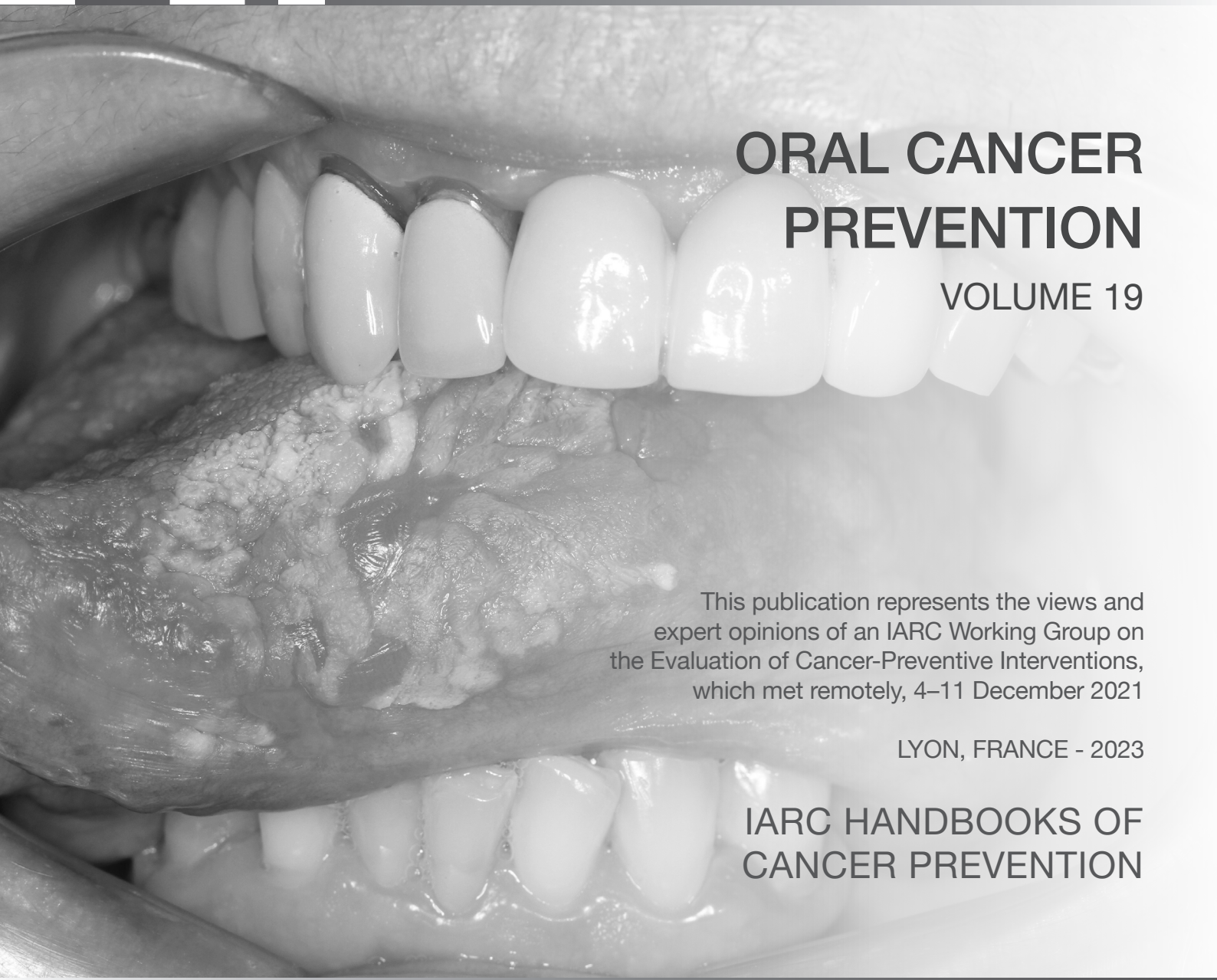
IARC HANDBOOKS



ORAL CANCER PREVENTION

VOLUME 19

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

1. ORAL CANCER AND ORAL POTENTIALLY MALIGNANT DISORDERS

1.1 Anatomy of the oral cavity and the oropharynx

1.1.1 Anatomy of the oral cavity

The oral cavity is the entrance to the gastrointestinal tract. It is bounded anteriorly by the lips, posteriorly by the faucial arches anterior to the tonsils, laterally by the cheeks (buccal mucosae), superiorly by the palate, and inferiorly by the muscular floor. The space between the labial mucosae of the lips or the buccal mucosae of the cheeks and the teeth is defined as the oral vestibule (labial or buccal vestibule) (Fig. 1.1).

The oral mucous membrane is covered by the stratified squamous epithelium, which comprises four different layers and protects the inside of the oral cavity. The oral mucosa is subdivided into masticatory mucosa (keratinized), lining mucosa (non-keratinized), and specialized mucosa. The mucosa has the capacity to undergo constant regeneration (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

The subsites of the oral cavity are described below according to the International Classification of Diseases for Oncology (ICD-O) coding: lip (C00), tongue (C02), gingivae (C03), floor of the mouth (C04), palate (C05), and buccal mucosa and oral commissures (C06).

(a) Lips

The lips surround the oral aperture, marking the external boundary of the mouth, and are used for speech, mastication, swallowing, and controlling the size of the oral aperture.

The upper lip extends from the inferior border of the nose and laterally up to the nasolabial grooves. The lower lip is bordered by the labiomental groove. The upper and lower lips meet at the oral commissures.

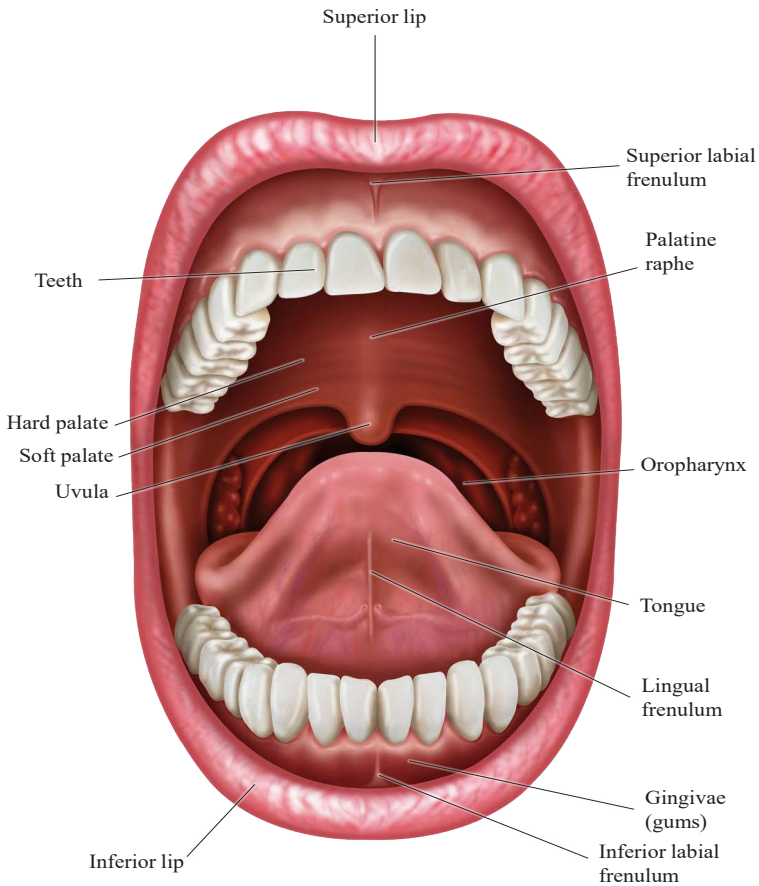
The lips are composed of a muscle that is covered externally by skin and internally by non-keratinized labial mucosa, with the vermilion zone in between. The vermilion zone has keratinized epithelium and is highly vascularized and densely innervated. Numerous mucous glands are present on the labial mucosa. The lymphatic drainage of the lips is primarily to the submandibular lymph nodes and to a lesser extent to the submental, intraparotid, or internal jugular lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(b) Tongue

The tongue is a muscular organ that occupies the floor of the mouth. It is attached to the mandible (lower jawbone) and the hyoid bone by the root. The anterior two thirds of the structure is free to move.

The dorsum is divided into an anterior oral part and a posterior pharyngeal part, which

Fig. 1.1 Anatomy of the oral cavity



forms the base of the tongue. The anterior two thirds of the dorsum is covered by specialized mucosa that contains numerous papillae, some of which bear taste buds. The posterior third slopes down towards the epiglottis and has a nodular appearance because of the underlying lingual tonsils. Two other important anatomical areas of the tongue are the lateral borders and the ventral surface (undersurface) of the tongue.

The extrinsic muscles stabilize and move the tongue, and the intrinsic muscles maintain its shape. The main functions of the tongue are mastication, swallowing, speech, oral cleansing, and taste.

The tongue is highly vascularized; lingual veins are visible on the inferior surface. The anterior two thirds of the tongue drains into the submental and submandibular nodes, which empty into the deep cervical lymph nodes. The posterior third of the tongue drains directly into the deep cervical lymph nodes. The lymphatic drainage is significant because some areas of the tongue drain into bilateral cervical lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(c) Gingivae (gums)

The gingiva is the highly keratinized mucosa that immediately surrounds the neck of an erupted tooth and is firmly attached to the alveolar margins of the jaws. At the gingival crest, the epithelium slopes towards the tooth to form a sulcus and is attached to the tooth surface. The part of the gingiva facing the oral cavity is masticatory mucosa, and the change from alveolar mucosa to gingival mucosa is identifiable by an abrupt colour change of the tissue. Healthy gingiva has some stippling on its surface. The lymphatic drainage of the gingivae is to the submandibular lymph nodes. In addition, the lower anterior gingiva drains into the submental nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(d) Floor of the mouth

The floor of the mouth is a horseshoe-shaped region situated between the movable part of the tongue and the mylohyoid muscles. The lingual frenulum is a mucosal fold that arises near the base of the tongue and extends onto the inferior surface of the tongue. The protuberance at the anterior floor of the mouth is called the sublingual papilla or caruncle; this is where the submandibular salivary ducts open into the oral cavity. On either side laterally and backward are the sublingual folds, which cover the submandibular ducts and the sublingual salivary glands. The covering epithelium is non-keratinized and is much thinner than for other subsites of the oral cavity. The lymphatic drainage is mainly to the submandibular lymph nodes; the anterior part drains into the submental nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(e) Hard palate

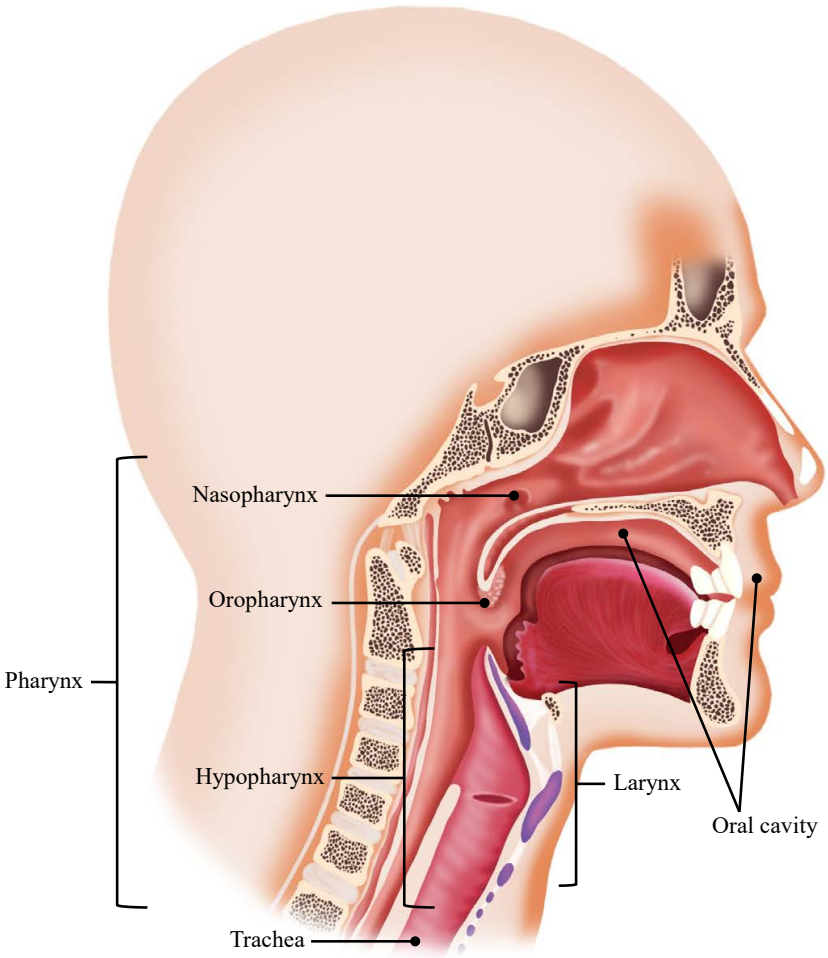
The palate forms the roof of the oral cavity and consists of two parts: the hard palate and the soft palate. The hard palate is part of the oral cavity, and the soft palate is part of the oropharynx.

