

Chapter 1

Epidemiology and Aetiology of Head and Neck Cancers

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Abstract Malignant neoplasms of the head and neck are among the most common in the world and constitute a major public health problem in most countries. Over 90% of these are squamous cell carcinomas arising in the mucous membranes of the upper aerodigestive tract (UADT). Their epidemiology and aetiology are considered in detail. We separate nasopharyngeal cancer, because it has a specific aetiology related to Epstein-Barr Virus (EBV) infection and dietary carcinogens. We then add those sites with the common major risk factors of alcohol, tobacco (including betel quid/areca nut habits) and diets poor in antioxidants and vitamins, and a minor role for Human Papillomavirus (HPV). Collectively, these UADT sites of oral cavity (including tongue), other pharynx, and larynx have a male incidence/mortality of 15.2/8.1 and for females of 4.6/2.4 cases per 100,000 pa. This ranks UADT cancer as the sixth most common site for men, eighth for women. Adding nasopharynx pushes head and neck cancer higher up the scale. If oesophagus were to be included as another alcohol and tobacco-related cancer, the rates add to 28.6/18.9 and 10.1/6.8 respectively. These cancers – which might be termed cancers of the mouth, throat and gullet – then rank second only to lung cancer in men, and fourth after breast, uterine cervix and large bowel in females, worldwide.

Detailed data are presented on geographical, ethnic, gender and time differences. The highest rates in the world are found in Melanesia, South Asia, parts of France, and much of Eastern Europe and the former Soviet republics. Many of these areas are showing rising trends, with a shift to involvement of younger individuals. This, and the fact that survival rates have improved little or not at all in much of the world over several decades, emphasises the need for effective primary and secondary prevention strategies – and for improved public policy to implement these.

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Introduction and Scope

The term *Head and Neck [H&N] Cancer* is usually taken to cover the range of malignant neoplasms of soft tissue origin that develop in the oral cavity including the lips, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands. The skin will be included in many descriptions, but not usually ocular and intracranial neoplasms, nor those of endocrine or lymphatic origin – thus excluding thyroid and parathyroid cancers, and lymphomas. Sarcomas, though more rare, must be included among these soft tissue neoplasms of the head and neck, be they of connective tissue, neural or vascular origin.

Summary data will be given on primary bone “tumours” and on those of odontogenic origin, though their pathology and management are not covered in detail in this volume. Readers are referred to the several excellent modern textbooks of surgical pathology and of oral and maxillofacial pathology: especially recommended are Fletcher DEM, Ed, *Diagnostic Histopathology of Tumours*, 3rd Edn., Elsevier 2007 and Gnepp DR, Ed., *Diagnostic Surgical Pathology of the Head and Neck*, 2nd Edn. Elsevier 2009. Reliable concise accounts created by a team of international experts appear in the series of WHO “blue books”, viz: *Pathology and Genetics of Head and Neck Tumours*, Brown L et al. Eds., IARC Press, 2005.

Metastases from distant primaries to the jaws (and occasionally to mucous membranes), must always be considered.

Most head and neck cancers, indeed 95% or more, are squamous cell carcinomas (SCC) and variants thereof, originating from the epithelium of the mucosal lining of the upper aerodigestive tract (UADT), and adenocarcinomas from associated secretory glands. Carcinomas everywhere in the head and neck spread readily to the lymph nodes of the neck, and this is often the first (and sometimes only) manifestation of the disease at the time of presentation. Head and neck

SCC is strongly associated with certain environmental and lifestyle risk factors, notably tobacco use, smoked and “smokeless”, heavy alcohol consumption, diets poor in antioxidant vitamins and minerals, UV light and occupational exposures to radiation or chemical carcinogens and, increasingly to certain viruses, perhaps sexually transmitted, notably “high-risk” genotypes of the human papillomavirus family (particularly HPV 16 and 18, and particularly when originating in the tonsil and elsewhere in the oropharynx), and some human herpes viruses (HHVs: Epstein-Barr virus with nasopharyngeal carcinoma and HHV-8 with Kaposi sarcoma at all sites): there is a modest inherited susceptibility.

SCC of the H&N are frequently aggressive in their biologic behaviour: patients with many of these types of cancer have very destructive disease above the clavicle, develop local (cervical) lymph node metastases early, develop distant metastases over time – even following effective local therapy, and a high proportion have recurrence of the primary lesion and/or develop a second primary neoplasm. This is especially so if risky life-styles continue: UADT cancers ought in fact to be considered systemic diseases; not only is there “field of change” with molecular lesions involving much or all of the regional mucosae, but also damage to the immune system and host defenses generally, and damage to key organs especially the liver. Indeed co-morbidities are common – especially respiratory and cardiovascular – resulting from common risk factors, especially tobacco and alcohol abuse, and poor nutrition.

H&N SCC is curable if detected early, usually with some form of surgery. For more advanced lesions, in modern best practice, surgery is usually accompanied by preceding or subsequent radiotherapy, with or without adjuvant chemotherapy. We are now entering an era of individualised biotherapies for many cancers, based on understanding of the precise molecular aberrations within a given neoplasm, and of the patient’s individual genetic polymorphisms, though such approaches have not yet been extensively trialled.

The evidence base as it was earlier this decade, with a focus on oral cancer, is exhaustively presented in Shah JP, Johnson NW & Batsakis JG, *Oral Cancer*, Martin Dunitz London/Thieme New York, 2003.

History

Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumour is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years. Some historians speculate that a high incidence of nasal cancer may have been present in some ancient populations because of the inhalation of wood smoke

in poorly ventilated huts. In approximately 400 BC, Hippocrates described a common chronic ulcer at the edge of the tongue that he attributed to the presence of sharp teeth rubbing against the tongue: a challenge to differential diagnosis which is still real today!

The ancient Indian physician Sushruta described the removal of tumours and developed great skill in plastic surgery, partly from defects created by frequent amputations of the nose and ears for punishments. Modern Western Medicine received its foundation from early Roman medical writings. Little medical advancement was made for head and neck cancers until the advent of anaesthesia and surgical excision in the eleventh century.

Cancer Registries

Cancer registries play a vital role in monitoring the incidence of and mortality from cancers. However, the quality of data available in many registries can be far from ideal. Furthermore, many parts of the world produce no data at all, in others (often among the most populous), the data may come from localised, atypical regions. Hospital-based cancer registries naturally gather biased information – those cases which present to hospital only; thus, in many developing countries, cases may not come to attention at all, either because of fear or the inability of poor people to access hospital services. Data may be even more unreliable because in many developing countries follow-up, even of treated cases, is impossible. Death certification is not always compulsory and there is limited international standardisation in the categories for cause of death, let alone calibration of those signing death certificates.

Fortunately, many nations have high quality national, often incorporating regional, population-based cancer registries, with compulsory reporting of all malignancies. These are guided by, and quality-assured by, both national authorities and the positive influence of the World Health Organisation (WHO), mostly through its constituent body, the International Agency for Research on Cancer headquartered in Lyon, France. Data from all over the world are collated and are available from the websites of both these bodies: this includes free access to programmes that allow online interrogation of the databases. Many of the tables and graphs in this chapter have been generated in this way. Within the USA, the SEER website provides similar sophisticated opportunities to registered users (SEER is the Surveillance, Epidemiology and End Results program of the National Cancer Institute. It is based on data from, nowadays, 18 population-based registries described at <http://seer.cancer.gov/registries/list.html>).

Why Collect Detailed Epidemiological Data?

Cancer epidemiology is a demanding but essential science. Some acquaintance with epidemiological method and data is required by all who participate in cancer care, from politicians, public health officials, hospital managers, individual clinicians in both general and the wide range of specialist practitioners concerned with diagnosis and treatment, palliative carers, nurses, speech and swallowing therapists, dieticians, social workers to spiritual advisors. *Descriptive epidemiology* provides the fundamental evidence base, but its value is dependent on the accuracy and completeness of the information therein: reliable, sufficiently detailed and safely stored hospital-based information is *sine qua non*. Increasingly, hospital records contain information on lifestyle and other known or suspected risk factors: the growth of biological “tumour banks” or “tissue banks” from which molecular markers and indeed molecular mechanisms can be researched is encouraging, but needs much more co-ordinated international action.

Population-based registries, as described above, are of even greater value. These permit *analytical epidemiology*, and thus the ability to address essential questions such as: Why is the incidence of a particular type or site of neoplasm rising or falling over time or in a particular ethnic group or age group? How should this inform government and public health policy? Are existing public awareness and screening campaigns effective and efficient? How do different treatment modalities compare? How does my hospital or my personal clinical practice compare to the national average or

world best practice? In respect of the latter, there is an ethical imperative for every clinician to keep detailed records, using standardised measures, of the outcomes of his or her care. Guidelines for Care Pathways and “Minimum Data-Sets” to facilitate quality control and recording of outcomes are available: those from the British Association of Head and Neck Oncologists (<http://www.bahno.org.uk/docs/>) and from the American Head and Neck Society (<http://www.headandneckcancer.org/>) can be recommended. In many countries, cancer is a notifiable disease and both the registration of all cases, and the provision of information on the patient, on the care provided, and on the outcomes – not just survival rates but information on complications and on quality-of-life measures – is mandatory.

The Global Scenario of Head and Neck Cancer: Differences by Country

Head and neck cancer is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cases and 350,000 cancer deaths worldwide every year [1]. Figure 1.1 compares several H&N cancers with cancers affecting other body sites: age-adjusted global incidence and mortality rates are given for males and females; males predominate in all H&N sites.

Head and Neck Cancers are among the Top Ten in the World: We separate nasopharyngeal cancer, because it has a specific aetiology related to EBV infection and dietary

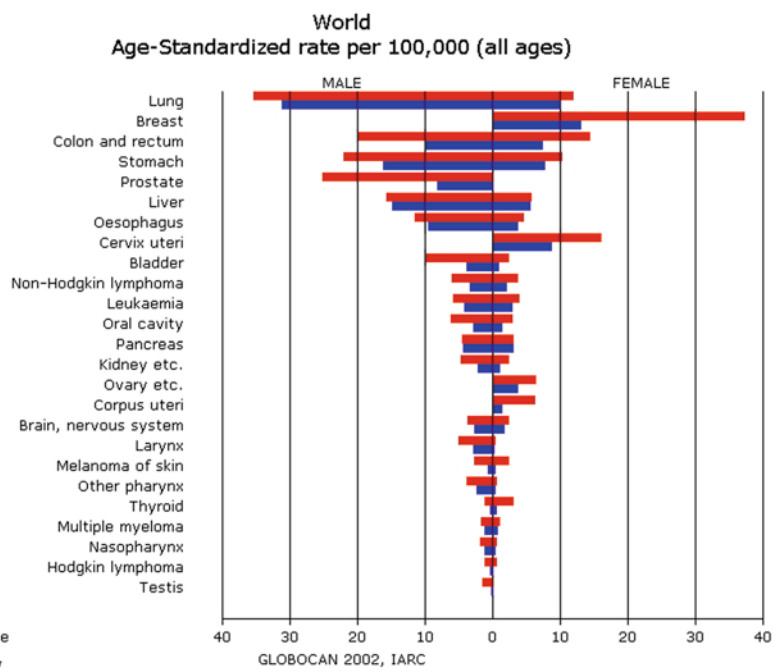


Fig. 1.1 Global scenario of age-standardised cancer incidence and mortality rates per 100,000 population

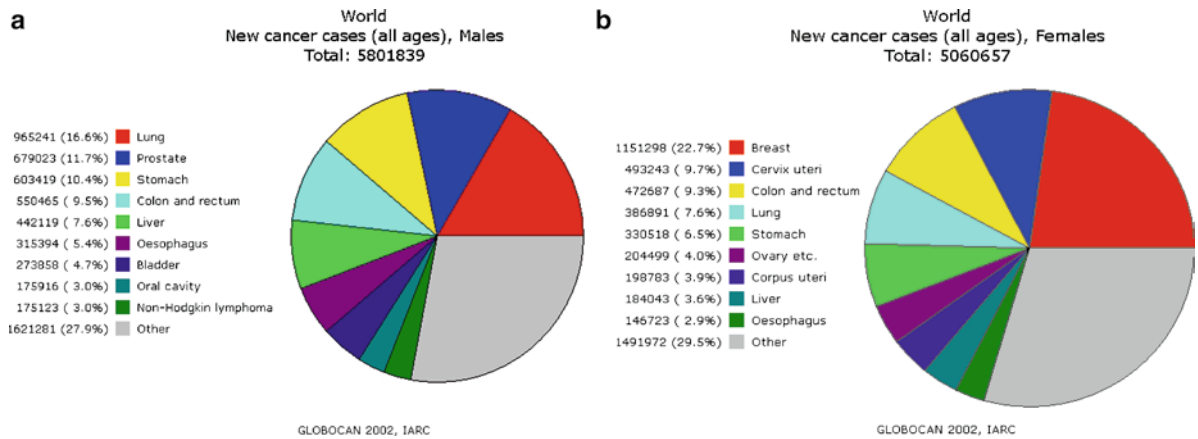


Fig. 1.2 Simple pie charts of the estimated number of new cases of cancer in the world in 2002, derived from the Globocan 2002 database, divided into the nine most common sites in males (a) and females (b). Note that oral cavity appears in eighth place for males

carcinogens. We then add together those sites with the common major risk factors of alcohol, tobacco and diets poor in antioxidants and vitamins, and a minor role for HPVirus – collectively termed *upper aerodigestive tract cancer (UADT)*: these sites are oral cavity (including tongue), other pharynx, and larynx. Male incidence/mortality is then 15.2/8.1 and female 4.6/2.4 cases per 100,000 pa. This would rank men approximately sixth in the table; women approximately eighth. Adding nasopharynx pushes head and neck cancer higher up the scale. If oesophagus were to be included as another alcohol and tobacco-related cancer, the rates add to 28.6/18.9 and 10.1/6.8, respectively. These cancers – which might be termed *cancers of the mouth, throat and Gullet* – then rank second only to lung cancer in men, and fourth after breast, uterine cervix and large bowel in females worldwide (Fig. 1.2a, b).

The geographical patterns of oral cancers are indicative of differences in the prevalence of risk factors among countries; tobacco and alcohol consumption, and quality of diet, in particular. Two-thirds of these malignancies occur in developing countries; and a high incidence continues to be observed in the Indian Subcontinent.

According to GLOBOCAN 2002, the highest incidence of oral cancer is found in Melanesia (astounding rates of 31.5 per 100,000 in men and 20.2 per 100,000 in women) [2]. In India alone, over 100,000 cases of oral cancer are registered every year. Though men predominate overall, among females, a very high incidence is found throughout southern Asia (8.3 per 100,000). In terms of countries, Sri Lanka has the highest incidence of oral cancer in the South Asia region. Poor access to health services contributes to high mortality.

Data extracted from the Cancer Incidence in Five Continents Database for the period 1998–2002 [3] also facilitate a global overview. When considering oral and pharyngeal cancer, the annual estimated incidence is around

275,000 cases for oral and 130,300 for pharyngeal cancers *excluding nasopharynx*: two-thirds of these cases occurring in developing countries [2]. There is a wide geographical variation in the incidence of oral cancer, nasopharyngeal cancer, other pharynx and larynx (Table 1.1).

