesions and oral cancer between 2-fold and 15-fold (Gupta and others 2011;

Gupta, Ariyawardana, and Johnson 2013; IARC 2004b, 2007; Javed and others 2010; Johnson and others 2011; 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 India. These products have been strongly implicated in oral submucous fibrosis (OSMF), which places individuals at high risk for malignancy.

More than 50 percent of oral cancers in India, Sudan, and the Republic of 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 conveniently packaged products made from areca nut and tobacco; 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 twofold to tenfold in 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 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 and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (IARC 2007). These are formed by N-nitrosation of nicotine, the major alkaloid responsible for addiction to tobacco.

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, an evidence-based international treaty, aims to reduce the demand for tobacco globally 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, because it is often wrapped in betel leaf, is now regarded as a type 1 carcinogen (IARC 2004b, 2007). It 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 twofold to sixfold 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

High consumption of fruits and vegetables is associated with a reduction of 40–50 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 HICs, selected aspects of diet—such as lack of vegetables and fruits—may account for 15–20 percent of oral cancers; this proportion is likely to be higher in LMICs. 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

Genetic Factors
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 (a polymorphism), the risk of many cancers is enhanced. This risk is particularly important with oral and other head and neck cancers, although the relative risks are modest at 1.5 or lower (that is, less than a doubling of risk) (Lu, Yu, and Du 2011).

Polymorphisms in alcohol-metabolizing enzymes also contribute to the risk. Individuals with the fast-metabolizing version (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 (Harty and others 1997).

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 the 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 precancerous lesions. The precancerous lesions include homogeneous leukoplakia, nonhomogeneous leukoplakia, verrucous leukoplakia, erythroplakia, OSMF, lichen planus, and chronic traumatic ulcers. The estimated annual frequency of malignant transformation of oral precancerous lesions ranges from 0.13 percent to 2.2 percent (Amagasa, Yamashiro, and Uzawa 2011; Napier and Speight 2008).

Very early preclinical invasive cancers (early-stage cancers without symptoms) 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—that have not 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 *nonhomogeneous*. Homogeneous lesions are thin, flat, uniform, smooth, and white. Nonhomogeneous lesions may have a white and red appearance or tiny, white, pinhead-size raised nodules on a reddish background or 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 Van Der Waal 2007). Erythroplakia has a higher probability than leukoplakia to harbor occult invasive cancer and to undergo malignant transformation.

Oral lichen planus may present as interlacing white lines (known as *Wickham's striae*) with a reddish border, or as a mix of reddish and ulcerated areas.

OSMF, mostly restricted to people of Indian subcontinent origin and in certain Pacific islands such as Mariana Islands, presents with a burning sensation, blanching of the oral mucosa, and intolerance to spicy food. Stiffening and atrophy of the oral and pharyngeal mucosa occurs as the disease progresses, leading to reduced mouth opening and difficulty in swallowing and speaking.

Palatal lesions are seen in populations who smoke with the lighted end of the tobacco product inside the mouth, known as *reverse smoking*, resulting in white or mixed reddish-white lesions of the palate.

A higher risk of malignant transformation may be associated with the following factors: female gender, lesions of long duration, large precancerous lesions, precancerous lesions in nonusers of tobacco, tongue and floor of mouth lesions, nonhomogeneous lesions, and lesions showing epithelial dysplasia and aneuploidy (Hsue and others 2007; Napier and Speight 2008). However, it is impossible to predict with certainty which precancerous lesion will become malignant during follow-up in patients. The malignant transformation of precancerous lesions 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, EFFICACY, AND POTENTIAL HARMS

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 treatment demand that screening generates. The target population for oral cancer screening consists of those age 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 efficacy and cost-effectiveness in reducing oral cancer mortality (Johnson and others 2011; Sankaranarayanan and others 2005; Sankaranarayanan and others 2013). Visual screening involves systematic visual and physical examination of the intraoral mucosa under bright light for signs of oral potentially malignant disorders (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.

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 conditions that may have no impact on oral cancer incidence; and false reassurance from false-negative tests.

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 (Ramadas and others 2008). Sensitivity ranges from 40 percent to 93 percent, and specificity ranges from 50 percent to 99 percent for detecting precancerous lesions 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).

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] 8–59 percent), and an 81 percent reduction in oral cancer mortality (95 percent CI 69–89 percent) in tobacco and/or alcohol users who were screened four times (Sankaranarayanan and others 2013). The studies (Sankaranarayanan and others 2005; Sankaranarayanan and others 2013) were the basis for the conclusions of the recent Cochrane Collaboration Review (Brocklehurst and others 2013) and an American Dental Association (ADA) expert panel review on population-based oral cancer screening (Rethman and others 2010). The ADA review recommended that clinicians look for signs of precancerous lesions 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 were more important than the potential harms incurred by those with benign or nonprogressive lesions (Rethman and others 2010). The Cochrane Review (Walsh and others 2013) concluded that evidence suggests that a visual examination as part of a population-based screening program reduces the mortality rate of oral cancer in high-risk individuals; in addition, it could result in diagnoses of oral cancer at an earlier stage of disease and improvement in survival rates across the population as a whole (Brocklehurst and others 2013).

The U.S. Preventive Services Task Force released a draft Recommendation Statement, which stated that for adults age 18 years or older seen in primary care settings, the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults. However, this statement overlooks the benefits of early detection of oral cancers among users of tobacco or alcohol or both, as well as other benign conditions whose early detection may improve oral health. Discouraging oral visual examination in primary care is clearly not in the interests of oral cancer control and improving oral health (Edwards 2013).