The palatine processes of the maxillae (upper jawbone) and the horizontal plates of the palatine bones form the hard palate, which is bounded anteriorly by the maxillary teeth (upper teeth) and continues posteriorly to the soft palate. The palatine raphe extends anteroposteriorly in the midline, and an irregular set of rugae radiates from it in the anterior part of the hard palate. The incisive papilla lies at the anterior end of the hard palate, which contains the opening of the incisive canal. The hard palate has a thick keratinized mucosa, which is tightly bound to the periosteum anteriorly and contains minor salivary glands in the posterior submucosa. The lymphatic drainage is primarily to the deep cervical lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(f) Buccal mucosa

The buccal mucosa is the mucosal lining of the cheeks, extending from the line of contact of the opposing lips to the pterygomandibular raphe. It extends to the line of attachment of the alveolar mucosa superiorly and inferiorly, which forms the anterolateral boundary of the oral vestibule. The buccal mucosa has a non-keratinized epithelium and is firmly attached to the underlying muscle. The submucosa contains minor salivary glands. A white line coinciding with the occlusal plane, called the linea alba, may be present. The parotid ducts of the parotid gland on either side pierce the buccal mucosa opposite the second maxillary molar tooth and present as the parotid papillae. The lymphatic drainage is primarily to the submandibular lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

Fig. 1.2 Anatomy of the pharynx



1.1.2 Anatomy of the oropharynx and the soft palate

The oropharynx is a tube-shaped fibromuscular structure behind the oral cavity, continuous with the nasopharynx superiorly and the hypopharynx inferiorly (Fig. 1.2). The oropharynx has functional roles in both the respiratory system and the digestive system. It extends from the lower surface of the soft palate to the upper border of the epiglottis and communicates with the oral cavity anteriorly. The posterior wall of the oropharynx is formed by the three constrictor muscles. The palatine tonsils project into the lateral wall of the oropharynx from the tonsillar fossa. The oropharynx is covered by a non-keratinized stratified squamous epithelium (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

The soft palate is a mobile flap that extends backward from the hard palate and fuses with the lateral wall of the oropharynx. It is made up of five paired muscles and an aponeurosis. The soft palate can be raised to make contact with the posterior wall of the oropharynx to close off the nasopharynx during swallowing.

The non-keratinized mucosa covers the oral side and the posterior part of the nasal side, and the respiratory mucosa covers the anterior part of the nasal side. The submucosa of both surfaces contains mucous glands and taste buds. Lymphoid follicles are scattered on the oral surface. The uvula hangs down at the midline of the posterior end of the soft palate and helps in phonation (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

1.2 Global burden of oral cancer, oropharyngeal cancer, and oral potentially malignant disorders

1.2.1 Oral cancer and oropharyngeal cancer

(a) Global incidence and mortality

Oral cancer, along with oropharyngeal cancer, is among the most common cancer types globally.

In 2020, there were an estimated 377 713 new cases of oral cancer worldwide, with global age-standardized incidence rates (ASIR) of 6.0 per 100 000 men and 2.3 per 100 000 women. There were an estimated 177 757 deaths from oral cancer, with global age-standardized mortality rates (ASMR) of 2.8 per 100 000 men and 1 per 100 000 women.

In 2020, there were an estimated 98 412 new cases of oropharyngeal cancer worldwide, with global ASIR of 1.8 per 100 000 men and 0.4 per 100 000 women. There were an estimated 48 143 deaths from oropharyngeal cancer, with global ASMR of 0.89 per 100 000 men and 0.17 per 100 000 women (Ferlay et al., 2020).

For both oral cancer and oropharyngeal cancer, the incidence increases with age (Fig. 1.3).

(b) Geographical variations in incidence and mortality

In 2020, the incidence rates of oral cancer (including lip cancer) were highest in Melanesia and South Asia (Ferlay et al., 2020; Miranda-Filho and Bray, 2020). The rates (ASIR, per 100 000, in both sexes) were highest in Papua New Guinea (21.2), followed by Pakistan (10.1), India (9.8), Sri Lanka (9.7), and Bangladesh (9.5) (Ferlay et al., 2020). For oral cancer mortality rates, the pattern was similar. The rates (ASMR, per 100 000, in both sexes) were highest in Papua New Guinea (8.3), followed by Pakistan (6.4), Bangladesh (5.6), India (5.4), and Sri Lanka (4.5) (Ferlay et al., 2020) (Fig. 1.4).

Both ASIR and ASMR were consistently higher in men than in women across the world (Ferlay et al., 2020; Miranda-Filho and Bray, 2020).

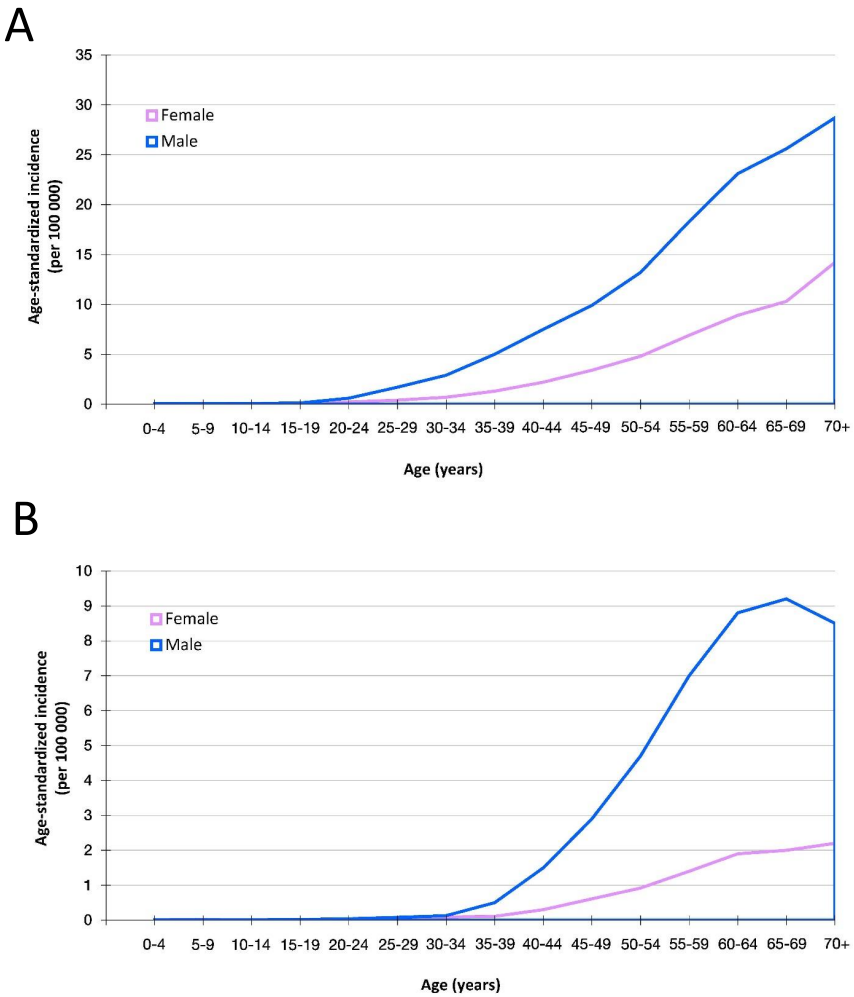
In 2020, the incidence rates of oropharyngeal cancer were highest in Europe. The rates (ASIR, per 100 000, in both sexes) were highest in Denmark (5.0), France (4.3), and Romania (4.3). For oropharyngeal cancer mortality, the rates (ASMR, per 100 000, in both sexes) were highest in Slovakia (2.5), followed by the Republic of Moldova (2.3) and Romania (2.3) (Ferlay et al., 2020).

(c) Socioeconomic status

For oral cancer (including lip cancer), the ASIR and ASMR were highest in countries with medium levels of the Human Development Index (HDI); for oropharyngeal cancer, the ASIR was highest in countries with very high HDI, and the ASMR was highest in countries with medium HDI (Ferlay et al., 2020) (Fig. 1.5). HDI was found to be negatively associated with the annual percentage change in the ASIR and ASMR for oral cancer (Ren et al., 2020).

A meta-analysis of 41 case–control studies revealed that low socioeconomic status increased the risk of oral cancer (pooled adjusted odds

Fig. 1.3 Age-specific incidence curves in the world population for oral cancer (A) and oropharyngeal cancer (B), 2020



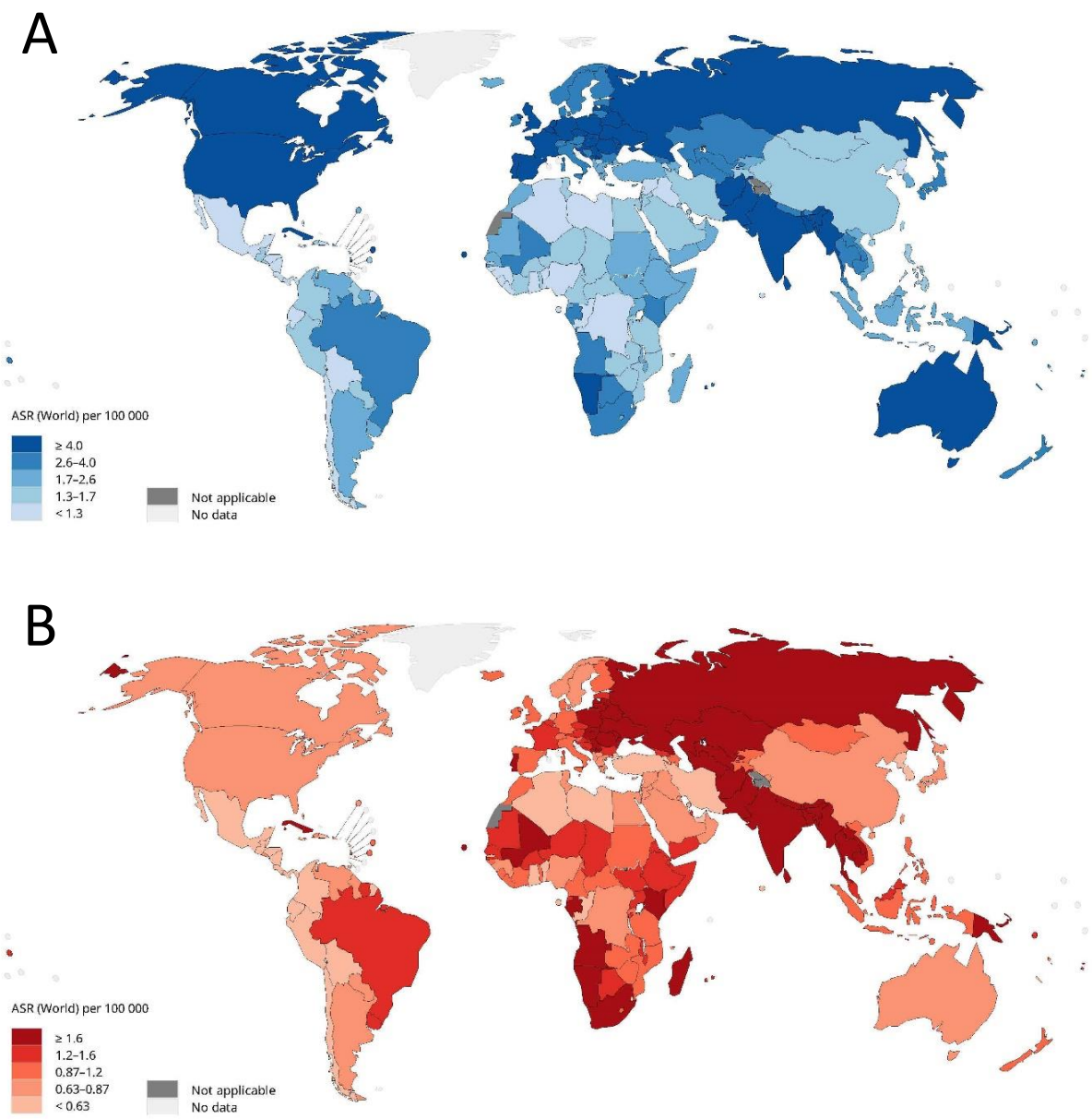
From Ferlay et al. (2020).

ratio [OR], 3.41; 95% confidence interval [CI], 2.14–5.44; n = 2), as did low occupational social class (pooled adjusted OR, 1.41; 95% CI, 1.10–1.79; n = 4) and low educational attainment (pooled adjusted OR, 1.74; 95% CI, 1.33–2.27; n = 17) (Conway et al., 2008). A large pooled analysis by the International Head and Neck Cancer Epidemiology (INHANCE) consortium found an association between low educational attainment and increased risk of oral cancer (OR, 1.33; 95% CI, 1.02–1.75) and oropharyngeal cancer (OR, 1.88; 95% CI, 1.23–2.88), independent of age, sex, centre, cigarette smoking, and alcohol consumption (Conway et al., 2015).