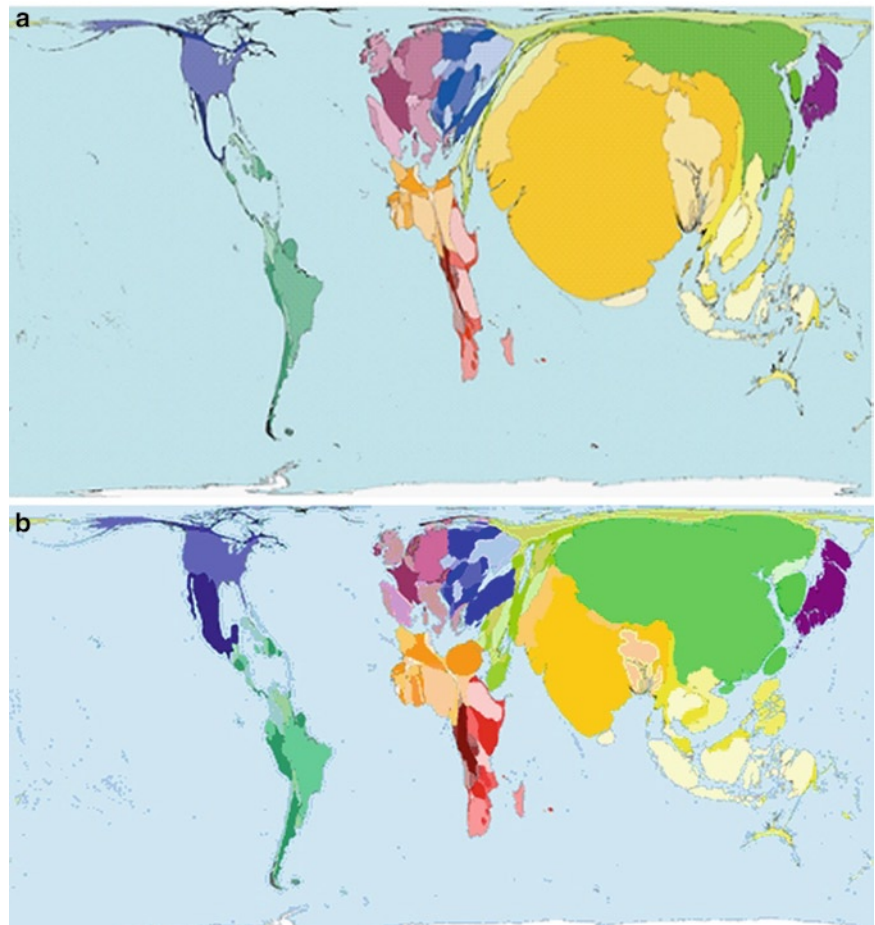
For oral cancer, the highest crude rates in the world are found in Melanesia, Hungary, France, Sri Lanka and Croatia [2]. There are marked differences among countries in the same geographical region [4, 5]. The extremely high rates in the relatively small populations of the Melanesian Islands have not been comprehensively researched, but good data from Papua New Guinea (see below) define the importance of areca nut (betel) chewing (called Buai in PNG) and smoking habits as the major risk factors.

The World maps reproduced below (Figs. 1.3–1.9), though simplifying data by aggregation to national averages, contain important information. As with the tables, maps are shown for each of the important head and neck sites. It has been apparent for decades that the global picture for head and neck cancer is dominated by the incidence of oral cancer in southern Asia and of oral cavity plus nasopharyngeal cancer in East Asia. In the 1980s, in India, Bangladesh, Pakistan and Sri Lanka, oral cancer was the most common site and accounted for about one-third of all cancers [6–8]. However, this proportion has fallen, mainly due to increased detection of other cancers by more extensive screening programmes and improved techniques [8]. Even within the subcontinent, there are striking differences in incidence rates. The highest rate for tongue and mouth is reported for men living in South Karachi, Pakistan; the second highest in Trivandrum city, Kerala, India. Extremely high rates for women are seen in the Tamil community in Malaysia – higher even than in Tamil Nadu itself: UADT sites in Indian females in Peninsular Malaysia are the second most common cancer, behind breast and above uterine cervix [9].

Table 1.1 World standardised *incidence* rates per 100,000 for H&N cancers. Data derived from the Globacan 2002 database: anatomic descriptors derived therefrom [2]

Country	Oral cavity		Nasopharynx		Other pharynx		Larynx	
	Male	Female	Male	Female	Male	Female	Male	Female
World	6.3	3.2	1.9	0.8	3.8	0.8	5.1	0.6
More developed	7.9	2.4	0.7	0.2	5.1	0.8	6.9	0.7
Less developed	5.7	3.5	2.4	1.0	3.4	0.8	4.3	0.6
Eastern Africa	5.9	4.8	2.3	0.9	1.6	0.5	3.5	0.7
Middle Africa	4.4	2.2	0.8	0.2	1.2	1.1	2.6	0.8
Northern Africa	3.1	1.5	2.7	1.1	1.0	0.2	4.0	0.6
Southern Africa	11.1	3.1	1.6	0.4	2.0	0.4	6.5	0.9
Western Africa	2.5	1.3	1.7	0.7	0.8	0.2	2.0	0.3
Caribbean	5.6	2.3	0.6	0.2	4.3	1.2	7.3	1.2
Central America	2.5	1.4	0.4	0.2	1.7	0.6	5.0	0.4
South America	6.1	1.8	0.3	0.1	3.5	0.7	7.2	0.7
Northern America	7.8	3.3	0.6	0.2	4.2	0.9	5.8	1.2
Eastern Asia	1.5	1.0	3.3	1.5	0.7	0.1	2.0	0.3
Southeastern Asia	3.6	2.5	5.8	2.1	2.2	0.7	3.7	0.5
South Central Asia	12.7	8.4	0.7	0.3	8.8	2.0	6.9	1.0
Western Asia	3.7	2.3	1.6	0.6	0.7	0.4	7.2	1.2
Central and eastern Europe	8.6	1.6	0.6	0.2	5.4	0.5	9.2	0.4
Northern Europe	5.3	2.6	0.4	0.2	2.6	0.7	4.3	0.7
Southern Europe	9.2	2.0	1.1	0.5	5.3	0.5	10.9	0.7
Western Europe	11.3	2.7	0.8	0.2	9.7	1.7	7.2	0.8
Australia	11.1	4.7	0.8	0.3	3.4	0.9	3.9	0.5
New Zealand	5.6	3.3	0.6	0.3	3.6	0.4	2.2	0.4
Melanesia	31.5	20.2	0.3	0.2	1.8	0.7	3.2	0.9
Micronesia	4.4	2.7	7.1	2.5	1.6	0.6	3.7	0.0
Polynesia	5.2	0.7	3.9	1.7	0.7	0.0	0.0	0.0

Fig. 1.3 Mouth Cancer Deaths, IARC 2002 International Classification of Diseases-10 codes: C00-C14. http://www.worldmapper.org/display_extra.php?selected=419. Accessed January 2010. These two maps (shown only for males here) distort countries on the basis of the number of deaths by mouth and pharynx cancer (a), and the number of smokers (b). They show that the public health burden is borne by Eastern Europe, Central and Eastern Asia and South Asia. China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia and Mongolia = Armenia, followed by Kenya are the top five-ranked countries for smoking prevalence, at 77%, 69%, 68% and 67%, respectively. *Territory size shows the proportion of men who smoke and live there*



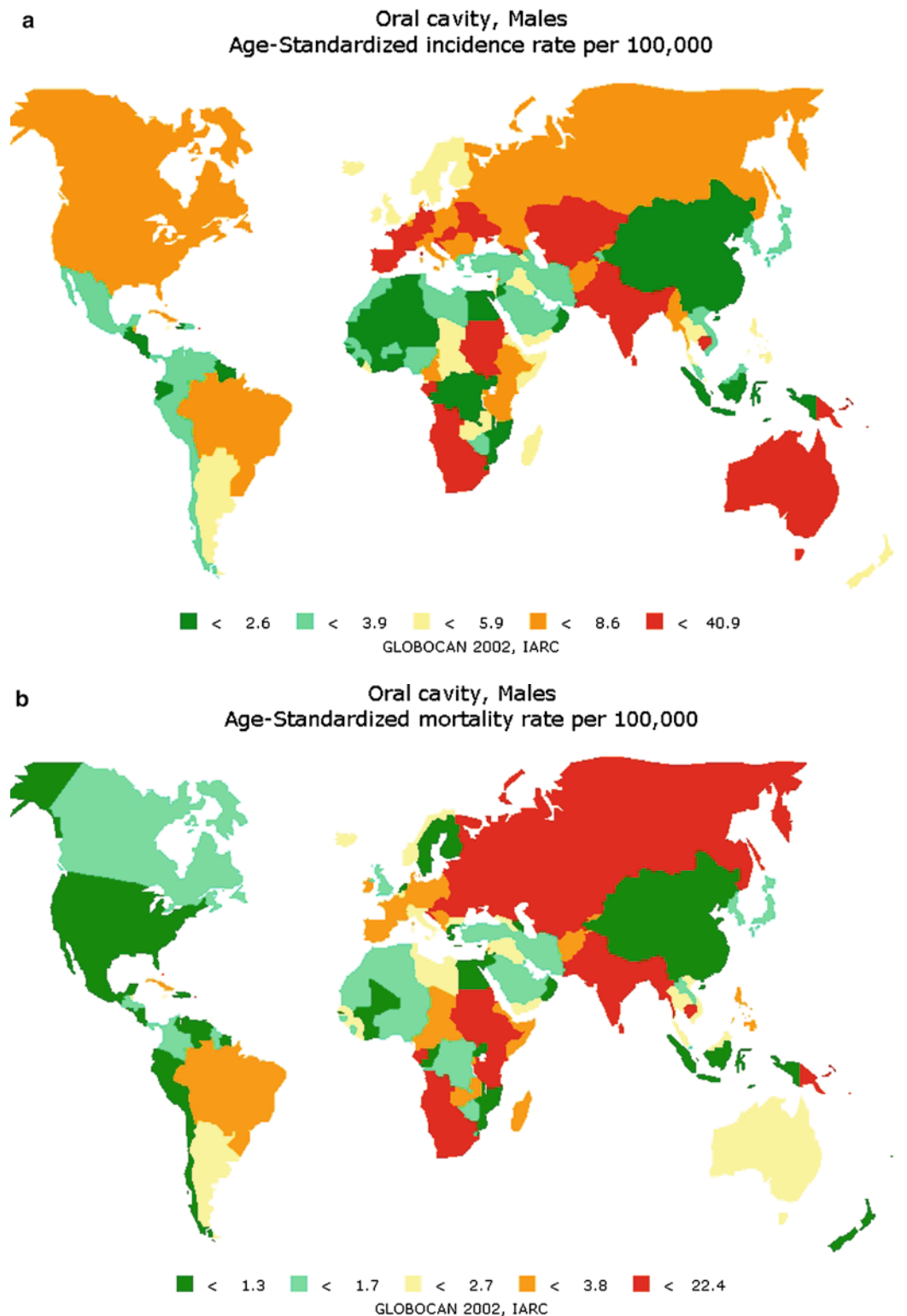


Fig. 1.4 Incidence (a) and mortality (b) rates for oral cavity cancer in males, in quintiles, by country. A quick comparison of these maps makes a number of points. The “traditional” high incidence areas of central Asia and the Indian sub-continent stand out: much of this is due to betel quid use, with or without smokeless tobacco, plus smoking, sometimes alcohol abuse, and poor diet. Note that parts of both Western and Eastern Europe remain in the top quintile – see text. The African data are not particularly robust. Australia shows a high incidence, due to ultraviolet light-induced lip cancer in a fair-skinned population:

mortality rates are not comparably high because lip cancer is comparatively easily treated. Eastern Europe and the former Soviet republics have high mortality, partly related to low socio-economic status, limited treatment facilities and the fact that many patients have substantial co-morbidities. As already mentioned, Papua New Guinea and surrounding Melanesian islands of the Western Pacific are in the top quintile both in incidence and mortality: indeed Melanesia has the highest recorded rates in the world at the beginning of this millennium – associated with chewing of areca nut and tobacco use

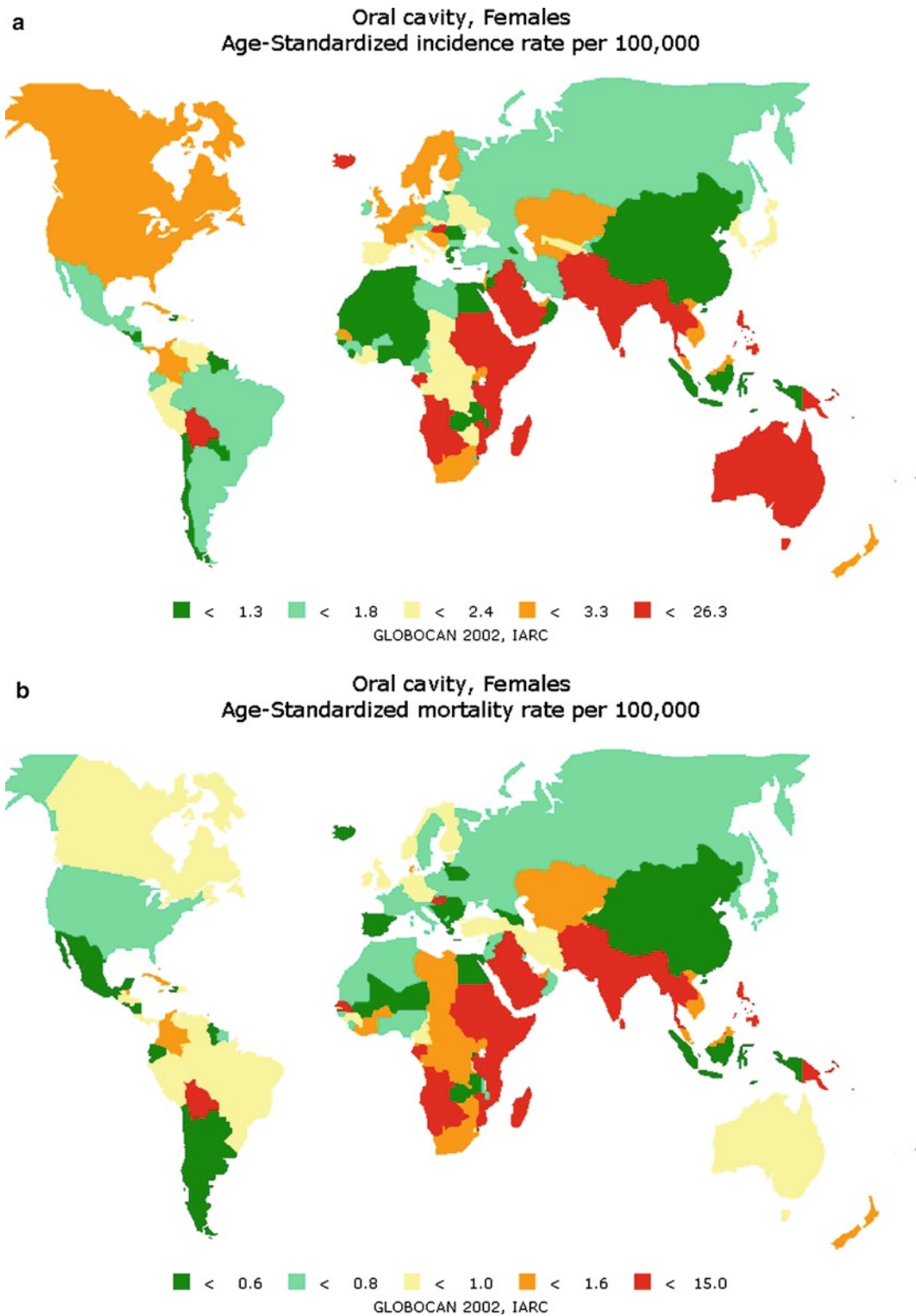


Fig. 1.5 Similar explanations relate to the national incidence (a) and mortality (b) data for women. Note the serious situation in the Indian Subcontinent and parts of SE Asia. In parts of India, oral cancer is the

leading cancer among women, because of heavy use of betel quids. Indeed emigrant Tamil women working on rubber and palm oil estates in Malaysia have among the highest rates, by population group, in the world