Self-Examination and Other Screening Methods

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 12–26 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). 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 conducted, 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.
- Oral cancer screening was initiated in Taiwan, China, in 2004, targeting those age 18 years and older who were smokers or betel nut chewers; the target population for oral cancer screening was revised in 2010 to cover smokers or chewers age 30 years and older. The screening program has led to almost half of the oral cancers diagnosed in stages I and II, with a declining trend in oral cancer mortality rates.

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 precancerous lesions may lead to early diagnosis of underlying 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 Tumor, Nodes, Metastasis (TNM) staging system is widely used for staging oral cancer (Patel and Shah 2005; Sobin and Wittekind 2002) (table 5.3): **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 IV, 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 the mandible, maxillary sinuses, and chest; computerized tomography (CT) scans; magnetic resonance imaging (MRI); and positron emission tomography (PET) imaging, depending on what resources are 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 LMICs.

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. Given the skills, expertise, and infrastructure required for staging and treatment with minimal physical, functional, and cosmetic morbidity, oral cancer treatment is usually provided in specialized cancer hospitals, such as comprehensive cancer centers, or in hospitals at the highest level of health services, third-level 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

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 cm or less (T1) and has not spread to regional organs, regional (neck) lymph nodes (N0), or distant organs (M0)	T1N0M0	Radical surgery or radical radiotherapy	> 90
II	Primary tumor is larger than 2 cm and smaller than 4 cm (T2) and has not spread to regional organs, regional (neck) lymph nodes (N0), or distant organs (M0)	T2N0M0	Radical surgery or radical radiotherapy; in selected cases, combination therapy	> 70
III	Primary tumor measures > 4 cm (T3) and has not spread to neck nodes (N0) or distant organs (M0); or tumor is any size (T1 to T3) and has spread to one lymph node measuring 3 cm 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	Tumor involves nearby structures, including the mandible, tongue muscles, maxillary sinus, and skin (T4); or tumor is any size but involves one lymph node measuring 3–6 cm on the same side of the neck (N2a) or one lymph node measuring no more than 6 cm on the opposite side of the neck (N2b), or two or more lymph nodes no more than 6 cm on any side of the neck (N2c); or lymph node involvement measuring more than 6 cm (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: Staging: Sobin and Wittekind 2002.
Note: cm = centimeter; TNM = Tumor, Node, Metastasis.

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 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).

External beam radiotherapy and brachytherapy—using radioactive sources implanted in the tumor—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, 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 IV)

Locally advanced tumors are aggressive, and locoregional treatment failure rates are high. A combined

modality approach integrating surgery, radiotherapy with or without chemotherapy, and planned and executed by a multidisciplinary team is always preferred. Appropriate importance should be given to factors such as functional and cosmetic outcomes 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 to radiotherapy alone in those with surgical margins showing cancerous changes indicating incomplete excision of the tumor (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 patients who have 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 who are in good general condition, 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 caused by 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 and peeling of the overlying skin, loss of hair 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 oral 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. 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 recurrence. Patients should be encouraged to give up tobacco and alcohol and know 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 report a five-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 survival rates for oral cancer for all stages combined from populations in LMICs such as China, Cuba, India, Pakistan, and Thailand ranged from 26 to 45 percent; for stages I and II, the survival rates ranged from 36 to 83 percent. The inferior survival rates in LMICs versus 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 LMICs

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 resource-limited settings, 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. 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. 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; the other, the only one from a resource-constrained environment, used data from a 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, screening was at ages 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 with the scenario of no screening. A variety of interventions was assessed, using 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 LMICs. 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 because of factors such as the underlying prevalence of disease and the

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, Bezemer, and Van Der Waal 2002	Netherlands	Individuals with OLP	Decision analytic model: all relevant clinical costs	Screening by oral specialist or dentist versus no screening	US$53,430 per ELS or US$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 ages 40 years and older in primary care settings	Decision analytic model: all relevant invitation and clinical costs	No screening compared with invitation and opportunistic screening	Opportunistic screening of high-risk individuals ages 40–60 years most cost-effective: US$19,000 per QALY
Subramanian and others 2009	India	13 clusters randomized in Kerala; those ages 35 years or older were eligible for the study	Cost-effectiveness assessment, including program and clinical costs	Visual inspection by trained health care workers compared with 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 men (ages 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 with no screening	A budget of US$3,363 per person over a 40-year cycle for screening is cost-effective

Note: ELS = equivalent life saved; LYS = life year saved; OLP = oral lichen planus; QALY = quality-adjusted life year.

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.

Future Research Needs

Primary prevention, especially smoking cessation, and secondary prevention, focused on high-risk individuals, are likely to be 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 are free of charge, patients may not be able to afford to lose a day's wages 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 interventions are affordable and cost-effective.

NOTES

The World Bank classifies countries according to four income groupings. Income is measured using gross national income per capita, in U.S. dollars, converted from local currency using the *World Bank Atlas* method. Classifications as of July 2014 are as follows:

- Low-income countries = US$1,045 or less in 2013
- Middle-income countries are subdivided:
  - Lower-middle-income = US$1,046–US$4,125
  - Upper-middle-income = US$4,126–US$12,745
- High-income countries = US$12,746 or more

1. Maps and figures in this chapter are based on incidence and mortality estimates for ages 0–69, consistent with reporting in all *DCP3* volumes. Global cancer statistics are estimates for the year 2012 and have been provided by the International Agency for Research on Cancer from its GLOBOCAN 2012 database. Observable population-based data were derived from Cancer Incidence in Five Continents, 10th edition and for trends over time from CI5 Plus (http://ci5.iarc.fr/CI5plus/Default.aspx). The discussion of burden (including risk factors), however, includes all ages unless otherwise noted. Interventions also apply to all age groups, except where age ranges or cutoffs are specified.

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