(d) Time trends in incidence

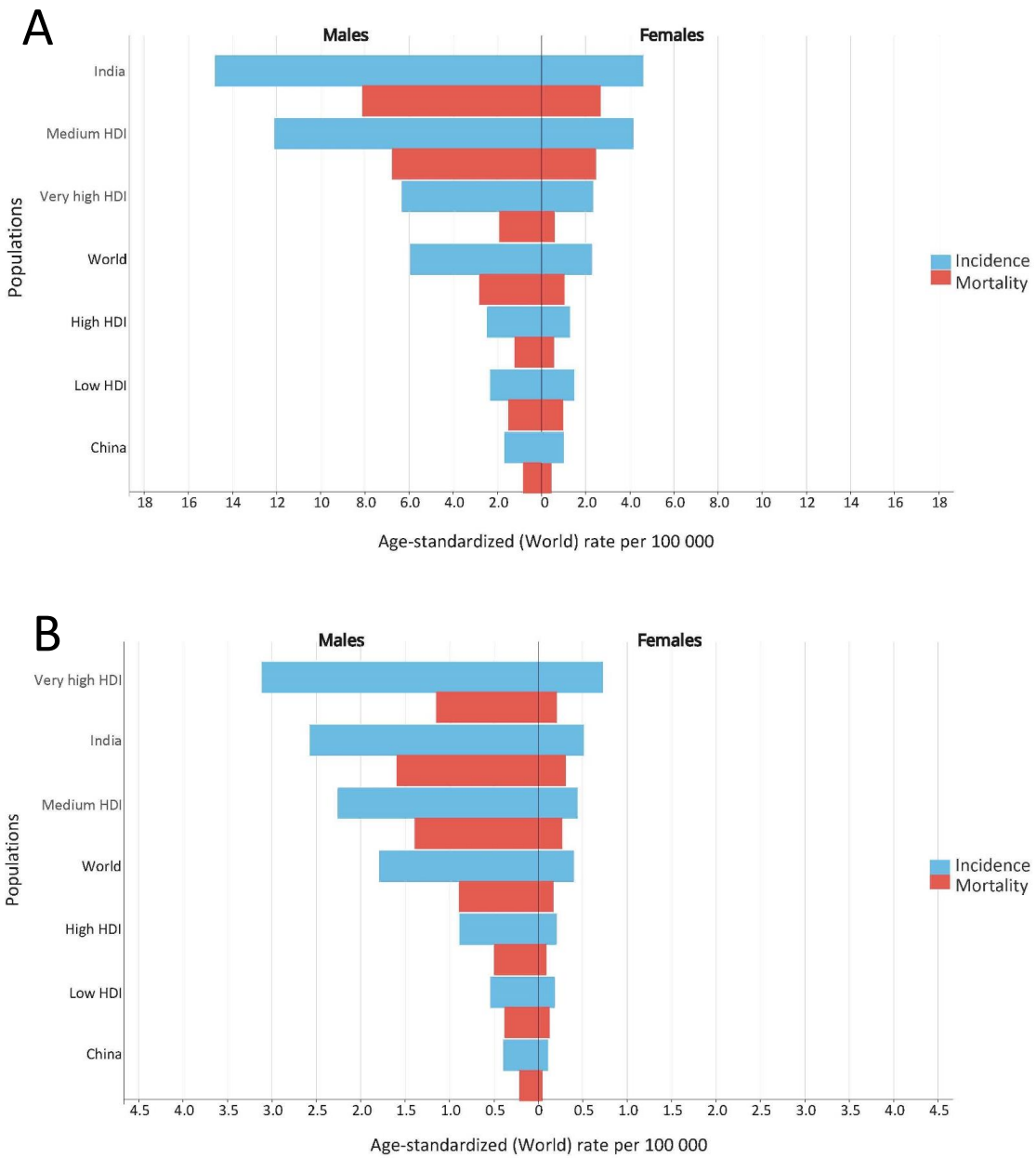
During the past two decades, incidence rates of oral and oropharyngeal cancers combined have decreased in several countries in North America, South-East Asia, and Europe, especially in males. However, in females, incidence rates have increased mainly in the European countries, and in males, incidence rates have increased in the United Kingdom, Japan, and

Fig. 1.4 Global distribution of estimated age-standardized (World) incidence rates (A) and mortality rates (B) per 100 000 for oral cancer in both sexes, 2020



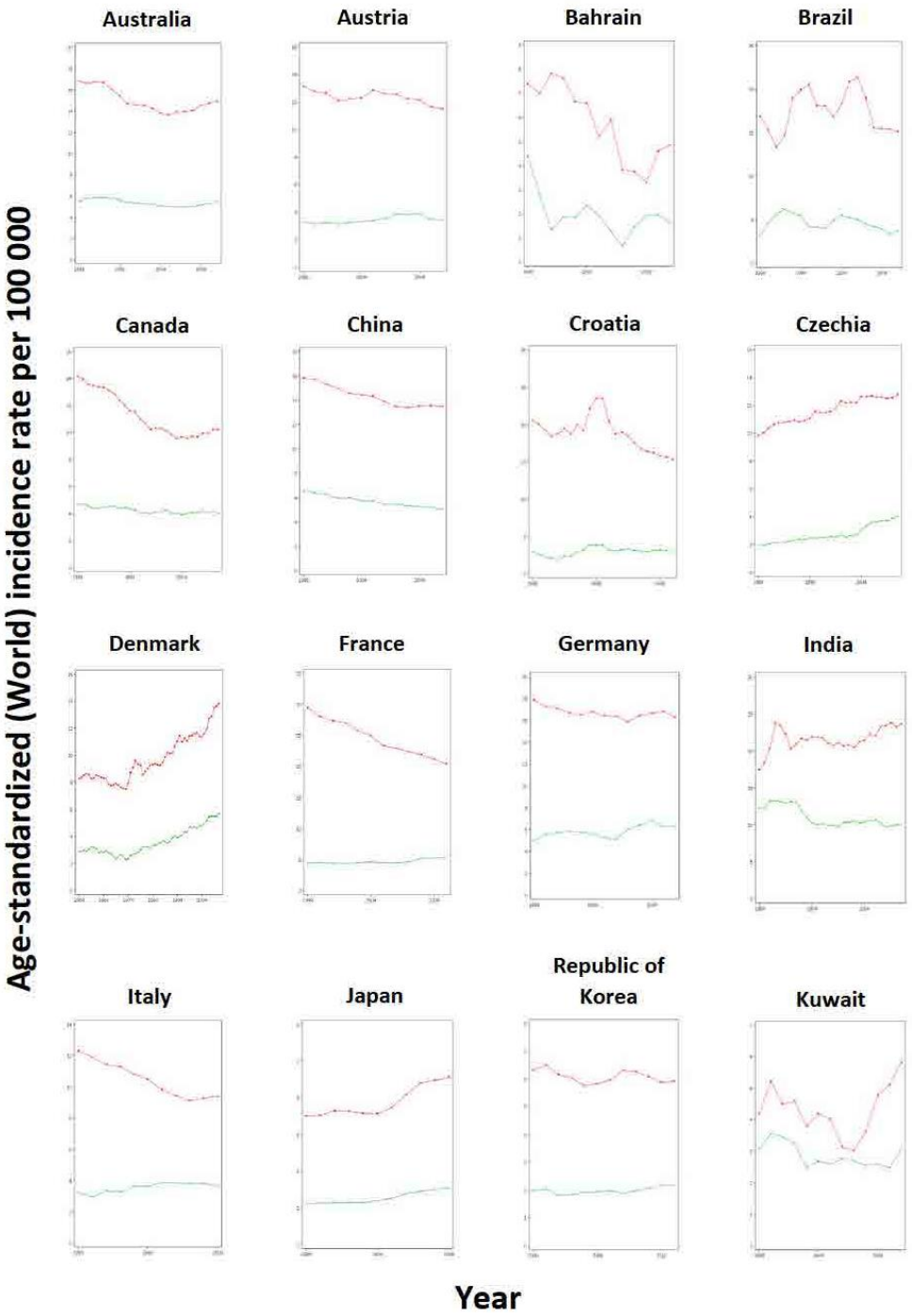
From Ferlay et al. (2020).

Fig. 1.5 Estimated age-standardized (World) incidence and mortality rates per 100 000 for oral cancer (A) and oropharyngeal cancer (B), by Human Development Index (HDI) level, 2020



From Ferlay et al. (2020).

Fig. 1.6 Time trends in age-standardized (World) incidence rates per 100 000 for oral cancer and oropharyngeal cancer combined, by country, in males (red) and females (green)



From Ferlay et al. (2020).

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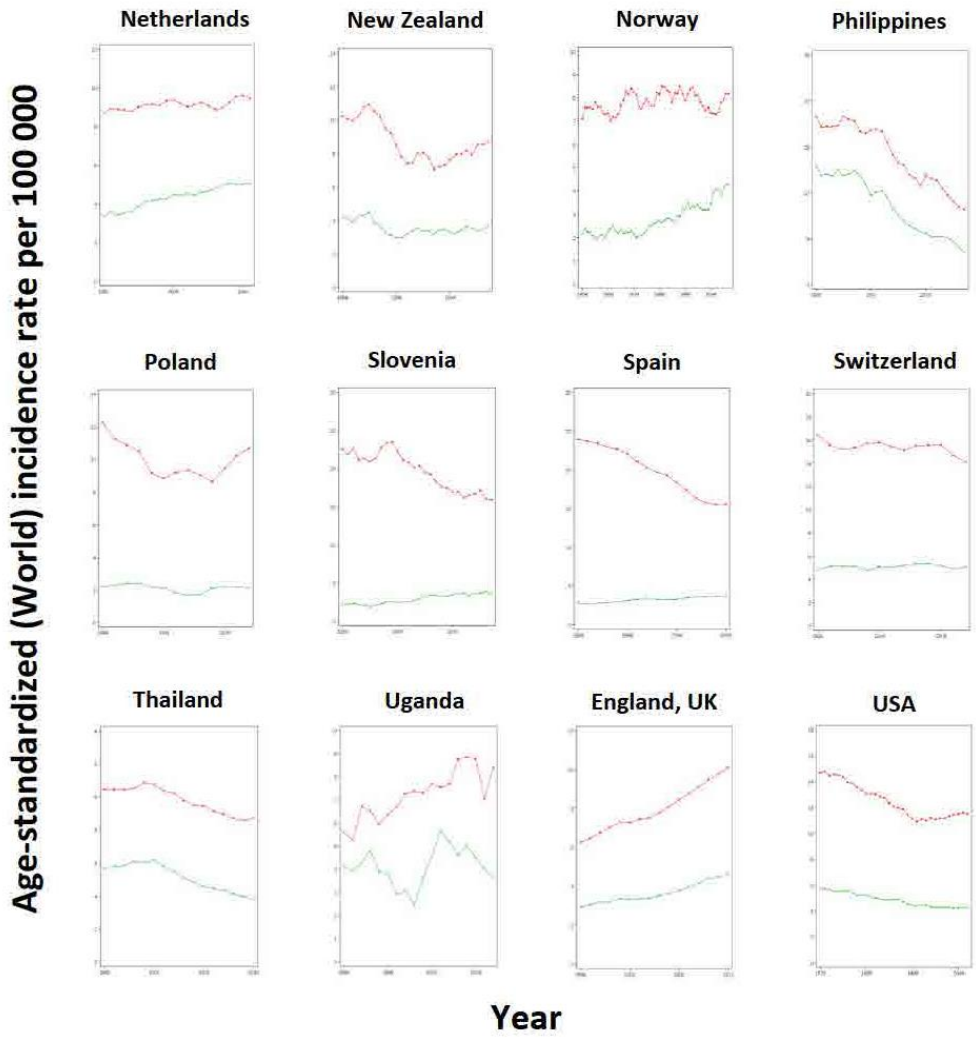


From Ferlay et al. (2020).