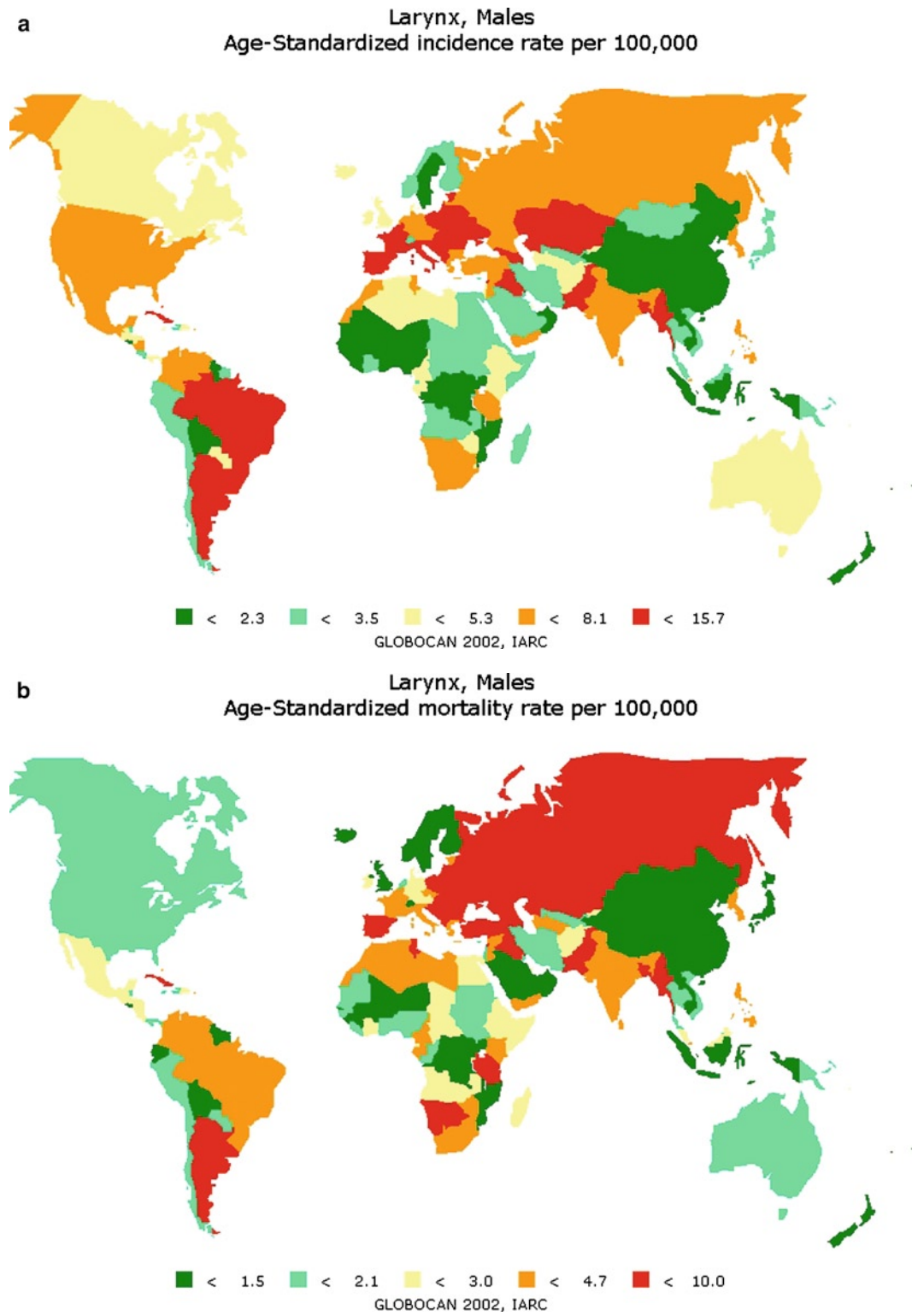


Fig. 1.6 Rates of laryngeal cancer largely reflect smoking rates around the globe, with the surprising exceptions of China and Japan who have comparatively low incidence (a) and mortality (b), in spite of male smoking prevalence being 50% or above: however as noted earlier

Japanese rates are on the rise. The proportionately higher death rate in Eastern Europe, Russia and the former Soviet Republics is again related to late stage at diagnosis and high co-morbidities associated with low socio-economic status and difficulties with access to care

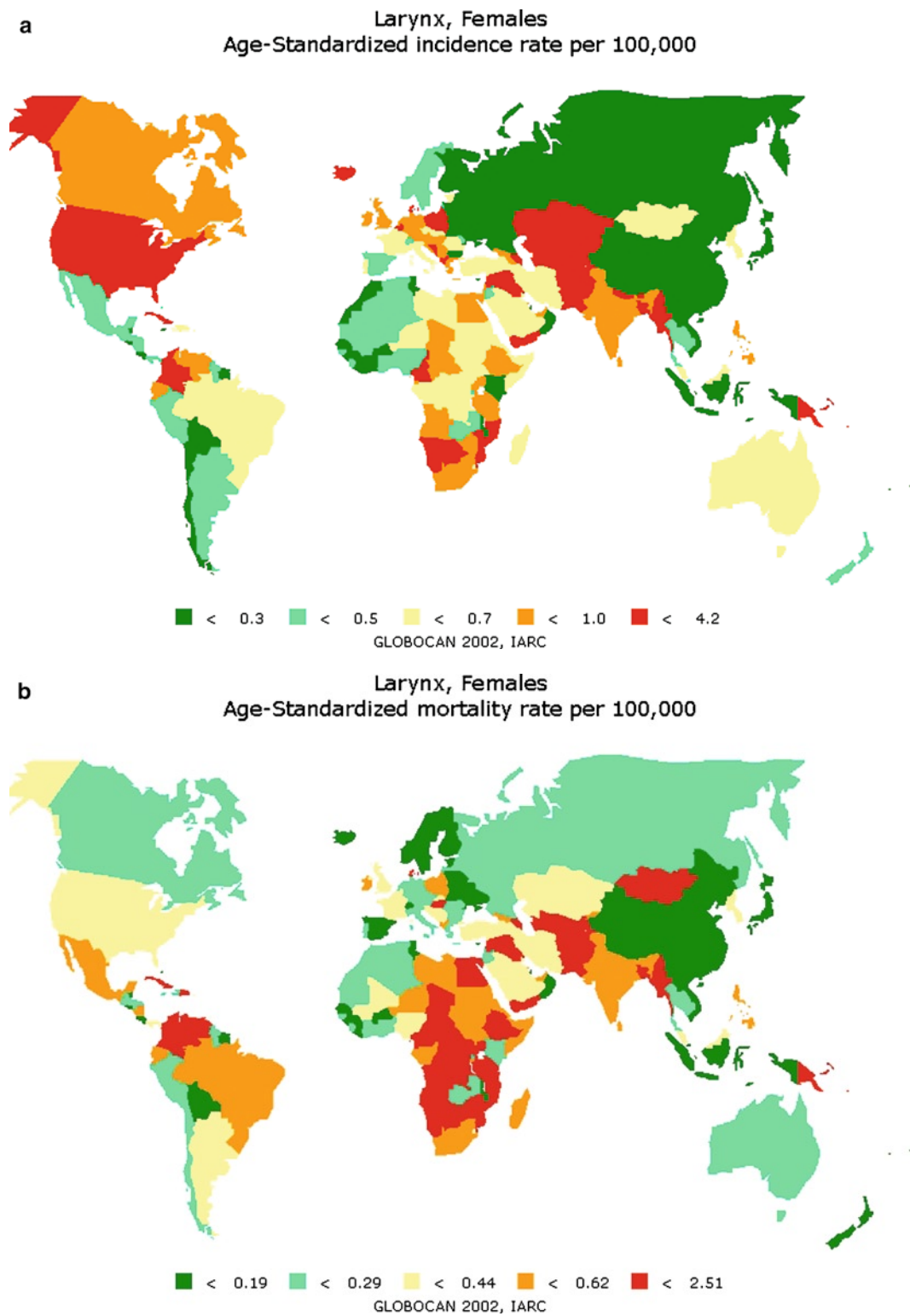


Fig. 1.7 (a and b) Because smoking is far less prevalent in women than men in most societies, the laryngeal cancer rates are low worldwide, and little can be read into this aspect of “geographical pathology”

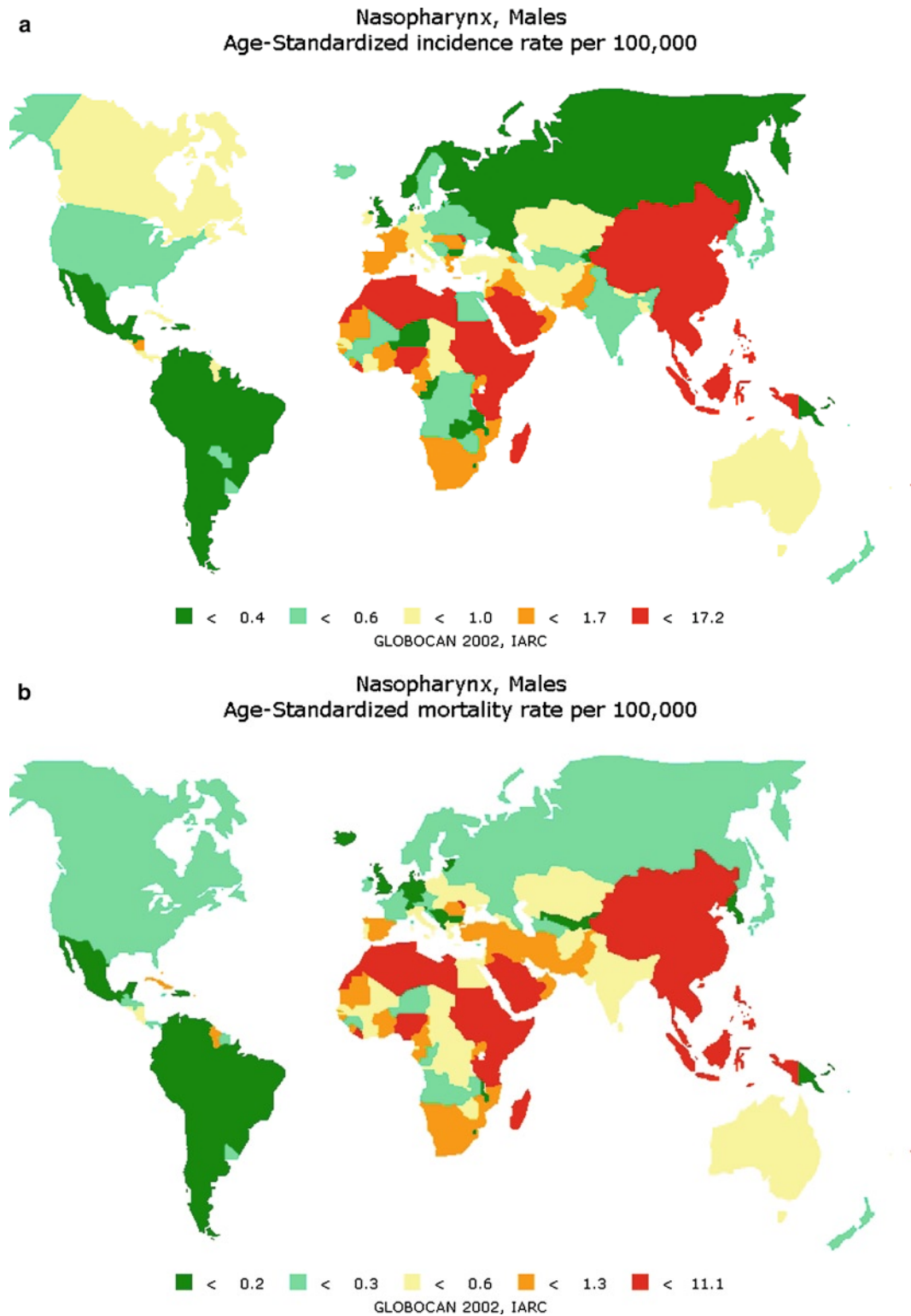


Fig. 1.8 Risk factors for nasopharyngeal cancer are comparatively well understood. It is a biologically distinct disease, driven by Epstein-Barr virus, in subjects with genetic susceptibility, compounded by toxins in particular cultural dietary practices. Both incidence (a) and

mortality (b) rates are historically high in North Africa and in China – particularly Guangdong Province, the Hong Kong SAR and emigrant communities there from

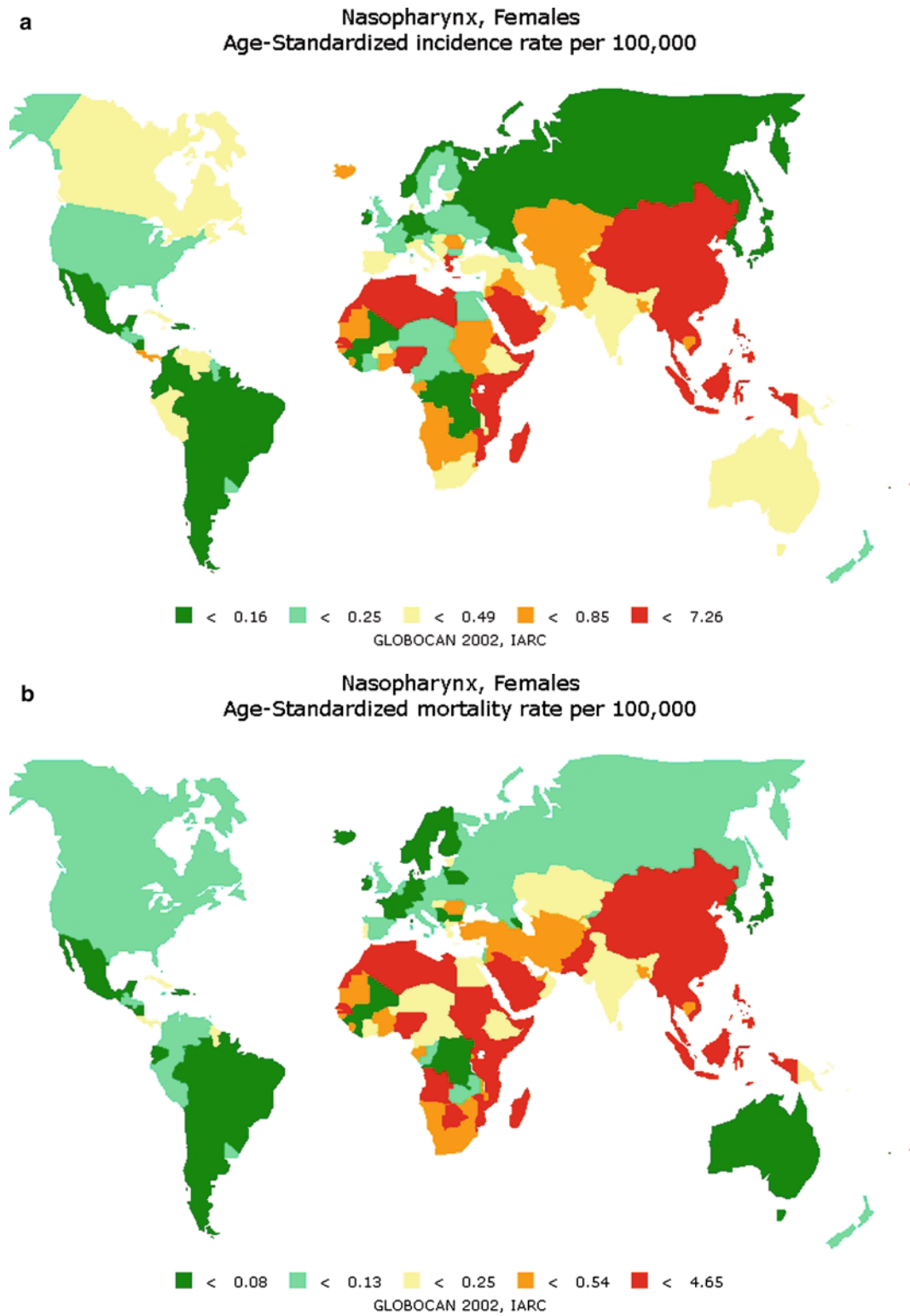


Fig. 1.9 (a and b) Female rates for NPC are lower than for men, but show the same geographical distribution

More than 180,000 cases of oral cancer occur every year in South and South-East Asia alone, with poor prospect of survival: about 90% of these cases are attributable to smoking and chewing habits [7]. It is encouraging that overall rates in India are showing a decreasing trend in successive birth cohorts, declining trends were observed for mouth (ICD10 C03–C06) and tongue (C01–C02) cancers among females and tongue cancers among males between 1982 and 2000 [10]. However, there is growing concern that commercial areca nut and tobacco products will contribute to future rises in the incidence of oral submucous fibrosis and of subsequent oral cancer [11].