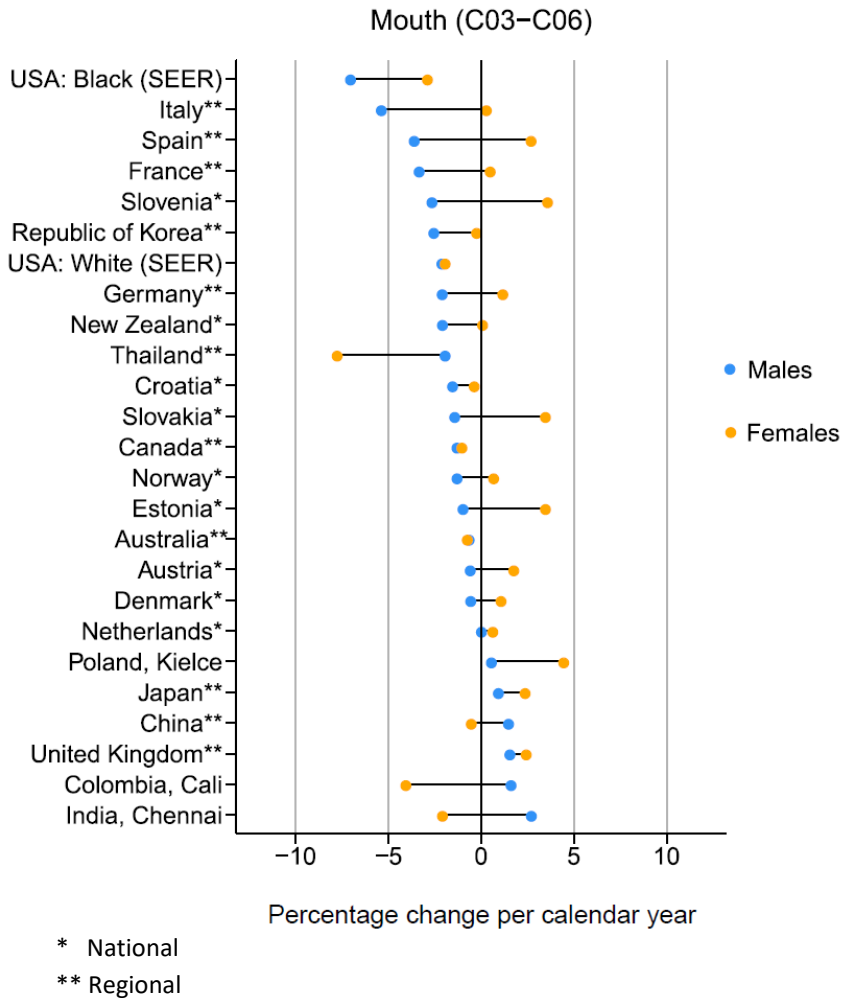
Czechia (Fig. 1.6; Bosetti et al., 2020; Ferlay et al., 2020; Lin, 2020). Incidence rates of oropharyngeal cancer specifically have increased in several countries in the Americas, Europe, and Asia, especially in males (Bosetti et al., 2020; Menezes et al., 2021).

In most countries, incidence rates of cancer of the oral cavity (excluding the lip and the tongue) have decreased more in males than in females. In females, incidence rates have decreased in Thailand, Colombia, and India (Fig. 1.7; Miranda-Filho and Bray, 2020). Incidence rates of tongue cancer have increased in the USA and Thailand (Argirion et al., 2019; Kim and Kim, 2020).

(e) Projections of incidence and mortality

Table 1.1 shows estimates of the incidence and mortality for oral cancer and oropharyngeal cancer in 2020 and projected to 2040, by HDI category and overall. Globally, the projected increase from 2020 to 2040 in the estimated

Fig. 1.7 Estimated annual percentage change (EAPC) of the trends in age-standardized rates of mouth cancer in selected registry populations by sex, in 1998–2012, sorted in descending order according to EAPC in men



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number of new cases per year is 49.6% for oral cancer and 40.2% for oropharyngeal cancer. For both oral cancer and oropharyngeal cancer, the highest increases by 2040 in the numbers of new cases and deaths are expected to occur in countries with low HDI (Table 1.1) (Ferlay et al., 2020).

(f) Lip cancer

Incidence rates of lip cancer are relatively high in certain parts of the world as a result of excessive exposure to ultraviolet radiation from sunlight. The incidence rates are highest in Australia in both sexes, followed by Spain and Poland in males and the Netherlands and Norway in females (Fig. 1.8A). Although incidence rates of lip cancer have decreased in most countries, incidence rates have increased in females in Germany, the Netherlands, Norway, China, Slovakia, and Japan and in males in India (Fig. 1.8B; Miranda-Filho and Bray, 2020).

Table 1.1 Global burden of oral cancer and oropharyngeal cancer: estimated annual numbers of incident cases and deaths, by HDI category and overall, in 2020 and projected to 2040

HDI category[a]	Population in 2020 (millions)	Number of new cases		Increase (%)	Number of deaths		Increase (%)
		2020	2040		2020	2040	
Oral cancer							
Very high HDI	1 564	118 036	147 172	24.7	37 048	48 590	31.2
High HDI	2 909	72 418	112 182	54.9	34 765	57 958	66.7
Medium HDI	2 327	177 018	285 228	61.1	99 662	161 437	62.0
Low HDI	990	10 126	20 163	99.1	6 251	12 554	100.8
World	7 791	377 598	564 745	49.6	177 726	280 539	57.8
Oropharyngeal cancer							
Very high HDI	1 564	47 971	56 233	17.2	18 592	23 522	26.5
High HDI	1 564	20 614	30 097	46.0	11 248	17 532	55.9
Medium HDI	2 327	27 932	47 869	71.4	17 053	29 241	71.5
Low HDI	990	1 839	3 727	102.7	1 230	2 510	104.1
World	7 791	98 356	137 926	40.2	48 123	72 805	51.3

HDI, Human Development Index.
[a] The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Created using data from Ferlay et al. (2020).

1.2.2 Oral potentially malignant disorders

An oral potentially malignant disorder (OPMD) is defined as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer (Warnakulasuriya et al., 2007). OPMDs share common risk factors with invasive carcinoma of the oral cavity. OPMDs include leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, actinic keratosis (actinic cheilitis), palatal lesion in reverse smokers (in reverse smoking, the smoker places the lit end of the cigarette, rather than the unlit end, into their mouth and inhales the smoke), oral lupus erythematosus, dyskeratosis congenita, oral lichenoid lesion, and oral graft-versus-host disease (Warnakulasuriya and Greenspan, 2020).

The overall global prevalence of OPMDs is 4.47% (95% CI, 2.43–7.08%), with geographical variations; the highest prevalence is observed in Asia (10.54%; 95% CI, 4.60–18.55%), followed by South America and the Caribbean (3.93%; 95% CI, 2.43–5.77%), the Middle East (3.72%; 95% CI, 2.91–4.67%), and Europe (3.07%; 95% CI, 1.64–4.93%) (Mello et al., 2018).

Globally, the highest prevalence is observed for oral submucous fibrosis (4.96%; 95% CI, 2.28–8.62%). Other common OPMDs include leukoplakia (4.11%; 95% CI, 1.98–6.97%), actinic cheilitis (2.08%; 95% CI, 0.94–3.67%), erythroplakia (0.17%; 95% CI, 0.07–0.32%) (Mello et al., 2018), and oral lichen planus (1.01%; 95% CI, 0.74–1.32%) (González-Moles et al., 2021).

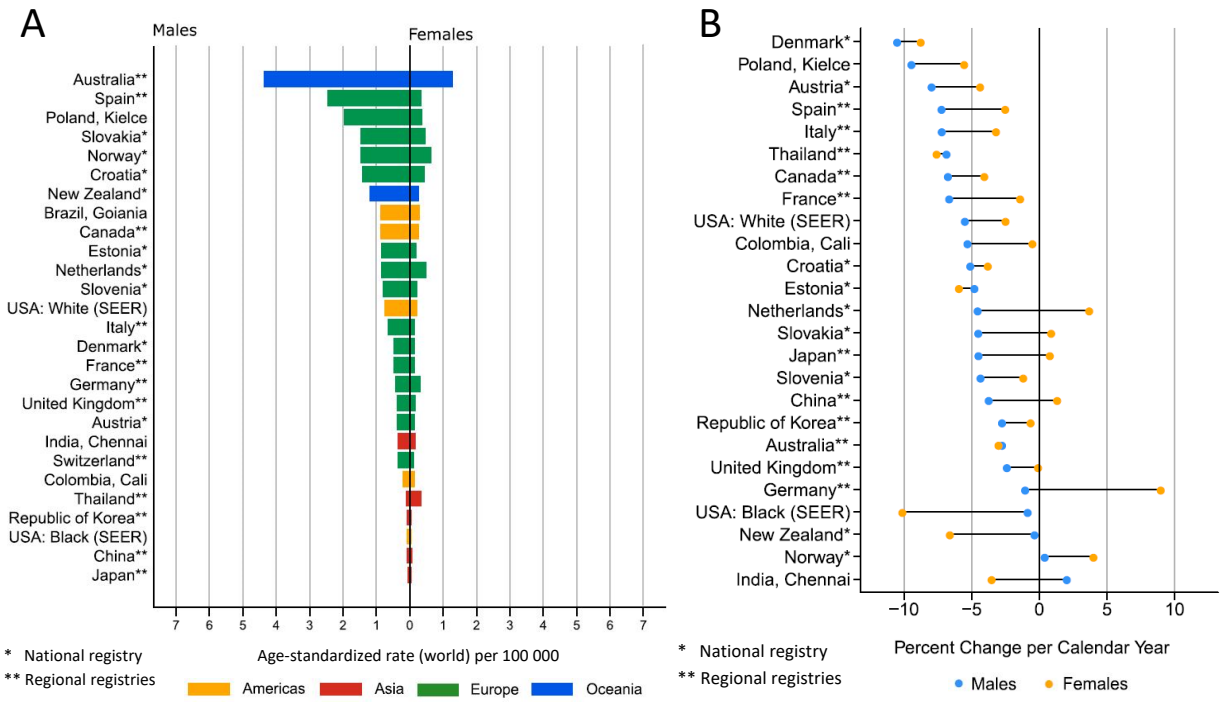
1.3 Oral neoplasia

1.3.1 Classification and natural history of OPMDs and oral cancer

Oral cancer includes cancers of the lip, other and unspecified parts of the tongue (excluding the lingual tonsils), gum, floor of the mouth, palate, and other and unspecified parts of the mouth (Conway et al., 2018).

The term OPMD was introduced in 2005, replacing the terms "oral precancerous/premalignant lesions and conditions" (Warnakulasuriya

Fig. 1.8 (A) Bar chart of age-standardized incidence rates of lip cancer in selected countries, by sex, all ages, in 2008–2012. (B) Estimated annual percentage change (EAPC) of the trends in age-standardized rates of lip cancer in selected registry populations by sex, in 1998–2012, sorted in descending order according to EAPC in men



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et al., 2007). OPMDs comprise a wide range of disorders (Box 1.1) with varying rates of malignant transformation into oral cancer, of which oral squamous cell carcinoma (OSCC) is the most common type (Holmstrup et al., 2006; Speight et al., 2018; Farah et al., 2019). In 2020, the World Health Organization (WHO) Collaborating Centre for Oral Cancer recommended a list of OPMDs, which include leukoplakia, proliferative verrucous leukoplakia (PVL), erythroplakia, oral submucous fibrosis, oral lichen planus (OLP), actinic keratosis (actinic cheilitis), nicotinic stomatitis in reverse smokers, oral lupus erythematosus, and dyskeratosis congenita. Oral lichenoid lesion and oral graft-versus-host disease were added to the list on the basis of the available evidence on their malignant potential (de Araújo et al., 2014; González-Moles et al., 2019; Warnakulasuriya and Greenspan, 2020). The diagnosis of an OPMD significantly increases the risk of developing oral cancer during a lifetime (Warnakulasuriya et al., 2007; Reibel et al., 2017; Speight et al., 2018; Warnakulasuriya and Greenspan, 2020).

(a) Clinical presentation of OPMDs

Leukoplakia is a predominantly white plaque of questionable risk having excluded other known diseases that carry no increased risk of cancer (Warnakulasuriya et al., 2007). This OPMD has a wide range of clinical appearances, ranging from homogeneous to non-homogeneous, including nodular leukoplakia, verrucous leukoplakia, and erythroleukoplakia

Box 1.1 Classified oral potentially malignant disorders (OPMDs)

Erythroplakia
Erythroleukoplakia
Leukoplakia
Proliferative verrucous leukoplakia
Oral submucous fibrosis
Palatal lesion associated with reverse smoking
Oral lichenoid lesion[a]
Oral lichen planus
Actinic keratosis (actinic cheilitis)
Smokeless tobacco keratosis[b]
Oral graft-versus-host disease
Oral lupus erythematosus
Familial cancer syndromes including Fanconi anaemia, dyskeratosis congenita, xeroderma pigmentosum, Li–Fraumeni syndrome, Bloom syndrome, ataxia–telangiectasia, and Cowden syndrome

[a] Oral lesion resembling lichen planus but lacking typical clinical or histopathological appearances.
[b] Risk varies with tobacco type.
Adapted from WHO Classification of Tumours Editorial Board (2023).

(Warnakulasuriya and Greenspan, 2020). Several other white lesions should be excluded to arrive at the clinical diagnosis of leukoplakia, such as white sponge naevus, acute pseudomembranous candidiasis, frictional keratosis, OLP, chronic hyperplastic candidiasis, leukoedema, chemical injury, uremic stomatitis, nicotinic stomatitis, skin grafts, and oral hairy leukoplakia (Warnakulasuriya, 2018).

Proliferative verrucous leukoplakia presents as multiple white patches at different sites in the oral cavity (usually on the gingiva, palate, and alveolar mucosa), with a preponderance in elderly women. PVLs start as flat lesions, and most of them progress to a verrucous appearance. In the early stages, PVL may mimic OLP clinically and histologically (McParland and Warnakulasuriya, 2021; Thompson et al., 2021).

Erythroplakia is a predominantly fiery red patch that cannot be characterized clinically or pathologically as any other definable disease (Warnakulasuriya et al., 2007). Other definable red lesions should be excluded to arrive at the clinical diagnosis of erythroplakia, such as erythematous candidiasis, inflammatory conditions, denture-induced stomatitis, erythema migrans, desquamative gingivitis, erosive OLP, oral lupus erythematosus, and vesiculobullous disorders (Reichart and Philipsen, 2005).

Most lesions of *oral lichen planus* present as white striae (reticular or annular) or plaques; some have papular, atrophic, erosive, bullous, or ulcerative features. The lesions are usually present bilaterally (Warnakulasuriya and Greenspan, 2020). Incipient PVL often mimics OLP lesions both clinically and histologically (Gilligan et al., 2021); this leads to diagnostic challenges.

Common signs and symptoms of *oral submucous fibrosis* are a burning sensation when eating spicy food, diffuse blanching of oral mucosa, and restricted mouth opening. In addition, restriction in tongue movement, palpable fibrous bands, a leathery feeling of the mucosa, depapillation of the tongue, shrunken uvula, and sunken cheeks are present to various degrees (Tilakaratne et al., 2006).

(b) Histopathological spectrum of OPMDs

Histopathological features vary depending on the type of OPMD. However, the presence of variable levels of epithelial dysplasia is the most

important histopathological feature common to all OPMDs, and this is a fairly reliable biological marker, which guides treatment stratification based on the risk of malignant transformation. Epithelial dysplasia in the oral mucosa is graded into three categories: mild, moderate, and severe. Grading of epithelial dysplasia using this scale is subjective and leads to significant intra-examiner and inter-examiner variability (Tilakaratne et al., 2019). In 2017, the fourth edition of the WHO Classification of Head and Neck Tumours introduced a new binary grading system: low-risk and high-risk epithelial dysplasia (Reibel et al., 2017).

The histopathological spectrum of leukoplakias varies from cases of keratosis without dysplasia to mild, moderate, or severe dysplasia. Erythroplakia is a high-risk lesion because most cases at diagnosis are either severe epithelial dysplasia or in situ OSCC. PVL is a lesion with minimal dysplasia, although about 50% of PVLs transform into OSCC. Early cases of PVL have histopathological features similar to those of OLP, which may lead to misdiagnosis (Thompson et al., 2021). OLP has orthokeratinized or parakeratinized surface epithelium with a band-like lymphocytic infiltrate in the upper corium and associated basal cell destruction and apoptosis. Epithelial dysplasia may be present in a minority of OLP lesions, and this feature increases the risk of malignant transformation. Oral submucous fibrosis has characteristic histopathological features, such as atrophy of the surface epithelium and hyalinization and fibrosis of the submucosa, which extend deep into the underlying connective tissue and muscle as the disease progresses. Atrophic surface epithelium may have features of epithelial dysplasia in some cases (Utsunomiya et al., 2005).

(c) Malignant transformation of OPMDs

OPMDs are a heterogeneous group of lesions, and the rates of transformation to cancer vary from 1.4% to 49.5% (Iocca et al., 2020). Rates of malignant transformation of OPMDs vary substantially depending on the study population, risk habits, and site in the oral cavity, and from study to study (Reibel, 2003; Bouquot et al., 2006; Napier and Speight, 2008).

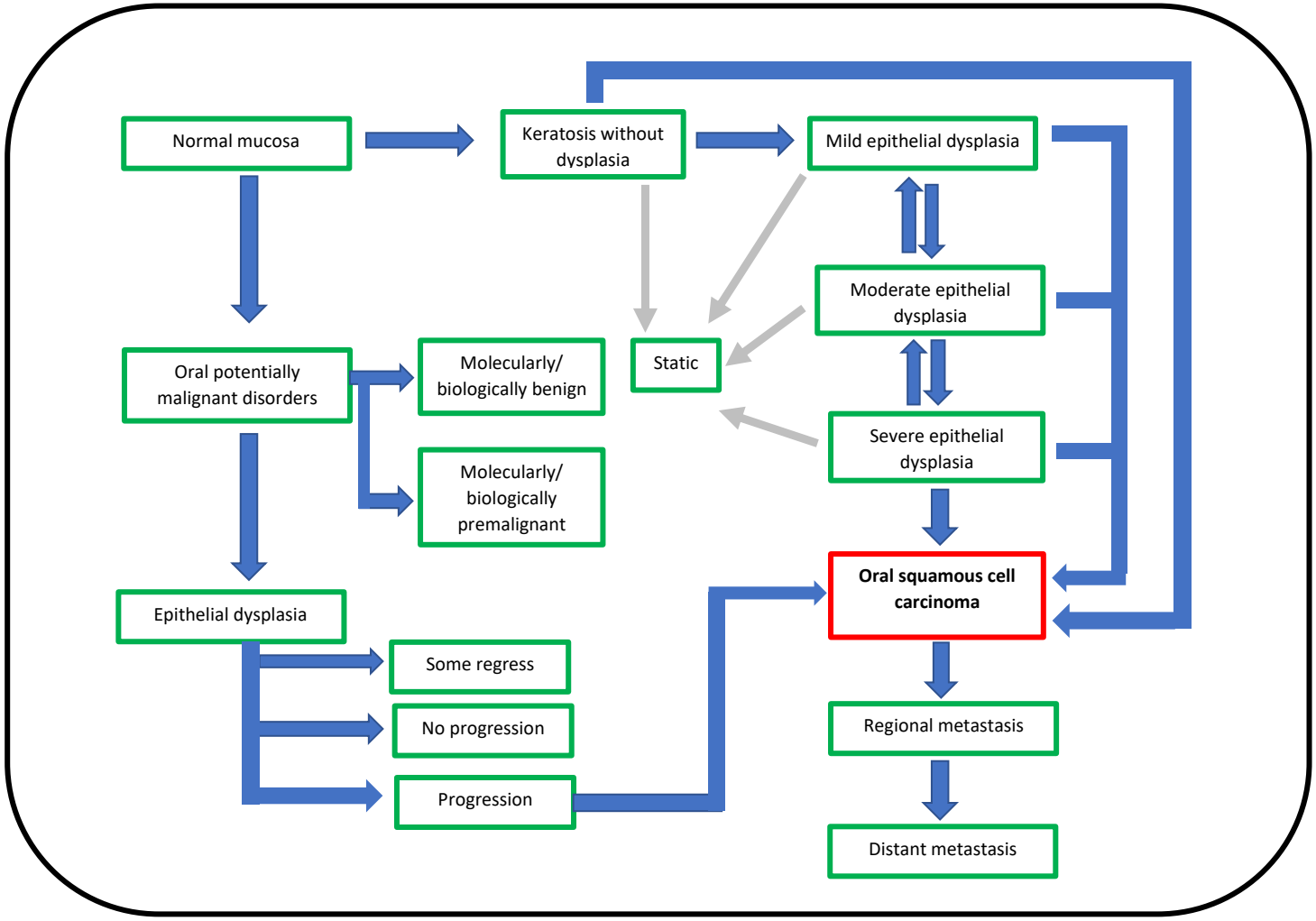
PVL and erythroplakia have the highest malignant transformation rates (30–50%), and OLP has the lowest (~1–2%) (Warnakulasuriya and Greenspan, 2020). The risk of transformation of leukoplakia depends on the clinical type and grade of epithelial dysplasia (Mehanna et al., 2009). Globally, the malignant transformation rate for leukoplakia was reported as 1.36% per year (95% CI, 0.69–2.03%) by Petti (2003) and as 9.8% (95% CI, 7.9–11.7%) in the systematic review and meta-analysis by Aguirre-Urizar et al. (2021) based on 5-year data. The natural history of leukoplakia is a dynamic rather than a static process with respect to malignant transformation. The malignant transformation rates of oral submucous fibrosis vary widely across studies, ranging from 7% to 13% (Tilakaratne et al., 2006; Ekanayaka and Tilakaratne, 2016).

Over time, OPMDs may persist unchanged, increase in size, regress in size, or even completely resolve (Fig. 1.9), which has been shown in many follow-up studies (Mehta et al., 1972; Gupta et al., 1980; Silverman et al., 1984; Holmstrup et al., 2006; Speight et al., 2018; Farah et al., 2019). Even in the absence of significant epithelial dysplasia, some OPMDs can progress to OSCC with time; therefore, lifetime clinical follow-up is highly recommended (Villa et al., 2019).

(d) Clinical features of oral cancer

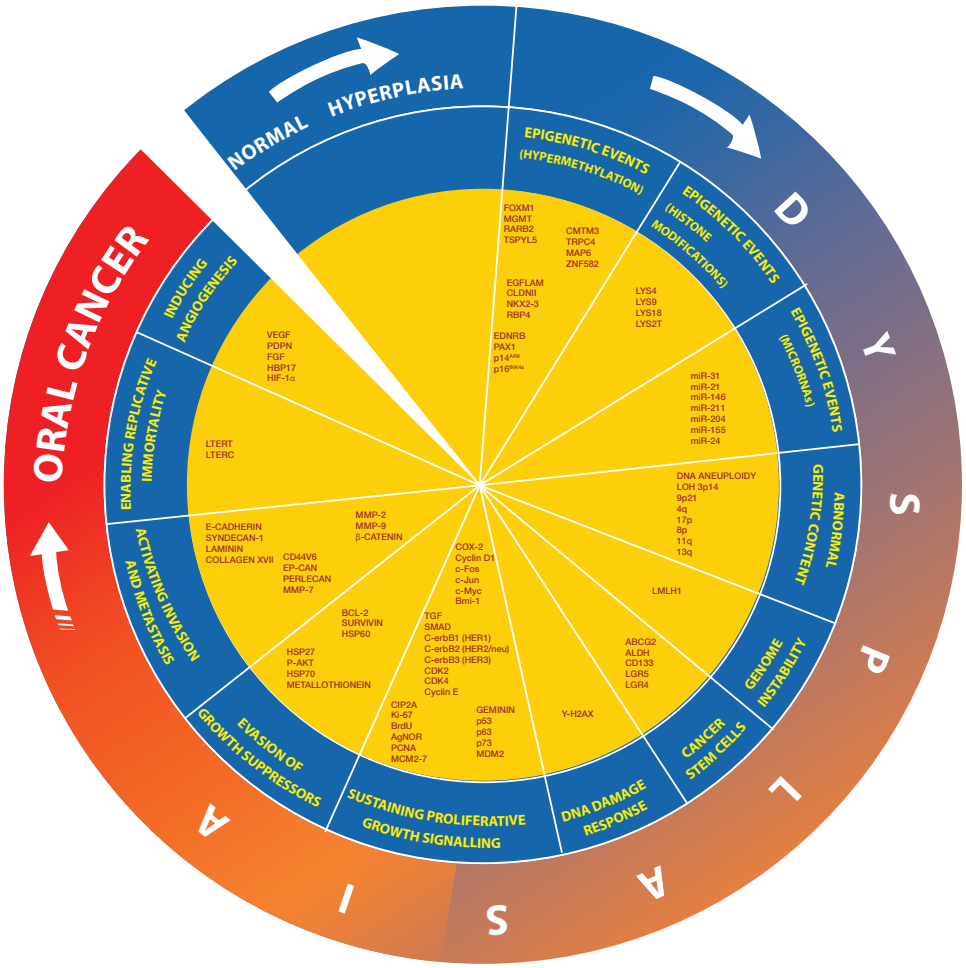
The clinical features of oral cancer vary depending on the site and the stage of clinical presentation (Bagan et al., 2010; Dissanayaka et al., 2012). The two most common sites for oral cancer are the tongue and the buccal mucosa. Other sites of involvement are the floor of the mouth, the gingivae, and the palate (Warnakulasuriya, 2009). The lesions have a variable size, ranging in diameter from a few

Fig. 1.9 Natural history of oral potentially malignant disorders and oral cancer



Created by the Working Group.