Data from Japan show a dramatic increase in oral and pharyngeal cancer incidence (ICD10 C01–C14) for both sexes; there is a 4.4-fold increase for males and 3.8-fold increase for females in the total numbers between 1965 and 1999 – noted from the data retrieved from Osaka Cancer Registry's database [12]. There is also an upward trend for both males and females in Australia and among the non-Maori population in New Zealand. Lip cancer in fair-skinned populations, particularly due to ultraviolet light, is a growing problem [13]. In Europe, Hungary has the highest incidence and mortality of oral and pharyngeal cancer for both sexes [14]. Between 1984 and 1994, the Hungarian mortality rates for oral cancers rose by 83.5 and 72.3% in males and females, respectively. Trends in the mortality rate among Italian and French males peaked in the 1980s and have decreased after 1990 [15]. However, some persisting upward trends were registered for Belgium, Denmark, Greece, Portugal, and Scotland [16].

In the USA, the estimated number of incident cancer cases for tongue, mouth and other oral cavity in 2008 was 15,250 cases for men and 7,650 for women; for the pharynx, the number of incident cases for men is 10,060 and 2,350 for women (3% of all cancer cases in men). For cancer of the larynx, 12,250 incident cases were estimated, of which 9,680 were men. In the USA, the mortality rates per 100,000 population pa for cancer of the oral cavity and pharynx for men was 5.61 in 1990 and 3.98 in 2004, the absolute decrease being 1.63 per 100,000, contributing to a 3% reduction in mortality of all sites. For women, the decrease across the same period was 0.56 contributing to a 2.5% reduction of all sites [12]. The incidence rates of cancers of the oral cavity and pharynx-throat were stable or declining for men and women in most age groups during the period 1973–2003 in the USA, probably related to changes in tobacco and alcohol consumption. This is a highly pleasing situation, common to many countries with advanced care facilities but not reflected in most of the high incidence countries elsewhere in the world. Furthermore, as described below, black citizens of the USA fare comparatively badly.

Cancer of the larynx has always been a serious public health problem in nations with high smoking prevalence, and

this remains a disaster in China and eastern Europe and the former Soviet Republics. Differences among selected countries are shown in detail in the time and birth cohort trends reproduced below.

For cancers of the oropharynx and tonsils, the highest combined rate is currently seen in France and for laryngeal cancer, it was Spain. For hypopharyngeal cancer specifically, the highest rate in men was in France. For women, the highest ASR(W) for mouth and tongue specifically was in Pakistan, almost the same as that for men [17].

Differences by Sex

As already noted, worldwide, the incidence of head and neck cancers overall is higher for males than females. According to the International Agency for Research on Cancer [2], the age-specific incidence of “oral cavity”, plus “nasopharynx” plus “other pharynx” cancers totalled 12 per 100,000 population for males in 2002 and 4.8 for females (see Table 1.1). This may be because of their greater indulgence in the most important risk factors, such as heavy alcohol and tobacco consumption for intra-oral cancer and sunlight for lip cancer in those who work outdoors. However, oral cancer in females is increasing in some parts of the world. For instance, a study from Argentina showed the male/female ratio to be 1.24:1 for the period 1992–2000 compared to 7.1:1 for the 1950–1970 period [18]. The incidence of tongue and other intra-oral cancers for women can be greater than or equal to that for men in high incidence areas such as India, where betel quid/areca nut chewing (and sometimes smoking) are common among women, although this varies considerably from region to region.

Within Europe, the incidence of oral cavity and pharyngeal cancers (C00–14) among males in the most recent period varied substantially between 5.9 (Finland) and 32 (France) per 100,000 pa [19]. Incidence rates among females were highest in northern and western Europe but were consistently lower than those for males. The male-to-female ratio decreased during the last 10 years and recently varied between 1.5 and 2.5 in northern Europe and 7.7 in Lithuania. Between 1990 and 1999, the UK incidence rates for oral cancers rose in males of all ages from 6.5 to 8.3 per 100,000 (an increase of 18%) and in females from 2.6 to 3.6 per 100,000 (an increase of 30%) [20].

In the USA, the death rate due to cancer of the oral cavity and pharynx per 100,000 population in 2005 was 3.8 for males and 1.4 for females, down from 6.9 to 2.3, respectively in 1975. This substantial improvement is not reflected in most of the rest of the world.

Apart from the traditional risk factors, it has been suggested that oestrogen deficiency may influence susceptibility to oral cancer in women: Significantly, younger mean age at

menopause and higher rates of hysterectomy may influence the higher rates of oral cancer seen among younger females [21]. Data presented in this chapter are, whenever possible, separated by sex.

Ethnic Variations

Variations by ethnicity are largely due to the social and cultural practices, and the influence of dietary and genetic factors, though the latter are less well quantified. Variations in outcome are also contributed to by differences in access to healthcare. Where cultural practices represent risk factors, their continuation by immigrants from high incidence regions to other parts of the world results in comparatively high cancer incidence in immigrant communities. This can also affect the sub-sites of oral cancer most commonly affected, as shown in a recent study from California [22]. The highest age-adjusted oral cancer rates in the USA are found among non-Hispanic black men (4.86/100,000) followed by non-Hispanic black women (4.71/100,000), with Asian and Hispanic populations showing intermediate incidence rates compared with white (Caucasian) ethnic groups. Tongue cancer was the most common type of oral cancer among every ethnicity. Asians were more likely to develop their malignancy in the buccal mucosa, a reflection of continuing areca and tobacco chewing habits. Another study showed that American Indians and Alaskan Natives overall had significantly lower incidence rates than non-Hispanic whites [23]. Several studies from the USA have demonstrated that black patients with oral cancer have poorer overall and disease-specific survival than whites, mainly because of their comparatively poor access to health care [24, 25]. This is especially concerning because the incidence of oral plus pharyngeal cancer for black men in the USA is so high, and is the sixth most common site for malignant disease among this group [26].

The age-adjusted incidence rate for oral and pharyngeal cancers is higher for South Asians than for other residents in England, particularly among females [27]. Interestingly, this study showed that British South Asian males have significantly better survival than their non-South Asian peers in the south east of England, possibly a reflection of the more indolent progress of tobacco/areca nut-induced lesions [27].

Worldwide there are four times more men who smoke than women. In 2002, there were 941 million male smokers, which was 43% of all men aged over 15 years old. The largest population of male smokers lives in China – where men are more likely to smoke than not to smoke. Even Puerto Rico and Sweden, with the lowest percentages of men who smoke still have 17% who are smokers (Fig. 1.3a, b).

When smoking is widespread, smokers not only just damage their own health, but also collectively damage the health of

people around them. Passive smoking by children can increase the risks of asthma, cot deaths and chest infections.

The prevalence of smoking increased dramatically during the world wars, mainly due to the policy of providing free cigarettes to allied troops as a “morale boosting” exercise.

The Cancer Council, 2006.

Age Distributions

Oral cancer is usually a disease that occurs in males after the fifth decade of life. The mean age at presentation is in the fifth and early sixth decades in Asian populations compared with the seventh and eighth decades in the North American population [28–33]. Statistics in the USA for 2001–2005 show that the median age at diagnosis for cancer of the oral cavity and pharynx was 62 years [34].

Several studies suggest that 4–6% of oral cancers now occur at ages younger than 40 years [35]. An alarming increase in incidence of oral cancers among younger people has been reported from many parts of the world [36–39], a trend that appears to be continuing. There was a significant increase in the incidence of cancers in the tongue and tonsil among 20–40 year olds in the USA between 1973 and 2001 [40]. In Germany, Czechoslovakia and Hungary, there has been an almost tenfold rise in mortality from oral cancer in men aged 35–44 [41], within one generation. Robinson and Macfarlane showed a dramatic increase in incidence rates for younger males in Scotland from the 1980s to the 1990s [42]. In the high prevalence areas of the world, in many cases patients are less than 40 years old, probably owing to heavy lifetime use of various forms of tobacco, although some recent Indian data have not shown this [43].

It is also clear that a number of cases of squamous cell carcinoma occur in both young and old patients, often in the absence of traditional alcohol and tobacco risk factors, and in which the disease may pursue a particular aggressive course. A study conducted in Southern England concluded that a substantial proportion of cases of younger people diagnosed with oral cancer occur in the absence of known risk factors [44]. This, together with the relatively short duration of exposure in users suggests that factors other than tobacco and alcohol are implicated in the development of oral cancer in a significant minority of cases. Diets poor in fresh fruits and vegetables were identified as conferring significant risk. HPV infections may also be relevant in a proportion of these cases. It is also suggested that greater attention should be paid to familial antecedents of malignant neoplasms in younger patients with oral cancer [45].

Age distribution curves for the major head and neck cancer sites are given for deliberately selected countries in Figs. 1.10–1.15.

Mouth & Pharynx, CO1-14 exc lip, saliv gland and nasopharynx, Male

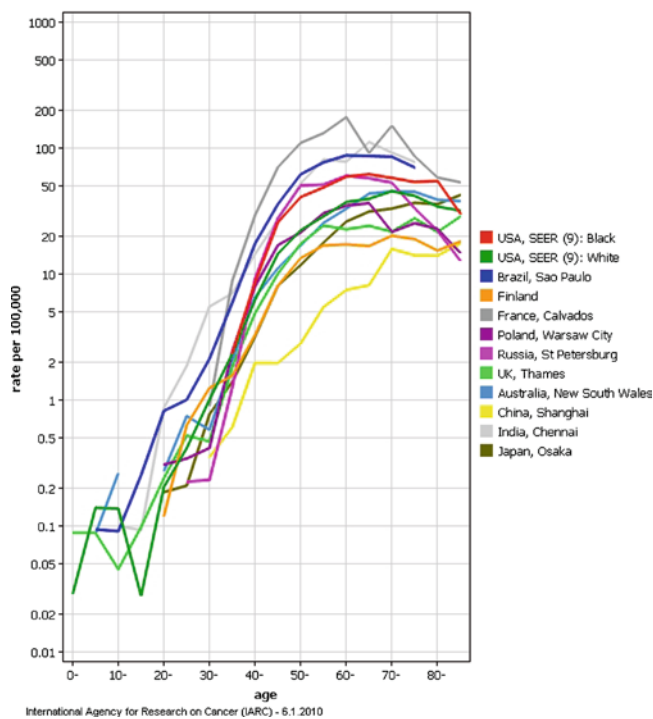


Fig. 1.10 Male age-specific incidence curves for mouth and pharynx for selected countries. All UADT cancers show a similar distribution. Most cases occur in the fifth to seventh decades of life, presumably because decades of exposure to tobacco, alcohol and poor nutrition take time to synergise with other agents in triggering malignant transformation – or in allowing this to survive the host response!! There are, nevertheless, a significant minority of cases appearing in the third and fourth decades of life: these attract much interest as, although associations with early commencement of smoking, and with unsafe alcohol use can be demonstrated, a substantial minority of cases arise without exposure to traditional risk factors: here dietary inadequacies and HPV infection are thought to be important, as may inherited predisposition. In the high incidence age bands there is a ~40–100-fold difference in incidence with, among the countries selected here, disturbingly high rates in NW France, Brazil and South India. Note the much worse situation in American blacks cf. whites, explained by a mixture of risk-factor and socio-economic reasons. Finland does comparatively well – not surprising in view of that nation’s success in reducing the prevalence of smoking, though alcohol abuse remains a social problem. What is surprising are the low rates recorded for Shanghai, in spite of high smoking prevalence in this large city. China is in the early stages of developing a comprehensive, nation-wide Cancer registry system and caution is necessary in interpreting some of the current data

Mortality Rates and Trends over Time

Table 1.2 gives mortality data again extracted from the Cancer Incidence in Five Continents Database for the period 1998–2002 [3], for comparison with the incidence data in Table 1.1. Trends of age-standardised (world population) mortality rates for the head and neck cancer sites of interest,

Mouth & Pharynx, CO1-14 exc lip, saliv gland and nasopharynx, Female

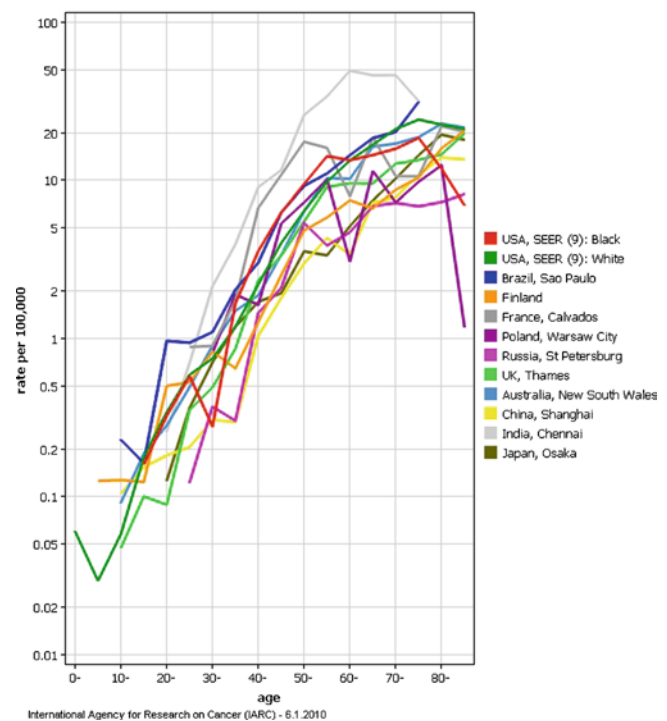


Fig. 1.11 Rates for females are lower and international differences are less marked. Women in South India stand out – related to use of betel quid and tobacco, together with low SES

within selected countries over the past three to six decades, are presented in Figs. 1.16–1.21.

Current male death rates for oral and pharyngeal cancer around the world are seen vividly in Fig. 1.16. There was a steady rise in oral cancer mortality in men from the 1950s to late 1980s in most Western European countries [46], but this trend has since declined, in France, China and Hong Kong, which had exceedingly high rates in the past. Unfortunately, in most countries in central and eastern Europe, oral cancer mortality in men has continued to rise, reaching exceedingly high rates in Hungary, Slovakia, Slovenia and the Russian Federation. Hungary, Ukraine, Estonia and Bulgaria show more than a 100% increase in mortality rates for men during the 20-year period up to the turn of the Millennium. Even though the rates of oral cancer are comparatively low among women, there is a steady increase in some countries in Europe (notably Hungary, Belgium, Denmark and Slovakia). Hungary also shows a 98% increase in mortality rates for women Fig. 1.17. These disturbing trends are thought to relate to high drinking and smoking patterns in these societies, together with poor diet in lower socio-economic groups.

Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (Figs. 1.18 and 1.19). Trends for naso-pharyngeal cancer, both good and bad, are shown for high-incidence countries (Figs. 1.20 and 1.21).

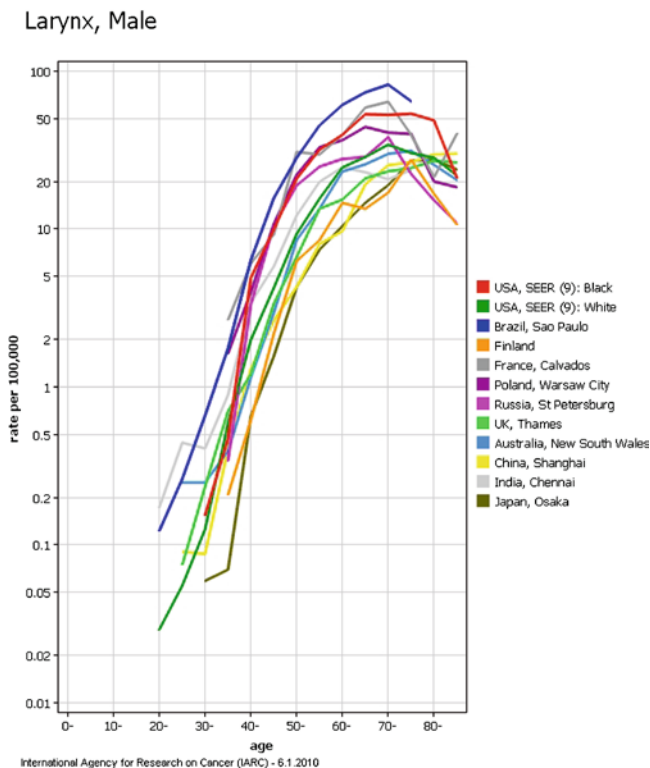


Fig. 1.12 Many of the differences between populations are likely to be explained by smoking and other traditional risk factors. Serious public health challenges exist in the Brazilian example. Poland and the Russian example are consistent with the major concerns we have for Eastern Europe, Russia and the former Soviet republics as a whole. Blacks do poorly in the USA. Finland provides encouragement: indeed this was the first country in the world to reach the WHO target for the year 2000 of having less than 20% of the adult population smoking. Japan and China remain enigmas

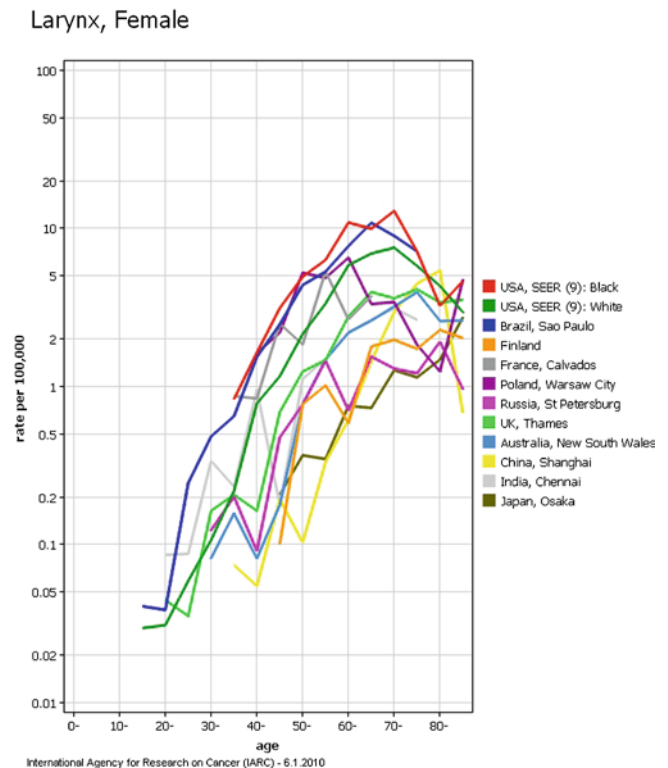


Fig. 1.13 Although at first glance the spread for women looks larger, the rates are much lower than for men. Again, however, Brazil and American blacks stand out

Mortality Trends by Birth Cohort

This is a valuable way for determining time trends. Cases of particular cancers are transformed back, in 5-year age groups, to the date of birth of the affected individuals. Curves for particularly instructive countries are given below. In general these show that for most UADT cancers, in most developed countries, rates fell in the latter part of the nineteenth and the first part of the twentieth centuries. This has been continued in, for example, the USA (Fig. 1.22) and the UK (Fig. 1.23). However in Hungary (Fig. 1.24: and the same is true for most of eastern Europe, Russia and the former Soviet republics), those born in the first half of the twentieth century showed alarming rises in death rates. All of these birth cohorts have now passed on, or they are in the highest risk age groups: in these countries, we have thus seen a growing epidemic of UADT cancer. The curves provide limited hope that Hungary at least, may be showing some control in younger people.

France (Fig. 1.25) is an interesting case: again the data show that this nation has “turned the corner” with a rise, and now a downturn for cohorts born since the end of the Second World War.

The SEER programme in the USA has reported an overall fall in the mortality from oral and pharyngeal cancer, between 1975 and 2004, of 1.87% per annum Table 1.3.

Table 1.3 shows a fall in all mortality rates for oral and pharyngeal cancer in the USA between 1975 and 2004. There is a considerable fall in mortality among both white and black women under 65 years of age (APC of -3.12 and -3.21 , respectively). Furthermore, the SEER data show higher 5-year relative survival rates for whites (61.8%) and blacks (39.5%), who were diagnosed during the period 1995–2001, than rates for those who were diagnosed during the period 1974–1976 (when rates for whites and blacks were 55 and 36.3%, respectively) [47]. The 5-year survival rates in the SEER Registries range from a high of 72.1% for white women in Utah to a low of 24.8% for black men in metropolitan Atlanta. These striking differences are likely to be explained by a number of factors including socio-economic condition, age, stage at diagnosis, continued presence or absence of environmental risk factors and access to

Nasopharynx, Male

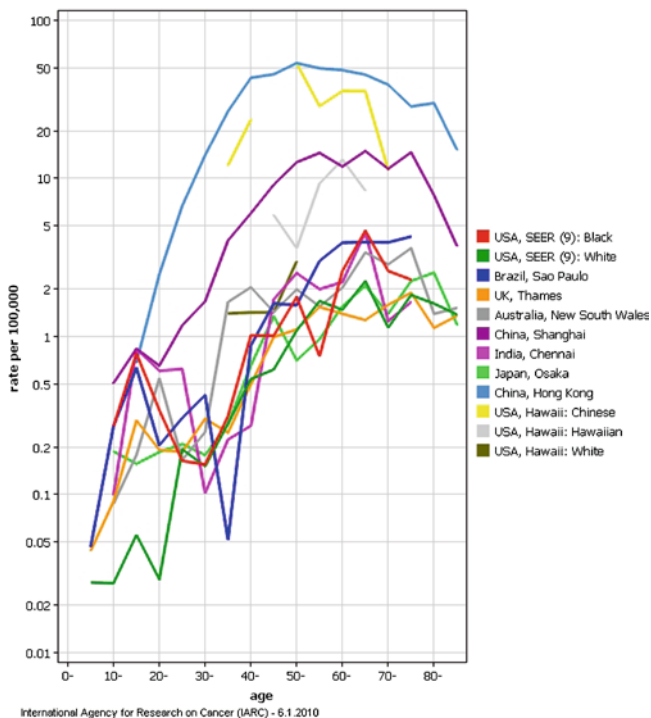


Fig. 1.14 NPC is a distinct disease. These countries have been chosen to reflect the differences by population. As mentioned in the legend to the cancer map, southern Chinese men are particularly susceptible: hence the alarming data from Hong Kong and to a lesser extent from Shanghai. Although the data are fragmentary, the markedly higher rates in Chinese Hawaiians than other racial groups there is consistent with the ethnic bias

hospital services. African-American patients have consistently poorer survival outcomes [48].

A study in Mumbai, India, indicated a decreasing trend in oral cancer incidence among Indian men, which it was suggested may be due to a decrease in the use of betel quid/pan and associated oral smokeless tobaccos over this period [49]. However, there continues to be a high prevalence of smokeless tobacco use among young adult men and women, especially in the form of Pan Parag/Gutka-type products, and cigarette smoking is increasing. Overall, UADT cancers are not likely to decrease.

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

Nasopharynx, Female

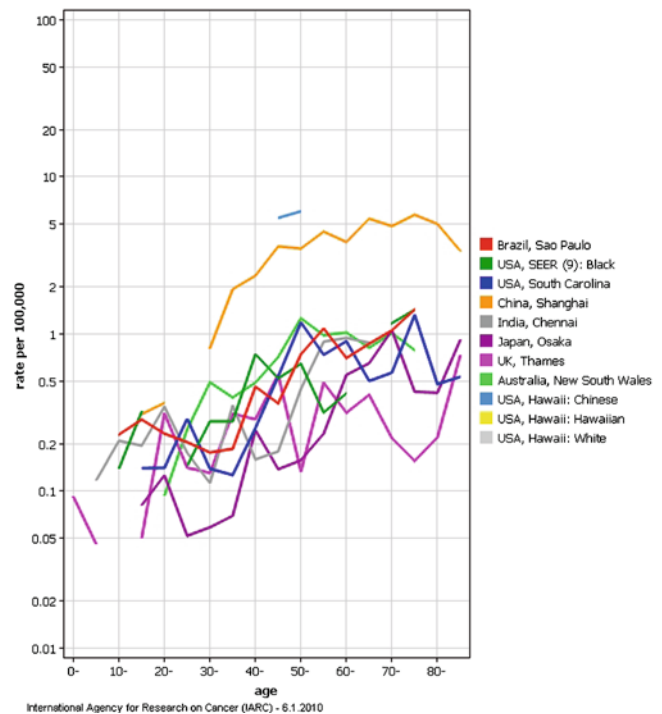


Fig. 1.15 The highest rates of NPC in women are again in Chinese – though only a tenth of those in males

Aetiology of Head and Neck Cancer

The majority of oral SCC are related to tobacco in various forms, betel quid chewing, heavy alcohol drinking and dietary micronutrient deficiency. In the developing world, tobacco and areca nut, used either alone or in combination, accounts for the vast majority of oral cancers and oral potentially malignant disorders (OPMD) [50]. The WHO has classified areca nut, a common component of many different chewing habits, as carcinogenic to humans [51]. UV radiation is relevant to lip cancer and there is an increasing evidence for a role for “high risk” genotypes of the HPV family, especially for tonsillar and other oropharyngeal sites.

Betel Quid

A betel quid generally contains betel leaf, areca nut and slaked lime, and may contain tobacco. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added according to local preference [51].

Table 1.2 World standardised global mortality rates per 100,000 for H&N cancers. Data derived from the Globocan 2002 database: anatomic descriptors derived therefrom [2]

Country	Oral cavity		Nasopharynx		Other pharynx		Larynx	
	Male	Female	Male	Female	Male	Female	Male	Female
World	2.7	1.5	1.2	0.5	2.5	0.5	2.9	0.4
More developed	2.7	0.7	0.3	0.1	2.5	0.4	3.3	0.3
Less developed	3.0	1.9	1.6	0.7	2.5	0.6	2.7	0.4
Eastern Africa	3.5	2.9	1.7	0.7	1.2	0.4	2.9	0.6
Middle Africa	2.7	1.3	0.6	0.2	0.9	0.8	2.1	0.7
Northern Africa	1.9	0.9	2.0	0.8	0.7	0.1	3.3	0.5
Southern Africa	6.3	1.7	1.1	0.3	1.5	0.3	4.2	0.5
Western Africa	1.5	0.8	1.2	0.5	0.6	0.2	1.6	0.3
Caribbean	2.7	1.0	0.5	0.1	2.4	0.7	4.5	0.8
Central America	1.0	0.5	0.2	0.1	1.0	0.3	2.5	0.4
South America	2.3	0.8	0.2	0.1	2.3	0.4	3.9	0.6
Northern America	1.4	0.6	0.3	0.1	1.3	0.4	1.7	0.3
Eastern Asia	0.7	0.4	2.1	0.9	0.3	0.1	1.0	0.2
Southeastern Asia	1.9	1.3	3.8	1.3	1.7	0.5	2.3	0.3
South Central Asia	7.0	4.6	0.5	0.2	6.7	1.5	4.5	0.6
Western Asia	1.8	1.1	1.0	0.4	0.5	0.3	4.4	0.7
Central and eastern Europe	5.1	0.7	0.4	0.1	3.9	0.3	6.8	0.3
Northern Europe	1.9	0.8	0.2	0.1	1.3	0.3	1.6	0.3
Southern Europe	2.7	0.6	0.4	0.1	2.5	0.3	4.8	0.2
Western Europe	2.9	0.8	0.2	0.1	4.0	0.6	2.9	0.3
Australia	1.8	0.9	0.3	0.1	1.5	0.3	1.6	0.2
New Zealand	1.3	1.0	0.3	0.1	1.0	0.2	0.9	0.2
Melanesia	17.3	11.7	0.2	0.2	1.4	0.5	1.9	0.7
Micronesia	2.4	1.5	4.9	1.6	1.2	0.5	2.1	0.0
Polynesia	2.8	0.3	2.5	1.1	0.6	0.0	0.0	0.0

Note again the stand-out rates for Melanesia! All head and neck cancers are highly morbid and lethal. Taking oral cavity, as defined in these tables, Death to Registration ratios (D/R) are 0.34 for males and little better at 0.29 for females in the more-developed countries: an appalling 0.52 and 0.54, respectively, in less-developed countries where they come late to diagnosis, where there are significant co-morbidities and where quality care is less available. This means that in most of the world, more than half of the individuals diagnosed with an oral cancer die of their disease

Fig. 1.16 Trends in mortality over time are important to track, and to understand. Hungary is a disaster, though hopefully the rise has been arrested. Russia remains a concern. France demonstrates what can be achieved, overall, in spite of the concerns shown by the Calvados registry data above. The overall downward trend in the other countries illustrated is encouraging

Mortality from Lip, oral cavity and pharynx Cancers
Age-standardized rate (World), Male all ages

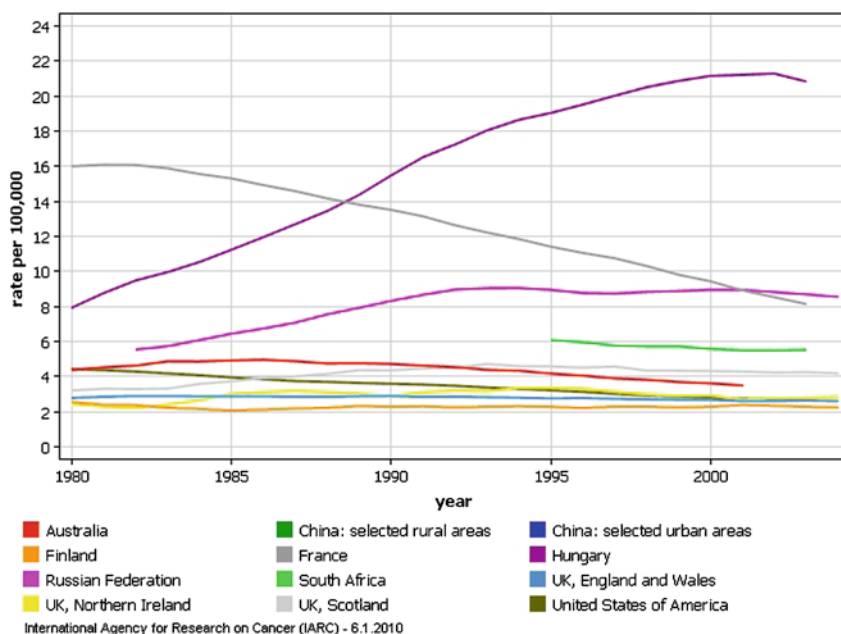


Fig. 1.17 Although only approximately a tenth of the male rate, Hungarian females remain a challenge

Mortality from Lip, oral cavity and pharynx Cancers
Age-standardized rate (World), Female all ages

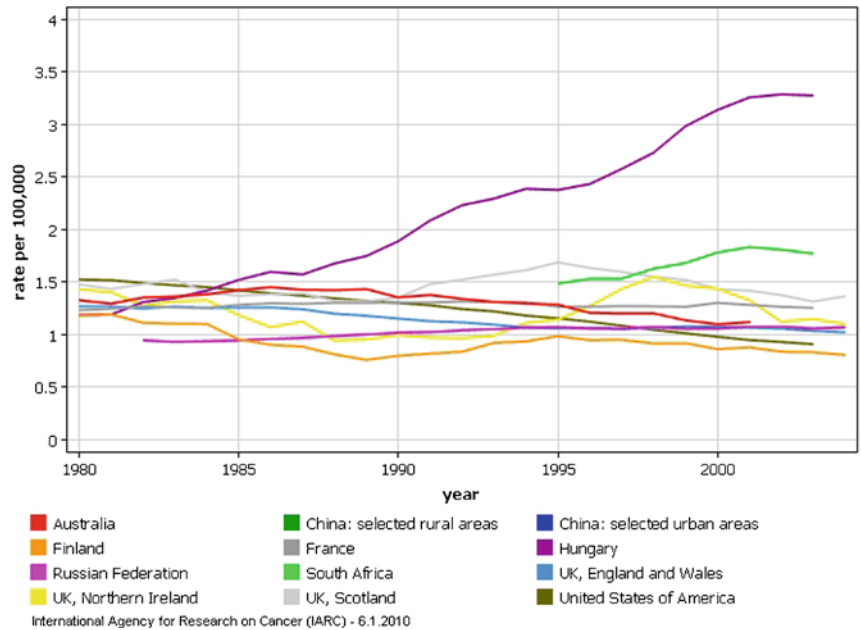


Fig. 1.18 Another success demonstrated for France. Have Russia and Hungary genuinely turned the corner?