Fig. 1.10 Molecular events in the natural history of oral cancer



LOH, loss of heterozygosity.
Created by the Working Group.

millimetres to several centimetres in advanced cases.

In the initial stages, oral malignant lesions present as well-demarcated erythroleukoplakic lesions consisting of red, white, or red and white areas with a slight roughness along with reduced elasticity or induration of the soft tissue. As the disease advances, there is ulceration and/or nodularity and fixation to underlying tissues. The tumours can be either exophytic or endophytic, and many of them may have residual red and white areas or a nodular and/or granular appearance, indicating their possible origin from an OPMD. The base of ulcerated tumours is indurated, and the surrounding mucosa has everted margins because of proliferation of the epithelium. Early cancers are asymptomatic, but advanced tumours can be very painful. Tongue cancer causes difficulty in swallowing and speaking, and restricted movements. Cancer of the buccal mucosa can lead to severe trismus when it has invaded into muscles. Enlarged and fixed cervical lymph nodes due to locoregional spread is a late presentation of the disease (Bagan et al., 2010).

(e) Histopathology of oral cancer

The histopathological hallmark of OSCC is the invasion of malignant epithelial cells into the underlying connective tissue. When the tumour cells resemble the surface normal squamous epithelium, with marked keratin formation, the cancer is categorized as well-differentiated OSCC. At the other end of the spectrum, when the tumour cells do not bear any resemblance to the squamous cells and there is no evidence of keratin formation, the cancer is categorized as poorly differentiated OSCC. The tumours in between these two extremes are categorized as moderately differentiated OSCC. In addition to the conventional types, some subtypes of OSCC have also been described; these include basaloid, adenoid (acantholytic), adenosquamous, papillary, spindle cell, cuniculatum, and verrucous carcinoma.

Histopathological parameters that must be contained in a pathology report include the level of differentiation, vascular and perineural invasion, pattern of invasion, depth of invasion, and immune response. In addition, the clearance distance of excision margins and lymph node status should be included in a report of surgical excision of the primary tumour with neck dissection (i.e. removal of the lymph nodes in the neck). Numerous molecular events have been described with respect to oral carcinogenesis (Dionne et al., 2015; Nikitakis et al., 2018; Farah, 2021; Fig. 1.10).

(f) Prognosis of oral cancer

Prognosis of oral cancer depends on multiple factors, including tumour-, host-, and treatment-related factors. The most significant prognostic factors are the stage of disease, depth of invasion, pattern of invasion, lymphovascular invasion, nodal status, and distant metastases (Dissanayaka et al., 2012; De Silva et al., 2018). The stage at diagnosis and the mortality rate vary according to the primary site of the tumour; for example, cancer of the lower lip is often diagnosed at an early stage, and the highest mortality rate is reported in patients with tongue cancer (Su et al., 2019). Positive regional lymph nodes, particularly with extracapsular spread, have a direct negative effect on prognosis (Abdel-Halim et al., 2021). Although the 5-year survival rate of OSCC is reported to be about 50%, recent data show an improvement to 66% in some centres (Liu et al., 2021).

1.3.2 Stage at diagnosis and stage-related survival

Prognosis of cancers of the lip, oral cavity, and oropharynx depends mainly on the stage of the disease at diagnosis. Table 1.2 shows survival rates for these cancer types by country or territory in five continents in 2006–2014 (IARC, 2022). Heterogeneity across countries is high; 5-year survival rates range from 0% to 64% (median, 39%) for patients with cancer of the lip or oral cavity and from 0% to 67% (median, 32%) for patients with oropharyngeal cancer.

The extent of the disease can be classified as localized (tumours confined to the organ of origin without invasion into the surrounding tissue or organs and without involvement of any regional or distant lymph nodes or organs), regional (tumours invading the surrounding tissue or organs, with or without the involvement of the regional lymph nodes, but not involving non-regional lymph nodes or organs), or with distant metastasis (spreading to the non-regional lymph nodes or distant organs; or unknown) (WHO Classification of Tumours Editorial Board, 2023). Overall, cancer of the lip or oral cavity is more frequently diagnosed with localized stage, compared with oropharyngeal cancer, which is more frequently diagnosed with regional disease. [Limitations of the study are significant, including a high proportion of unclassified cancers (~10% to 50%) and the variability in the number of patients analysed per country, which

Table 1.2 Survival (at 1 year, 3 years, and 5 years) of oral cancer and oropharyngeal cancer, by country or territory in 2006–2014, for both sexes combined

Country or territory	Survival (%)					
	Oral cancer			Oropharyngeal cancer		
	1 year	3 years	5 years	1 year	3 years	5 years
Algeria	94	31	0	50	0	0
Argentina	62	42	35	57	38	34
Bahrain	71	52	52	75	75	38
Brazil	77	55	49	58	39	31
Chile	61	43	34	52	36	29
China	72	53	47	54	35	30
Colombia	56	39	39	50	0	0
Costa Rica	73	57	52	67	49	42
Ecuador	65	50	45	80	46	31
India	71	47	40	61	32	24
Israel	82	66	58	85	63	55
Republic of Korea	80	62	57	81	65	58
Malaysia	58	36	31	68	53	47
Martinique, France	65	45	39	71	41	41
Peru	65	45	37	72	57	44
Puerto Rico, USA	65	27	16	60	27	15
Saudi Arabia	81	64	64	100	67	67
Seychelles	45	29	19	N/A	N/A	N/A
South Africa	49	29	18	44	31	31
Thailand	51	32	26	49	28	23
Turkey	83	68	59	74	51	40
Uruguay	60	37	31	56	38	32

N/A, not available.
Compiled from IARC (2022).

is very small in some cases (ranging from 13 to 3453).]

The Surveillance, Epidemiology, and End Results (SEER) database tracks 5-year relative survival rates for oral cancer and oropharyngeal cancer in the USA. In patients with oral cancer, based on different anatomical subsites (lip, tongue, or floor of the mouth), the 5-year relative survival rates were 73–94%, 42–70%, and 23–41% for localized, regional, and distant disease, respectively; survival was worse for patients with cancer of the floor of the mouth than for those with tongue cancer. In patients with oropharyngeal cancer, the 5-year relative survival rates were 59%, 62%, and 29% for localized, regional, and distant disease, respectively (American Cancer Society, 2023).

The treatment of cancer of the lip, oral cavity, and oropharynx is driven mainly by staging of the disease. Since its conception in 1959, the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumour–node–metastasis (TNM) staging system has become the main modality of tumour staging and is used to tailor the treatment of patients (Tirelli et al., 2018a). New editions of the AJCC TNM staging system are regularly published to improve the ability to predict patient outcomes. The eighth edition, which was published in 2017 (AJCC, 2017), had two major changes in TNM

Table 1.3 Tumour–node–metastasis staging system for carcinomas of the oral cavity

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in situ	N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(–)	N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(–)		
T1	Tumour ≤ 2 cm with DOI ≤ 5 mm	N2	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–); **or** Metastases in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE(+); **or** Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–); **or** Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, and ENE(–)		
T2	Tumour ≤ 2 cm, with DOI > 5 mm and ≤ 10 mm; **or** Tumour > 2 cm and ≤ 4 cm, with DOI ≤ 10 mm	N2a	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–)	N2a	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE(+); **or** Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–)		
T3	Tumour > 2 cm and ≤ 4 cm with DOI > 10 mm; **or** Tumour > 4 cm with DOI ≤ 10 mm	N2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)		

Table 1.3 (continued)

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
T4	Moderately advanced or very advanced local disease	N2c	Metastases in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2c	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, and ENE(–)		
T4a	Moderately advanced local disease Tumour > 4 cm with DOI > 10 mm; **or** Tumour invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/ tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T4.	N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–); **or** Metastasis in any lymph node(s) and clinically overt ENE(+)	N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–); **or** Metastasis in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE(+); **or** Metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, any ENE(+); **or** Metastasis in a single contralateral lymph node of any size and ENE(+)		
T4b	Very advanced local disease Tumour invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery	N3a	Metastasis in a lymph node > 6 cm in greatest dimension, and ENE(–)	N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–)		

Table 1.3 (continued)

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
T4b (cont.)		N3b	Metastasis in any lymph node(s) and clinically overt[c] ENE(+)	N3b	Metastasis in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE(+); **or** Metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, any ENE(+); **or** Metastasis in a single contralateral lymph node of any size and ENE(+)		

AJCC, American Joint Committee on Cancer; DOI, depth of invasion; ENE, extranodal extension; TNM, tumour–node–metastasis.

[a] DOI is depth of invasion and **not** tumour thickness.

[b] A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

[c] The presence of skin involvement or soft tissue invasion with deep fixation or tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical ENE.

Adapted from AJCC (2017). The original source for this information is the AJCC cancer staging manual, 8th edition, published by Springer International Publishing. Corrected at 4th printing, 2018.

Table 1.4 Tumour–node–metastasis staging system for carcinomas of the oral cavity: prognostic stage groups

T category	N category	M category	Stage group
Tis	N0	M0	Stage 0
T1	N0	M0	Stage I
T2	N0	M0	Stage II
T3	N0	M0	Stage III
T1, T2, T3	N1	M0	Stage III
T4a	N0, N1	M0	Stage IVA
T1, T2, T3, T4a	N2	M0	Stage IVA
Any T	N3	M0	Stage IVB
T4b	Any N	M0	Stage IVB
Any T	Any N	M1	Stage IVC

Adapted from AJCC (2017). The original source for this information is the AJCC cancer staging manual, 8th edition, published by Springer International Publishing. Corrected at 4th printing, 2018.

categorization compared with previous editions (Amin et al., 2017) (Table 1.3 and Table 1.4): inclusion of the depth of invasion (DOI) of the tumour (≤ 5 mm, 5–10 mm, and > 10 mm) affects the T categorization, and inclusion of the extranodal extension (ENE) affects the N categorization. The T1–3 but not the T4 classification is dependent on both the size of the tumour and the DOI. Also, extrinsic muscle involvement has been excluded as a criterion for T4 staging of tongue cancer. Finally, the absence of ENE is a prerequisite to classify N stage as N1, N2, or N3a disease, except if there is ENE of less than 3 cm in diameter in a single node (pN2a) (Zanoni and Patel, 2020).

Based on data from the United States National Cancer Database and staging with the eighth edition of the TNM staging system, the 5-year overall survival rate of patients with oral cancer who received treatment was 78.8% (median survival not reached) for stage 0, 72.2% (median survival not reached) for stage I, 57.5% (median survival, 5.70 years) for stage II, 55.1% (median survival, 5.59 years) for stage III, 39.7% (median survival, 3.08 years) for stage IVA, 27.1% (median survival, 1.45 years) for stage IVB, and 15.8% (median survival, 1.27 years) for stage IVC (Cramer et al., 2018).

Besides disease staging, many other factors may affect the prognosis of individual patients: access to specialized care, associated comorbidities, and the quality of treatment planning, which is multidisciplinary in nature and is strongly linked to the experience of the team (Hansen et al., 2020). Finally, it is important to note that one quarter to one third of deaths in patients with head and neck squamous cell carcinoma are attributable to a second primary malignancy in the field of cancerization; this may affect the upper aerodigestive tract again, the oesophagus, or the lung, which are among the most frequent anatomical sites (Braakhuis et al., 2002; Baxi et al., 2014).

1.3.3 Treatment and management of OPMDs and oral cancer

(a) Treatment and management of OPMDs

OPMDs are heterogeneous in their clinical presentation. Some OPMDs remain stable for many years or even regress; some eventually transform into oral cancer (see Section 1.3.1). Therefore, one of the main challenges of clinical management is to identify such high-risk lesions (Lingen et al., 2017).

After the clinical diagnosis of an OPMD (Warnakulasuriya et al., 2021), a biopsy is recommended for histopathological diagnosis, which is the current reference standard for confirmation of diagnosis, treatment guidance, and prognostication (Lingen et al., 2017). The histopathological diagnosis of oral epithelial dysplasia, which is routinely classified by grade (mild, moderate, and severe), has both intra-rater and inter-rater variability, which is linked to pathologists' training and experience. Patients with OPMDs that harbour high-grade dysplasia are at a greater risk for development of OSCC than are patients with OPMDs with low-grade dysplasia. Different in vivo optical imaging techniques may reduce diagnostic variability, but they have not been thoroughly evaluated (see Section 4.1.6). Predictive biomarkers, such as loss of heterozygosity (LOH) at specific chromosomal sites and aneuploidy, have been suggested, but none has entered routine clinical use (William et al., 2009; Woo, 2019; Vermorken et al., 2021).

There is no evidence-based international consensus on management algorithms for OPMDs. After diagnosis, the management of OPMDs may include one or more strategies, depending on the grade of dysplasia and other clinical factors. These include preventive strategies (e.g. lifestyle risk modification: cessation of tobacco use and/or alcohol consumption and/or use of areca nut, improvement of diet), disease monitoring or surveillance (i.e. a watchful waiting approach), medical interventions (i.e. use of topical or systemic agents, chemoprevention), surgical management, and others (Warnakulasuriya, 2020; Kerr and Lodi, 2021; Birur et al., 2022). Consensus guidelines for clinical management of patients with OPMDs, focusing on leukoplakia or erythroplakia, oral submucous fibrosis, and OLP, have recently been proposed (Birur et al., 2022). For low-risk lesions, clinical management may be limited to lifelong close surveillance, as an alternative to potentially morbid, repeated, multistep surgical treatments, such as excision or ablation using various techniques, including cold blade or electrocautery, laser, cryotherapy, and photodynamic therapy (Birur et al., 2022). Surgical excision was shown to decrease the rate of malignant transformation of oral dysplasia but not totally eliminate it (Mehanna et al., 2009).

(b) Treatment and management of oral cancer

The different modalities of treatment of oral cancer are surgery, radiotherapy, chemotherapy, and immunotherapy. Treatment planning is done at a multidisciplinary level; the patient is evaluated by a surgeon, a radiation oncologist, and a medical oncologist.

Patients with early-stage and locally advanced oral cancer (stage I and stage II) are typically offered surgical resection. Ipsilateral and sometimes bilateral neck dissection may be recommended. Depending on the depth of invasion and the presence of lymphovascular or perineural invasion, postoperative radiotherapy to the primary site and the neck (unilateral or bilateral) may be recommended.

Management of locoregionally advanced oral cancer (stage III and stage IVA–B) requires multimodality treatment: surgical resection of the primary tumour and neck dissection, followed by postoperative radiotherapy or chemoradiotherapy (Pignon et al., 2000; Shaw et al., 2020). Patients who experience recurrent disease despite these treatments may be candidates for targeted anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies and, more recently, immunotherapy (Bernier, 2016; Vermorken et al., 2021).

Certain adjunct methods used in secondary prevention of oral cancer may also have utility for tertiary prevention. In some studies, autofluorescence and narrow-band imaging (see Section 4.1.3) have demonstrated utility to guide surgical margin assessment for the excision of oral cancer (Farah et al., 2016; Poh et al., 2016; Farah, 2018; Guillaud et al., 2018; Tirelli et al.,

2018b; Schorn et al., 2020). Among vital staining techniques (see Section 4.1.3), toluidine blue and Lugol's iodine have demonstrated utility in the surveillance of patients with a history of oral cancer, when used by experts for tertiary prevention (Epstein et al., 2003; Simões et al., 2017).

References

Abdel-Halim CN, Rosenberg T, Larsen SR, Høilund-Carlsen PF, Sørensen JA, Rohde M, et al. (2021). Histopathological definitions of extranodal extension: a systematic review. *Head Neck Pathol*. 15(2):599–607. doi:10.1007/s12105-020-01221-4 PMID:32918710

Aguirre-Urizar JM, Lafuente-Ibáñez de Mendoza I, Warnakulasuriya S (2021). Malignant transformation of oral leukoplakia: systematic review and meta-analysis of the last 5 years. *Oral Dis*. 27(8):1881–95. doi:10.1111/odi.13810 PMID:33606345

AJCC (2017). AJCC cancer staging manual. 8th ed. American Joint Committee on Cancer, American College of Surgeons. Chicago (IL), USA; Cham, Switzerland: Springer Cham.

American Cancer Society (2023). Survival rates for oral cavity and oropharyngeal cancer. Available from: https://www.cancer.org/cancer/types/oral-cavity-and-oropharyngeal-cancer/detection-diagnosis-staging/survival-rates.html.

Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. (2017). The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 67(2):93–9. doi:10.3322/caac.21388 PMID:28094848

Argirion I, Zarins KR, Defever K, Suwanrungruang K, Chang JT, Pongnikorn D, et al. (2019). Temporal changes in head and neck cancer incidence in Thailand suggest changing oropharyngeal epidemiology in the region. *J Glob Oncol*. 5(5):1–11. doi:10.1200/JGO.18.00219 PMID:30860955

Bagan J, Sarrion G, Jimenez Y (2010). Oral cancer: clinical features. *Oral Oncol*. 46(6):414–7. doi:10.1016/j.oraloncology.2010.03.009 PMID:20400366

Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB (2014). Causes of death in long-term survivors of head and neck cancer. *Cancer*. 120(10):1507–13. doi:10.1002/cncr.28588 PMID:24863390

Berkovitz BKB, Holland GR, Moxham BJ (2018). Oral anatomy, histology and embryology. Amsterdam, Netherlands: Elsevier.

Bernier J, editor (2016). Head and neck cancer: multimodality management. 2nd ed. Switzerland: Springer.

Birur PN, Patrick S, Warnakulasuriya S, Gurushanth K, Raghavan SA, Rath GK, et al. (2022). Consensus guidelines on management of oral potentially malignant disorders. *Indian J Cancer*. 59(3):442–53. doi:10.4103/ijc.IJC_128_21 PMID:36412324

Bosetti C, Carioli G, Santucci C, Bertuccio P, Gallus S, Garavello W, et al. (2020). Global trends in oral and pharyngeal cancer incidence and mortality. *Int J Cancer*. 147(4):1040–9. doi:10.1002/ijc.32871 PMID:31953840

Bouquot JE, Speight PM, Farthing PM (2006). Epithelial dysplasia of the oral mucosa – diagnostic problems and prognostic features. *Curr Diagn Pathol*. 12(1):11–21. doi:10.1016/j.cdip.2005.10.008

Braakhuis BJ, Tabor MP, Leemans CR, van der Waal I, Snow GB, Brakenhoff RH (2002). Second primary tumors and field cancerization in oral and oropharyngeal cancer: molecular techniques provide new insights and definitions. *Head Neck*. 24(2):198–206. doi:10.1002/hed.10042 PMID:11891950

Conway DI, Brenner DR, McMahon AD, Macpherson LMD, Agudo A, Ahrens W, et al. (2015). Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. *Int J Cancer*. 136(5):1125–39. doi:10.1002/ijc.29063 PMID:24996155

Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD (2008). Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. *Int J Cancer*. 122(12):2811–9. doi:10.1002/ijc.23430 PMID:18351646

Conway DI, Purkayastha M, Chestnutt IG (2018). The changing epidemiology of oral cancer: definitions, trends, and risk factors. *Br Dent J*. 225(9):867–73. doi:10.1038/sj.bdj.2018.922 PMID:30412558

Cramer JD, Reddy A, Ferris RL, Duvvuri U, Samant S (2018). Comparison of the seventh and eighth edition American Joint Committee on Cancer oral cavity staging systems. *Laryngoscope*. 128(10):2351–60. doi:10.1002/lary.27205 PMID:29658104

de Araújo RL, Lyko KF, Funke VA, Torres-Pereira CC (2014). Oral cancer after prolonged immunosuppression for multiorgan chronic graft-versus-host disease. *Rev Bras Hematol Hemoter*. 36(1):65–8. doi:10.5581/1516-8484.20140016 PMID:24624039

De Silva RK, Siriwardena BSMS, Samaranayaka A, Abeyasinghe WAMUL, Tilakaratne WM (2018). A model to predict nodal metastasis in patients with oral squamous cell carcinoma. *PLoS One*. 13(8):e0201755. doi:10.1371/journal.pone.0201755 PMID:30091996

Dionne KR, Warnakulasuriya S, Zain RB, Cheong SC (2015). Potentially malignant disorders of the oral cavity: current practice and future directions in the clinic and laboratory. *Int J Cancer*. 136(3):503–15. doi:10.1002/ijc.28754 PMID:24482244

Dissanayaka WL, Pitiyage G, Kumarasiri PVR, Liyanage RL, Dias KD, Tilakaratne WM (2012). Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 113(4):518–25. doi:10.1016/j.oooo.2011.11.001 PMID:22668430

Ekanayaka RP, Tilakaratne WM (2016). Oral submucous fibrosis: review on mechanisms of malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 122(2):192–9. doi:10.1016/j.oooo.2015.12.018 PMID:27289264

Epstein JB, Feldman R, Dolor RJ, Porter SR (2003). The utility of tolonium chloride rinse in the diagnosis of recurrent or second primary cancers in patients with prior upper aerodigestive tract cancer. *Head Neck*. 25(11):911–21. doi:10.1002/hed.10309 PMID:14603451

Farah CS (2018). Narrow band imaging-guided resection of oral cavity cancer decreases local recurrence and increases survival. *Oral Dis*. 24(1–2):89–97. doi:10.1111/odi.12745 PMID:29480612

Farah CS (2021). Molecular landscape of head and neck cancer and implications for therapy. *Ann Transl Med*. 9(10):915. doi:10.21037/atm-20-6264 PMID:34164549

Farah CS, Dalley AJ, Nguyen P, Batstone M, Kordbacheh F, Perry-Keene J, et al. (2016). Improved surgical margin definition by narrow band imaging for resection of oral squamous cell carcinoma: a prospective gene expression profiling study. *Head Neck*. 38(6):832–9. doi:10.1002/hed.23989 PMID:25545703

Farah CS, Shearston K, Nguyen AP, Kujan O (2019). Oral carcinogenesis and malignant transformation. In: Brennan PA, Aldridge T, Dwivedi RC, editors. Premalignant conditions of the oral cavity. Singapore: Springer Singapore; pp. 27–66. doi:10.1007/978-981-13-2931-9_3

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

Gilligan G, Garola F, Piemonte E, Leonardi N, Panico R, Warnakulasuriya S (2021). Lichenoid proliferative leukoplakia, lichenoid lesions with evolution to proliferative leukoplakia or a continuum of the same precancerous condition? A revised hypothesis. *J Oral Pathol Med*. 50(2):129–35. doi:10.1111/jop.13133 PMID:33225541

González-Moles MA, Ruiz-Ávila I, González-Ruiz L, Ayén Á, Gil-Montoya JA, Ramos-García P (2019). Malignant transformation risk of oral lichen planus: a systematic review and comprehensive meta-analysis. *Oral Oncol*. 96:121–30. doi:10.1016/j.oraloncology.2019.07.012 PMID:31422203

González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, González-Ruiz L, Ayén Á, Lenouvel D, et al. (2021). Worldwide prevalence of oral lichen planus: a systematic review and meta-analysis. *Oral Dis*. 27(4):813–28. doi:10.1111/odi.13323 PMID:32144836

Guillaud M, MacAulay CE, Berean KW, Bullock M, Guggisberg K, Klieb H, et al. (2018). Using quantitative tissue phenotype to assess the margins of surgical samples from a pan-Canadian surgery study. *Head Neck*. 40(6):1263–70. doi:10.1002/hed.25106 PMID:29451953

Gupta PC, Mehta FS, Daftary DK, Pindborg JJ, Bhonsle RB, Jalnawalla PN, et al. (1980). Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol*. 8(6):283–333. doi:10.1111/j.1600-0528.1980.tb01302.x PMID:6937277

Hansen CC, Egleston B, Leachman BK, Churilla TM, DeMora L, Ebersole B, et al. (2020). Patterns of multidisciplinary care of head and neck squamous cell carcinoma in Medicare patients. *JAMA Otolaryngol Head Neck Surg*. 146(12):1136–46. doi:10.1001/jamaoto.2020.3496 PMID:33090191

Holmstrup P, Vedtofte P, Reibel J, Stoltze K (2006). Long-term treatment outcome of oral premalignant lesions. *Oral Oncol*. 42(5):461–74. doi:10.1016/j.oraloncology.2005.08.011 PMID:16316774

IARC (2022). SURVCAN: Cancer survival in countries in transition. Lyon, France: International Agency for Research on Cancer. Available from: https://survival.iarc.fr/survcan/.