Mortality from Larynx Cancer
Age-standardized rate (World), Male all ages

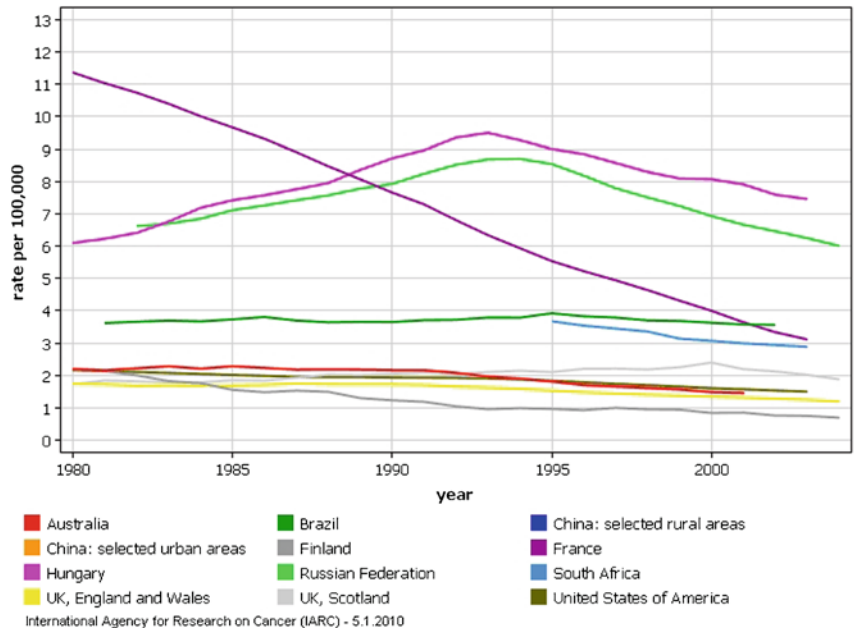


Fig. 1.19 This is a “noisy” curve because of the comparatively low mortality rates in women. Worryingly, but not surprisingly, it suggests an upward trend in Hungary

Mortality from Larynx Cancer Age-standardized rate (World), Female all ages

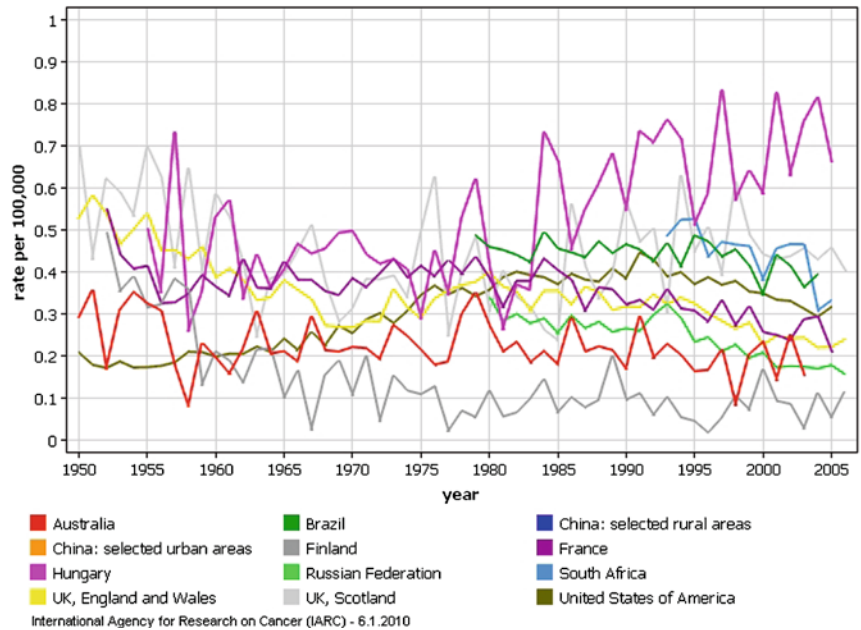


Fig. 1.20 One hopes the successes in Hong Kong can be replicated in other high risk groups

Mortality from Nasopharynx Cancer Age-standardized rate (World), Male all ages

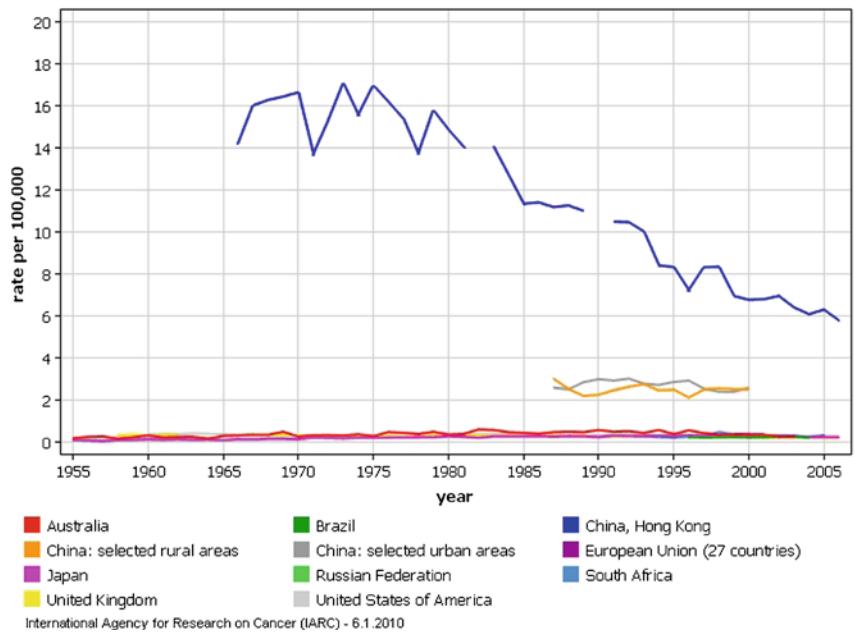
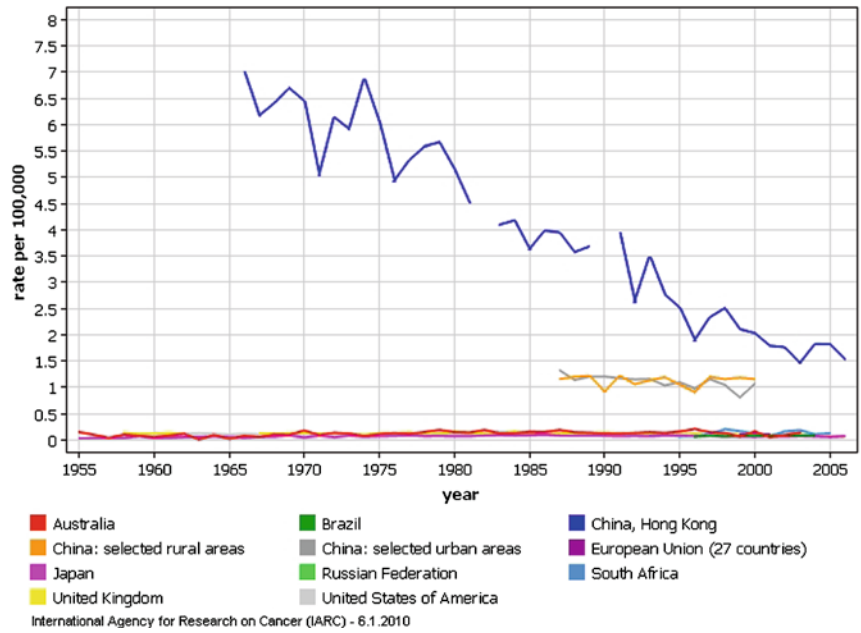
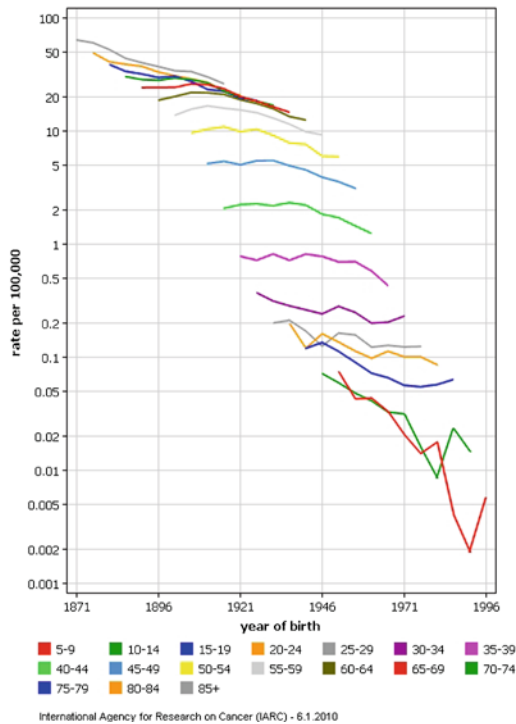


Fig. 1.21 From a lower initial base, Hong Kong women share this success story

Mortality from Nasopharynx Cancer Age-standardized rate (World), Female all ages



a
United States of America: Male
Mortality from Lip, oral cavity and pharynx Cancers



b
United States of America: Female
Mortality from Lip, oral cavity and pharynx Cancers

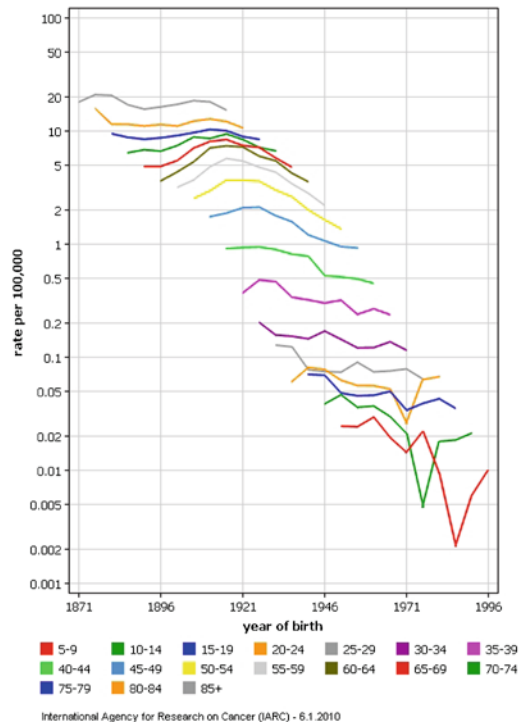


Fig. 1.22 Birth-cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for USA males (a) and females (b)

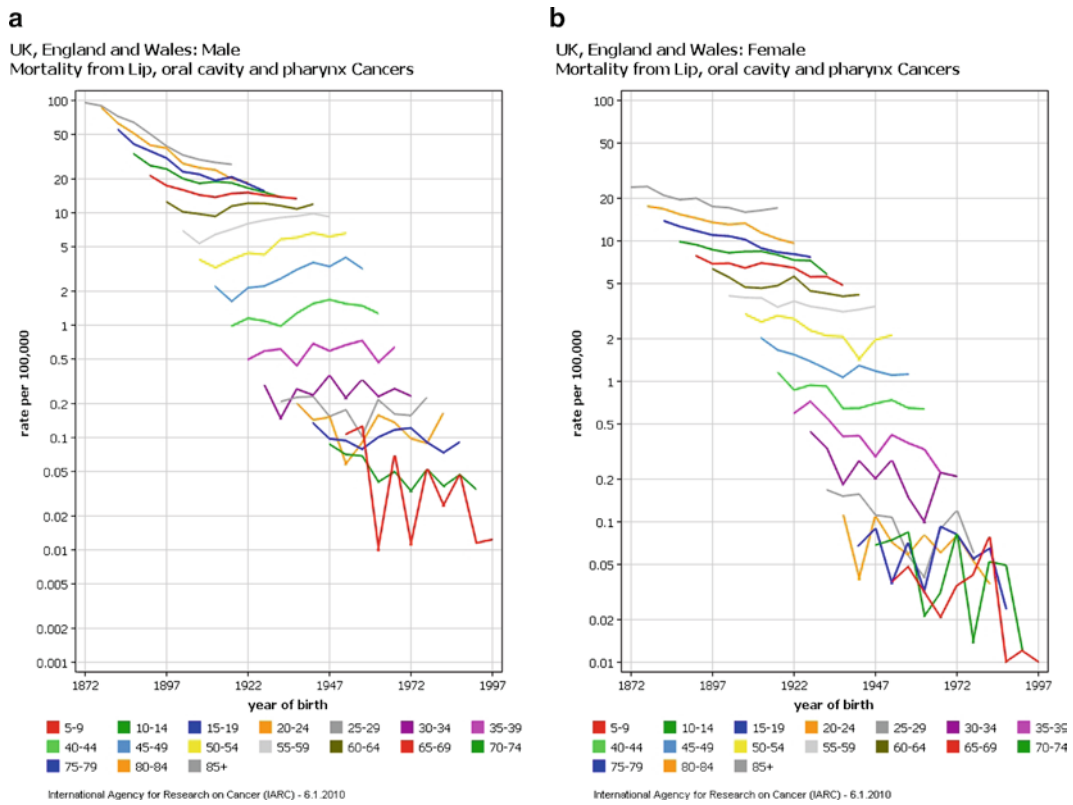


Fig 1.23 Birth-cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (a) and females (b) England and Wales