Iocca O, Sollecito TP, Alawi F, Weinstein GS, Newman JG, De Virgilio A, et al. (2020). Potentially malignant disorders of the oral cavity and oral dysplasia: a systematic review and meta-analysis of malignant transformation rate by subtype. *Head Neck*. 42(3):539–55. doi:10.1002/hed.26006 PMID:31803979

Kerr AR, Lodi G (2021). Management of oral potentially malignant disorders. *Oral Dis*. 27(8):2008–25. doi:10.1111/odi.13980 PMID:34324758

Kim Y-J, Kim JH (2020). Increasing incidence and improving survival of oral tongue squamous cell carcinoma. *Sci Rep*. 10(1):7877. doi:10.1038/s41598-020-64748-0 PMID:32398670

Lin Y-H (2020). Trends in incidence of cancer of oral cavity, oropharynx and hypopharynx in Taiwan: data from the nationwide cancer registry, 1979–2016. *Clin Otolaryngol*. 45(2):302–3. doi:10.1111/coa.13488 PMID:31789484

Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, et al. (2017). Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: a report of the American Dental Association. *J Am Dent Assoc*. 148(10):712–727.e10. doi:10.1016/j.adaj.2017.07.032 PMID:28958308

Liu TPJ, Fisher BM, Chua B, Clark JR, Low TH, Batstone MD (2021). Survival outcomes following modern multidisciplinary management of oral squamous cell carcinoma in Australia. *Oral Surg Oral Med*

Oral Pathol Oral Radiol. 131(1):92–8. doi:10.1016/j.oooo.2020.09.012 PMID:33187950

McParland H, Warnakulasuriya S (2021). Lichenoid morphology could be an early feature of oral proliferative verrucous leukoplakia. *J Oral Pathol Med*. 50(2):229–35. doi:10.1111/jop.13129 PMID:33185900

Mehanna HM, Rattay T, Smith J, McConkey CC (2009). Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head Neck*. 31(12):1600–9. doi:10.1002/hed.21131 PMID:19455705

Mehta FS, Shroff BC, Gupta PC, Daftary DK (1972). Oral leukoplakia in relation to tobacco habits. A ten-year follow-up study of Bombay policemen. *Oral Surg Oral Med Oral Pathol*. 34(3):426–33. doi:10.1016/0030-4220(72)90319-2 PMID:4505755

Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, et al. (2018). Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. *J Oral Pathol Med*. 47(7):633–40. doi:10.1111/jop.12726 PMID:29738071

Menezes FDS, Fernandes GA, Antunes JLF, Villa LL, Toporcov TN (2021). Global incidence trends in head and neck cancer for HPV-related and -unrelated subsites: a systematic review of population-based studies. *Oral Oncol*. 115:105177. doi:10.1016/j.oraloncology.2020.105177 PMID:33561611

Miranda-Filho A, Bray F (2020). Global patterns and trends in cancers of the lip, tongue and mouth. *Oral Oncol*. 102:104551. doi:10.1016/j.oraloncology.2019.104551 PMID:31986342

Nanci A, editor (2017). Ten Cate's oral histology: development, structure and function. 9th ed. Maryland Heights (MO), USA: Mosby, Elsevier.

Napier SS, Speight PM (2008). Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med*. 37(1):1–10. doi:10.1111/j.1600-0714.2007.00579.x PMID:18154571

Nikitakis NG, Pentenero M, Georgaki M, Poh CF, Peterson DE, Edwards P, et al. (2018). Molecular markers associated with development and progression of potentially premalignant oral epithelial lesions: current knowledge and future implications. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 125(6):650–69. doi:10.1016/j.oooo.2018.03.012 PMID:29709496

Petti S (2003). Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncol*. 39(8):770–80. doi:10.1016/S1368-8375(03)00102-7 PMID:13679200

Pignon JP, Bourhis J, Domenge C, Designé L (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. 355(9208):949–55. doi:10.1016/S0140-6736(00)90011-4 PMID:10768432

Poh CF, Anderson DW, Durham JS, Chen J, Berean KW, MacAulay CE, et al. (2016). Fluorescence visualization-guided surgery for early-stage oral cancer. *JAMA Otolaryngol Head Neck Surg*. 142(3):209–16. doi:10.1001/jamaoto.2015.3211 PMID:26769431

Reibel J (2003). Prognosis of oral pre-malignant lesions: significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med*. 14(1):47–62. doi:10.1177/154411130301400105 PMID:12764019

Reibel J, Gale N, Hille J (2017). Oral potentially malignant disorders and oral epithelial dysplasia. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. 4th ed. Lyon, France: International Agency for Research on Cancer; pp. 112–5.

Reichart PA, Philipsen HP (2005). Oral erythroplakia – a review. *Oral Oncol*. 41(6):551–61. doi:10.1016/j.oraloncology.2004.12.003 PMID:15975518

Ren ZH, Hu CY, He HR, Li YJ, Lyu J (2020). Global and regional burdens of oral cancer from 1990 to 2017: results from the global burden of disease study. *Cancer Commun (Lond)*. 40(2–3):81–92. doi:10.1002/cac2.12009 PMID:32067418

Schorn L, Rana M, Madry A, Ipaktchi R, Möllmann H, Gellrich NC, et al. (2020). Does autofluorescence help detect recurrent squamous cell carcinoma? A prospective clinical study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 130(3):258–63. doi:10.1016/j.oooo.2020.04.809 PMID:32593620

Shaw RJ, O'Connell JE, Bajwa M (2020). Basic surgical principles and techniques. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of oral cancer: prevention, diagnosis and management. Cham, Switzerland: Springer Nature; pp. 253–82. doi:10.1007/978-3-030-32316-5_20

Silverman S Jr, Gorsky M, Lozada F (1984). Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer*. 53(3):563–8. doi:10.1002/1097-0142(19840201)53:3<563::AID-CNCR2820530332>3.0.CO;2-F PMID:6537892

Simões CA, Durazzo MD, de Aquino Xavier FC, Gallottini MHC, Lourenço SV, Pinto Júnior DDS, et al. (2017). Lugol chromoscopy in the follow-up of head and neck carcinoma. *Ann Maxillofac Surg*. 7(2):188–93. doi:10.4103/ams.ams_95_17 PMID:29264284

Sinnatamby CS (2011). Last's anatomy: regional and applied. 11th ed. London, UK: Churchill Livingstone, Elsevier.

Speight PM, Khurram SA, Kujan O (2018). Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 125(6):612–27. doi:10.1016/j.oooo.2017.12.011 PMID:29396319

Standring S, editor (2020). Gray's anatomy: the anatomical basis of clinical practice. 42nd ed. Amsterdam, Netherlands: Elsevier.

Su WW, Su CW, Chang DC, Chuang SL, Chen SL, Hsu CY, et al. (2019). Impact of varying anatomic sites on advanced stage and survival of oral cancer: 9-year prospective cohort of 27 717 cases. *Head Neck*. 41(5):1475–83. doi:10.1002/hed.25579 PMID:30652378

Thompson LDR, Fitzpatrick SG, Müller S, Eisenberg E, Upadhyaya JD, Lingen MW, et al. (2021). Proliferative verrucous leukoplakia: an expert consensus guideline for standardized assessment and reporting. *Head Neck Pathol*. 15(2):572–87. doi:10.1007/s12105-020-01262-9 PMID:33415517

Tilakaratne WM, Jayasooriya PR, Jayasuriya NS, De Silva RK (2019). Oral epithelial dysplasia: causes, quantification, prognosis, and management challenges. *Periodontol 2000*. 80(1):126–47. doi:10.1111/prd.12259 PMID:31090138

Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S (2006). Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol*. 42(6):561–8. doi:10.1016/j.oraloncology.2005.08.005 PMID:16311067

Tirelli G, Gatto A, Boscolo Nata F, Bussani R, Piccinato A, Marcuzzo AV, et al. (2018a). Prognosis of oral cancer: a comparison of the staging systems given in the 7th and 8th editions of the American Joint Committee on Cancer Staging Manual. *Br J Oral Maxillofac Surg*. 56(1):8–13. doi:10.1016/j.bjoms.2017.11.009 PMID:29198482

Tirelli G, Piovesana M, Marcuzzo AV, Gatto A, Biasotto M, Bussani R, et al. (2018b). Tailored resections in oral and oropharyngeal cancer using narrow band imaging. *Am J Otolaryngol*. 39(2):197–203. doi:10.1016/j.amjoto.2017.11.004 PMID:29150027

Utsunomiya H, Tilakaratne WM, Oshiro K, Maruyama S, Suzuki M, Ida-Yonemochi H, et al. (2005). Extracellular matrix remodeling in oral submucous fibrosis: its stage-specific modes revealed by immunohistochemistry and in situ hybridization. *J Oral Pathol Med*. 34(8):498–507. doi:10.1111/j.1600-0714.2005.00339.x PMID:16091118

Vermorken JB, Budach V, Leemans CR, Machiels J-P, Nicolai P, O'Sullivan B, editors (2021). Critical issues in head and neck oncology: key concepts from the seventh THNO meeting. Cham, Switzerland: Springer Nature. doi:10.1007/978-3-030-63234-2

Villa A, Hanna GJ, Kacew A, Frustino J, Hammerman PS, Woo SB (2019). Oral keratosis of unknown significance shares genomic overlap with oral dysplasia. *Oral Dis*. 25(7):1707–14. doi:10.1111/odi.13155 PMID:31295753

Warnakulasuriya S (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*. 45(4–5):309–16. doi:10.1016/j.oraloncology.2008.06.002 PMID:18804401

Warnakulasuriya S (2018). Clinical features and presentation of oral potentially malignant disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 125(6):582–90. doi:10.1016/j.oooo.2018.03.011 PMID:29673799

Warnakulasuriya S (2020). Potentially malignant disorders of the oral cavity. In: Warnakulasuriya W, Greenspan JS, editors. Textbook of oral cancer: prevention, diagnosis and management. Cham, Switzerland: Springer Nature; pp. 141–58. doi:10.1007/978-3-030-32316-5_12

Warnakulasuriya S, Greenspan JS (2020). Epidemiology of oral and oropharyngeal cancers. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of oral cancer: prevention, diagnosis and management. Cham, Switzerland: Springer Nature; pp. 5–21. doi:10.1007/978-3-030-32316-5_2

Warnakulasuriya S, Johnson NW, van der Waal I (2007). Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med*. 36(10):575–80. doi:10.1111/j.1600-0714.2007.00582.x PMID:17944749

Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, et al. (2021). Oral potentially malignant disorders: a consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. *Oral Dis*. 27(8):1862–80. doi:10.1111/odi.13704 PMID:33128420

WHO Classification of Tumours Editorial Board (2023). Head and neck tumours. 5th ed. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, Vol. 9). (forthcoming) Available from: https://publications.iarc.fr/.

William WN Jr, Heymach JV, Kim ES, Lippman SM (2009). Molecular targets for cancer chemoprevention. *Nat Rev Drug Discov*. 8(3):213–25. doi:10.1038/nrd2663 PMID:19247304

Woo SB (2019). Oral epithelial dysplasia and premalignancy. *Head Neck Pathol*. 13(3):423–39. doi:10.1007/s12105-019-01020-6 PMID:30887394

Zanoni DK, Patel SG (2020). New AJCC: how does it impact oral cancers? *Oral Oncol*. 104:104607. doi:10.1016/j.oraloncology.2020.104607 PMID:32208339