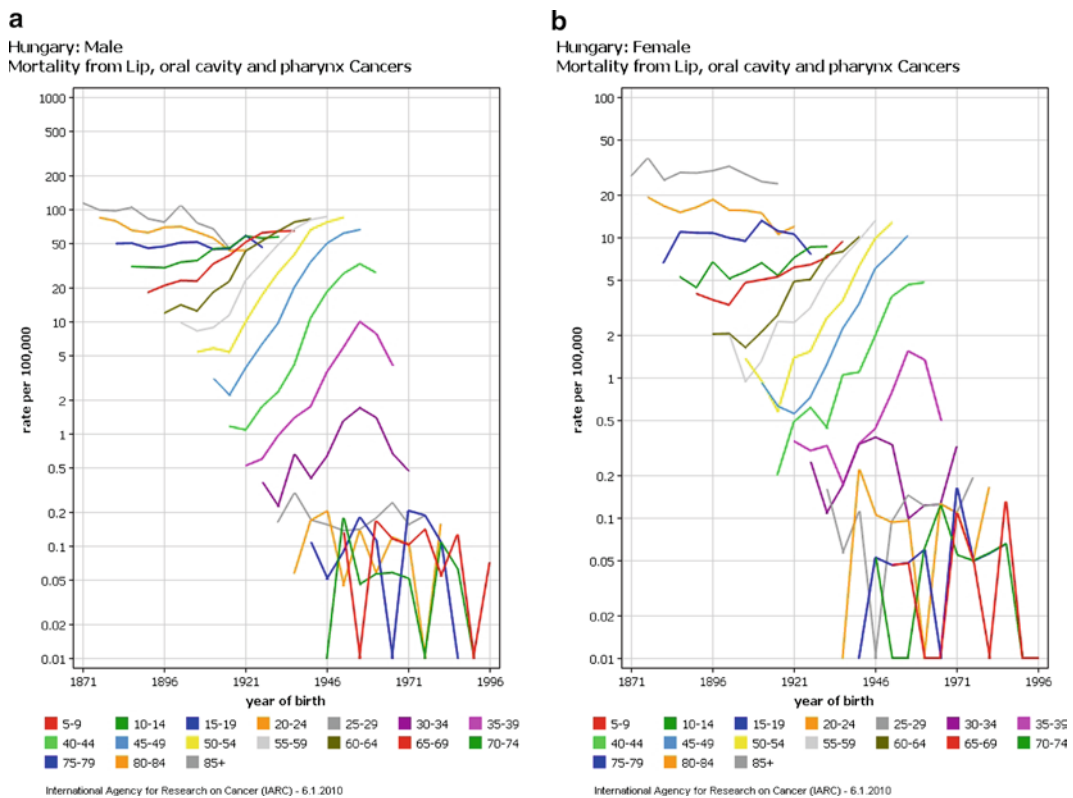


Fig. 1.24 Birth-cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (a) and females (b), and for laryngeal cancer (c, d) in Hungary. The challenge for Hungary, apparent in other

curves, is confirmed here. Males born in the first half of the twentieth century had rising rates or death from oral and pharyngeal cancer. There are indications that those born after 1950 may be less at risk

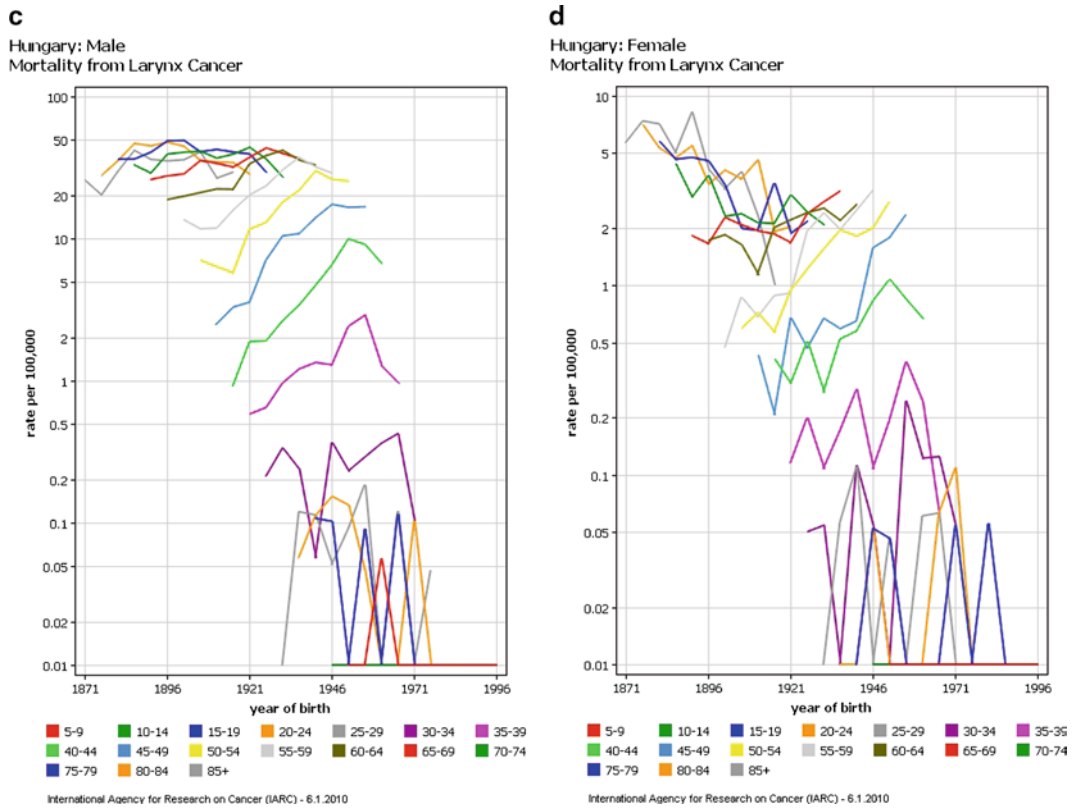


Fig. 1.24 (continued)

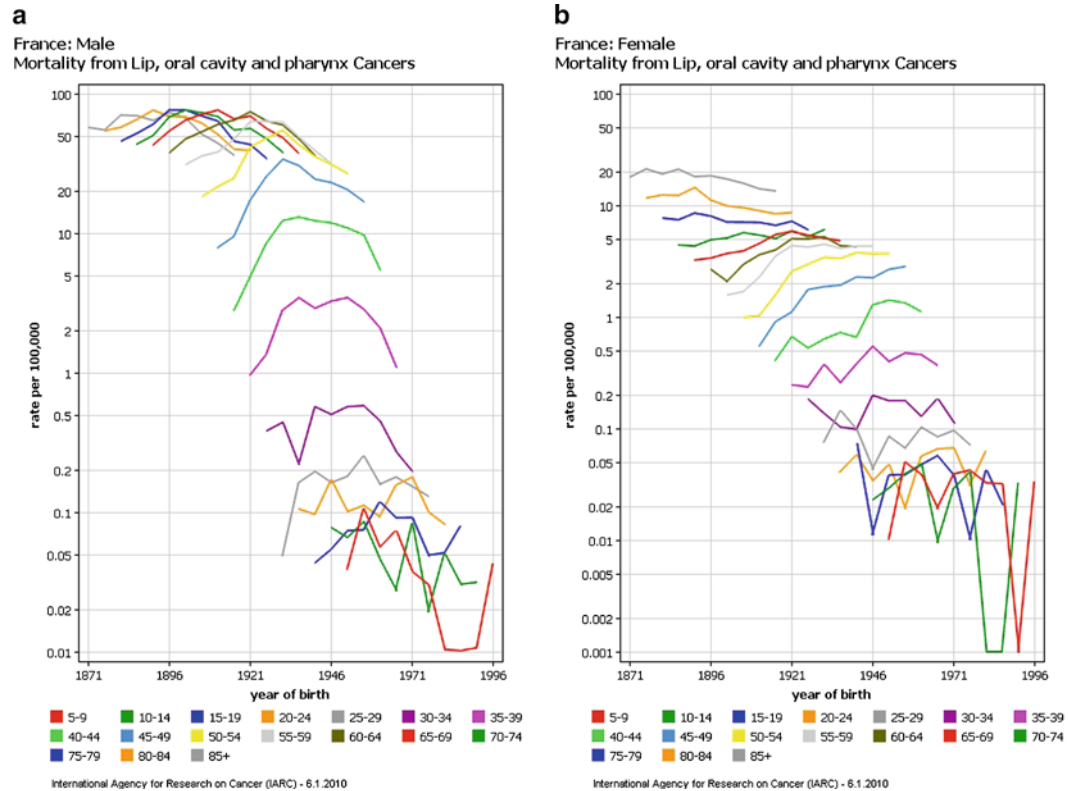


Fig. 1.25 Birth-cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (a) and females (b), and for laryngeal cancer (c, d) in France. Birth cohort curves are instructive. For males born in the nineteenth century and the first few decades of the twentieth

century, death rates from oral and pharyngeal cancer were extremely high. Those born from around 1940 and later are generating the national average downward trends seen above

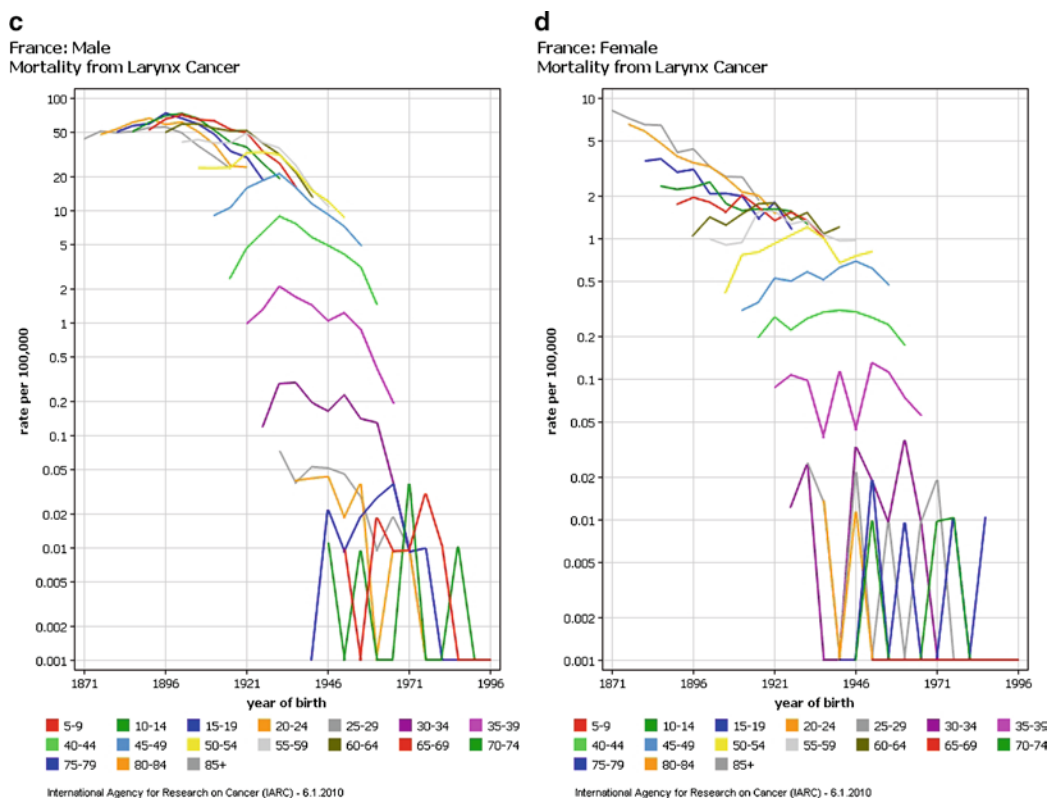


Fig. 1.25 (continued)

Table 1.3 Mortality trends (APC) for oral and pharyngeal cancer in the USA between 1975 and 2004, by race and sex. (SEER Cancer Statistics Review, 1975–2004) [34]

	All races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	-1.87 ^a	-2.12 ^a	-1.63 ^a	-1.87 ^a	-2.15 ^a	-1.62 ^a	-1.94 ^a	-1.91 ^a	-1.71 ^a
Under 65	-2.41 ^a	-2.24 ^a	-3.06 ^a	-2.38 ^a	-2.18 ^a	-3.12 ^a	-2.88 ^a	-2.80 ^a	-3.21 ^a
65 and over	-1.45 ^a	-1.99 ^a	-0.75 ^a	-1.53 ^a	-2.14 ^a	-0.79 ^a	-0.46 ^a	-0.59 ^a	-0.26

APC annual percentage change

^aThe annual percentage change in rate is statistically significantly different from zero ($p < 0.05$).

Betel Leaf

The leaves of the *Piper betel* vine (a member of the pepper family) contain betel oil, a volatile liquid, which contains several phenols including hydroxychavicol, eugenol, betel phenol and chavicol. These compounds may, to some extent, be protective, sharing some of the antioxidant properties of many plant polyphenols. Vitamin C, a large amount of carotene and 36 trace elements have also been reported in the betel leaf, clearly beneficial micronutrients [52].

Betel Inflorescence

Apart from the leaf, other parts of the vine such as stem, inflorescence (the flowers or pods) or catkins are also consumed with areca nut. Consumption of the inflorescence is common in Melanesia and parts of Taiwan, and in China, and it is mostly added to the quid for its aromatic flavour [51]. Betel inflorescence contains a high concentration of phenolic compounds including hydroxychavicol, eugenol, isoeugenol, eugenol methyl ester and safrole. Safrole itself, a major

phenolic compound, is classified as a weak carcinogen in rats and is banned as a food and cosmetic additive by the FDA in the USA, *inter alia*, however, there is no direct evidence for its carcinogenicity in man.

Areca Nut

Areca nut is the seed of the fruit of the oriental palm *Areca catechu*. It is the basic ingredient of a variety of widely used chewed products. The consumption of areca nut is indigenous to India, Sri Lanka, Bangladesh, Myanmar, Taiwan and numerous islands in the South Pacific. It is also popular in parts of Thailand, Indonesia, Malaysia, Cambodia, Vietnam, Philippines, Laos and China, and in emigrant communities from these countries. It is believed that *Areca catechu* may be native to Sri Lanka, West Malaysia and Melanesia. Areca nut is used as a masticatory substance by approximately 600 million people worldwide. It is estimated that 10–20% of the world's population chew areca nut in some form, often mixed in betel quid (pan) [51].

The major constituents of the nut are carbohydrates, fat, proteins, fibre, polyphenols (flavonols and tannins), alkaloids and mineral matter. Among the chemical constituents, alkaloids are the most important chemical. The nut has been shown to contain at least six related alkaloids, of which four (arecoline, arecaidine, guvacine and guacoline) have been conclusively identified [53].

Nitrosamine derivatives from each of the four major arecal alkaloids are produced by nitrosation of the alkaloids in dried-stored nuts, in the mouth and especially in the acid conditions found in the stomach, in the presence of nitric oxide generated by bacterial action. Two of these derivatives are accepted as carcinogenic in animal studies, especially MNPN (methylnitrosaminopropionitrile). Endogenous nitrosation is significantly higher in subjects with poor oral hygiene as determined by volumes of dental plaque [54]. This implies that, on the basis of the availability of substrates from both areca nut and tobacco, there is a more extensive formation of nitrosamine in subjects with poor oral hygiene if they also chew tobacco [55]. Moreover direct evidence that reactive oxygen species, such as the hydroxyl radical (HO), are generated in the oral cavity due to auto-oxidation of polyphenols contained in areca nut and enhancement by the alkaline pH from slaked lime has been reported [51, 56].

Areca Nut-Based Industrial Packaged Products

A variety of packaged areca products are now available. These are mostly manufactured in India and Pakistan, and

exported worldwide where they are used by old and new habitués. The most common are *gutka* and *pan masala*. Gutka is a dry, relatively non-perishable commercial preparation containing areca nut, slaked lime, catechu, condiments and powdered tobacco. The same mixture without tobacco is called pan masala [57].

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

(a) Lichenoid Lesions

Areca-induced lichenoid lesions, mainly on buccal mucosa and tongue, are recognised. This is considered to be a type IV contact hypersensitivity-type lesion that resembles oral lichen planus clinically [58].

(b) Betel Chewer's Mucosa

This condition was first described by Mehta et al. (1971), and is characterized by a brownish-red discoloration of the oral mucosa. It is often accompanied by encrustation of the affected mucosa with quid particles, which are not easily removed, and with a tendency for desquamation and peeling. Both chemical and traumatic effects of the betel quid are likely on the oral mucosa. The presence of tobacco in the quid is not essential for the development of chewer's mucosa [58].

(c) Oral Leukoplakia

A case control study conducted in Taiwan, where areca is chewed without tobacco, found the odds ratio for developing leukoplakia to be 7.43 (95% CI 1.94–156.27) for areca nut chewers. These authors demonstrated that the cessation of areca chewing resulted in regression of 62% of leukoplakias [59].

(d) Oral Submucous Fibrosis (OSF)

It is now accepted that chewing areca is the single most important etiological factor for the development of OSF [60], although the pathogenesis is not fully understood. In vitro studies have shown that areca nut alkaloids such as arecoline and its hydrolysed product arecaidine can stimulate cultured fibroblasts to proliferate and synthesise collagen. In addition, flavonoids from the nut have been shown to enhance the cross-linking of collagen, thereby increasing its resistance to degradation by collagenases, as part of normal tissue homeostasis. The copper content of areca nut is high and the possible role of copper as a mediator of fibrosis is supported by the demonstration of up-regulation of lysyl oxidase in OSF biopsies [61].

(e) Oral squamous cell carcinoma (OSCC)

Historical evidence dating back nearly a century indicates that areca nut is involved in the development of OSCC. Subsequently, many case-control studies [62, 63] have confirmed that betel quid chewing increases the

risk of developing OSSC, especially when the quid contains tobacco. A South African study found that 68% of cheek cancer and 84% of tongue cancers developed in subjects consuming areca *without* tobacco [64]. A large number of animal studies have confirmed that areca products and derivatives such as arecoline and areca-derived nitrosamines have the ability to induce neoplastic changes in experimental models, and the IARC has now formally designated areca and betel quids without tobacco as carcinogenic to man [51].

Slaked Lime

Slake lime (calcium hydroxide) is added to betel quids in most of South Asia. In coastal areas of Sri Lanka and the Pacific, it is obtained by heating sea shells or harvested from corals. In inland areas, it is quarried from limestone. When added to betel quids, it causes erosions of oral mucous membranes, which facilitate penetration of betel-quid carcinogens through the mucosa.

Smokeless or Chewing Tobacco

Tobacco is often added to the quid mixture. Edible tobacco in the Indian subcontinent is prepared from sun-dried and partly fermented, coarsely cut leaves of *Nicotiana rustica* and *Nicotiana tabacum* without further processing. Chewing tobacco results in a local exposure of oral mucosa to at least 16 carcinogens, including tobacco-specific nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH) [65]. Unusually high levels of carcinogenic TSNA (e.g. NNN – *N*-nitrosornicotine, and NNK) were reported in saliva of oral snuff users in the Sudan [66] and tobacco chewers in India [67]. NNK is a potent carcinogen and human buccal epithelial cells (in culture) have been shown to be to metabolise NNK: The formation of macromolecular DNA adducts following NNK metabolism is correlated with carcinogenesis in animal models [68].

Betel chewing also releases large amounts of a reactive oxygen species (ROS), especially while the betel quid is actually present. Both TSNA and ROS are major genotoxic agents involved in chewing tobacco-associated oral cancer [51]. Clear dose–response relationships between quid use and the risk of oral cancer and of potentially malignant oral disorders have been demonstrated in many epidemiological studies.

Most forms of oral smokeless tobacco – oral snuff – consumed in Scandinavia and in North America are not flue-cured, and contain relatively low amounts of TSNA. Although

the topic is controversial, many of these products are not highly carcinogenic and it has even been suggested that they have a role as nicotine replacement products in achieving smoking cessation [69]. It is, however, important to remember that there is no such thing as safe tobacco: most smokeless tobaccos have high levels of nicotine and are addictive; indeed, there is an evidence that they can be initiators of smoking [70]. Furthermore, they have significant cardiovascular effects [71] and certainly produce oral mucosal lesions and local damage to the periodontium [72].

Contaminants

Areca nut can be contaminated with fungi such as *Aspergillus flavus*, *A. niger* and *Rhizopus* spp. Almost 40% of samples of areca nut from India analysed using thin layer chromatography contained aflatoxins [73]. These are established carcinogens.

Tobacco Smoking

Tobacco is identified as the leading preventable cause of premature death worldwide. It is estimated that 4.9 million people died of tobacco-related illness in 2000, and by 2020, it is expected that this figure will rise to 10 million deaths per year, of which 70% will be in developing countries [68]. Tobacco is a major independent risk factor for the development of oral and pharyngeal cancer and other malignancies of the upper aerodigestive tract. Tobacco is consumed in different ways as a form of smoking: cigarettes, cigar, beedi, reverse smoking and smokeless tobacco like oral snuff or in moist pouches. Tobacco smoke contains more than 60 carcinogenic combustion products. In particular, NNK, NNN and polycyclic aromatic hydrocarbons (PAHs) have been causally linked to UADT cancer. The activity of carcinogens is generally exerted through DNA adducts [74, 75]. Both tobacco smoking and quid chewing cause oxidative stress to tissues, that is, the sustained presence of reactive oxygen species (ROS), which initiate free radical reactions. ROS can damage proteins, lipids, carbohydrates and DNA. Minor DNA damage can result in mutations that can be part of the causal chain for malignant transformation, while sustained DNA damage can result in further perturbations of cell cycle control [76].

In addition to an extensive literature on the carcinogenicity of tobacco smoke in cell and animal models, numerous case–control and cohort studies affirm its key role in man, and the super-multiplicative synergism with alcohol drinking [77]

Alcohol

Unsafe consumption of alcohol, including so-called binge drinking, is a major public health problem worldwide, for example, contributing between 5,000 and 40,000 deaths in the UK annually [78]. The possible beneficial effects of moderate alcohol consumption have been widely canvassed, because of the so-called J-shaped relationship between alcohol intake and all-cause mortality, as shown in a number of meta-analyses [79]. The upstroke of this J-curve is thought to be due to the cardio protective effect of moderate alcohol consumption: In particular, alcohol increases high density lipoprotein levels, inhibits platelet aggregation, and promotes fibrinolysis [80]. It has always been recognised that above an intake of around 10 g of alcohol per day the detrimental effects of alcohol predominate [79].

The recent increases in oral cancer reported in younger subjects in the UK were related, at least in part, to growing alcohol use/abuse in that society [44]. The difficulty of accurately quantifying the influence of alcohol in the aetiology of H&N cancer stems from the fact that most people who drink heavily also smoke. It is also difficult to obtain reliable information from individuals on their intake of alcohol.

The health education council in the UK recommends a weekly intake of no more than 14 units for women and 21 units for men. Using these criteria one in four men and one in ten women in that country are believed to be drinking over this limit, with the number of habitual heavy drinkers estimated at four million [81]. Although the legal age for drinking is 18 years, the average age at which drinking starts has fallen since the early 1970s from around 17 to around 11 years, in boys and girls. The recent emergence of “Alcopops” (alcoholic drinks that mimic the taste of non-alcoholic drinks) has resulted in wide uptake among those under 18.

Internationally there is a developing view that *any* consumption of alcohol is detrimental, and even the French government now publicly recommends severe constraint or even abstinence: the French National Cancer Institute has declared “there is no amount of alcohol, however small, which is good for you” [82]. WHO policy is to minimise the use of alcohol throughout all of society [83], and the 2009 Australian Guidelines to Reduce Health Risks from Drinking Alcohol summarises the science cogently [84].

Ethanol and water are the main components of most alcoholic beverages, which also contain volatile and non-volatile flavour compounds. The major alcohol metabolising enzymes are alcohol dehydrogenase that oxidises ethanol to acetaldehyde, and aldehyde dehydrogenase that detoxifies acetaldehyde to acetate. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol, owing to its multiple mutagenic effects on DNA. Specific alcoholic beverages have been shown to contain specific impurities or contaminants

that can be carcinogenic. *N*-nitrosodiethylamine is present in some beer and whisky and has been associated with an increased risk of oral cancer. Polycyclic aromatic hydrocarbons, some of which are considered to be carcinogenic, are found in many brands of whisky [85].

Alcohol also acts in the following ways to promote oncogenesis [85].

Ethanol:

- Damages the phospholipids of cell membranes and increases permeability. It has been shown to enhance the penetration of tobacco-specific carcinogens across the oral mucosa [86].
- Impairs DNA repair mechanisms.
- Acts as a solvent, allowing the carcinogens from tobacco to penetrate into tissue.
- Perhaps catalyses the activation of tobacco carcinogens.
- Alcohol is highly calorific. It lessens the protective effect of beneficial foods such as fruits and vegetables by depressing hunger.
- Is hepatotoxic, thus reducing the effectiveness of those enzyme systems central to detoxification of carcinogens, especially the glutathione-*S*-transferases and cytochrome-p450 systems.

A case-control study in Uruguay conducted between 1992 and 1996 is worthy of note [87]. Histologically confirmed cases ($n=471$) of squamous cell carcinoma of the oral cavity and pharynx in males admitted to four major hospitals in Montevideo were matched with the same number of other patients admitted for a variety of non-smoking and non-drinking-related conditions as controls. Alcohol consumption was assessed by interview and the number of grams of ethanol consumed per day was calculated. Ever-drinking was associated with a 4.5-fold increased risk of oral-pharyngeal cancer compared to non-drinkers, though no clear dose-response relationship was observed. Consumption of hard liquor was associated with a 3.6-fold increased risk, whereas pure wine drinking showed only a 2.1-fold increased risk. When risks were analysed by sub-sites, the highest odds ratios were observed for oral cavity cancer.

Another case-control study conducted in Italy and Switzerland between 1992 and 1997 included 749 cases of oral/pharyngeal cancer and 1,772 hospital controls. Alcohol consumption was measured by the number of drinks consumed per day, one drink corresponding to ~125 ml of wine, 330 ml of beer or 30 ml of spirits (i.e. about 12 g of ethanol). Compared to light drinkers (1–2 drinks per day), the adjusted OR for 3–4 drinks was 2.1(95% CI 1.5–2.9) and 21.1(95%CI 14.0–31.8) for more than 12 drinks per day. Wine drinkers who consumed more than 12 drinks per day were at a 16.1-fold risk compared to the abstainers. Consumption of more than 3 beers per day resulted in a 2.3-fold risk compared to the non-beer drinkers. In contrast to the Uruguayan study,

there was only a 1.9-fold risk for consumption of spirits as compared to non-spirit drinkers [88].

There are many confounders in such studies. Most people drink a variety of beverages, and accurate controlling for tobacco, diet, socio-economic status and other variables is challenging.

Mouthwashes

There has been considerable interest in the possible risks of H&N cancer associated with use of alcohol-containing mouthwashes recently, leading some manufacturers to use “alcohol-free” as a marketing tool. Epidemiological findings have not been consistent and control for other major risk factors, including smoking, not always easy to ascertain from the published work [89]. Some reviews have argued that using mouthwash daily may be an independent cause of cancers of the head, neck and oesophagus [90, 91]. It is well established that ethanol increases the permeability of lining mucosa, allowing carcinogens to penetrate more freely. Acetaldehyde, the proximal metabolite of ethanol can accumulate in the mouth from bacterial action, and as explained above this is an established carcinogen. However, four case-control studies have shown non-significant, lower or similar oral cancer risks among self-reported mouth wash users compared to non-users [92, 93]. The most recent meta-analysis has not demonstrated excess risk for oral cancer from alcohol-containing mouthwashes [94, 95]. There is, however, a plausible biological basis for risk associated with alcohol-containing mouthwashes, especially in smokers and it is always prudent to remember that absence of evidence is not evidence for absence.

Diet and Nutrition in the Aetiology of Head and Neck Cancer

Dietary factors are estimated to account for approximately 30% of all cancers in Western countries [96]. This proportion is currently thought to be about 20% in developing countries and is projected to increase in the future [97]. Poor diet is a significant risk factor for all H&N cancers [98–104] and appears to be second only to tobacco as a cause of oral cancers worldwide [3]. A case-control study of laryngeal cancer in Italy and Switzerland between 1992 and 2000, revealed that a diet not only rich in, but also varied in, fruit and vegetables confers decreased risk of laryngeal cancer [101].

Evidence comes from case-control and cohort studies, from animal and from in vitro experiments. Protective and unhealthy foods are well understood, and form the basis of health

education messages in most countries. The micronutrients that confer these benefits are also well understood. Vitamin A and related carotenoids (in particular beta-carotene), vitamins C and E and selenium appear to be particularly protective against most epithelial cancers [105–107], and much of the effect is attributable to their antioxidant activities. Antioxidants act by reducing free radical reactions which can cause DNA mutations and changes in lipid peroxidation of cellular membranes [108]. Other protective roles of micronutrients are modulation of carcinogen metabolism, maintenance of appropriate cell differentiation, inhibition of cell proliferation and oncogene expression, maintenance of immune function and inhibition of formation of endogenous carcinogens [76].

A recent meta-analysis on oral cancer, based on 15 case-control studies and one cohort study, was able to utilise diet data from nearly 5,000 subjects: this estimated that each portion of fruit or vegetables consumed per day reduced the risk of oral cancer by around 50% [109]. These effects are also demonstrable with OPMD: In a population-based case-control study in Japan, where there were 48 cases of oral leukoplakia and 192 control subjects, serum levels of lycopene and beta-carotene were significantly lower in those with leukoplakia; logistic regression showed that high levels of beta-carotene were related to low risk of oral leukoplakia (OR=0.16) [110].

Intervention studies are also encouraging in this respect. In a major double-blind placebo-controlled trial in Kerala [111], up to one third of subjects showed regression of their oral leukoplakias after 12 months supplementation with oral beta-carotene. Extensive studies from the MD Anderson Cancer Centre in the USA are progressively identifying the most effective combinations of anti-oxidants in the regression of OPMD and the prevention of recurrences and second primary neoplasms in H&N cancer, although it has to be recognised that these agents do not always prevent the progression of an OPMD to overt cancer [112].

There is current interest in the protective effects of tea, especially green tea, which contains high levels of polyphenols [113]. These are powerful antioxidants able to counteract both initiation and promotion of carcinogenesis [108].

Genetic Predisposition

There is considerable evidence for a minor component of inherited, genetic predisposition in UADT cancers, related to polymorphisms in carcinogen-metabolising enzyme systems [114]. A recent extensive meta-analysis [91] pooled individual-level data across 12 case-control studies including 8,967 HNC cases and 13,627 controls. After adjusting for potential confounding factors a family history of H&N cancer in first-degree relatives increased the risk (OR=1.7, 95% CI 1.2–2.3).

The risk was higher when the affected relative was a sibling (OR=2.2, 95% CI 1.6–3.1) rather than a parent (OR=1.5, 95% CI 1.1–1.8) and for more distal H & N sites (hypopharynx and larynx). The OR rose to 7.2 (95% CI 5.5–9.5) among subjects with family history, who were alcohol and tobacco users. No association was observed for family history of nontobacco-related neoplasms and the risk of HNC (OR=1.0, 95% CI 0.9–1.1). Rare cancer syndromes can involve the H&N: Cowden syndrome, caused by mutations in the tumour suppressor gene PTEN; and dyskeratosis congenita, in which oral white lesions in young people have a risk of malignant transformation [115].

Microorganisms

Microorganisms have been implicated in the aetiology of oral leukoplakia for more than a century, beginning with the classic dorsal leukoplakia of syphilitic glossitis. Today tertiary syphilis is rare, but the fungus, *Candida albicans*, a common oral commensal, is frequently found invading the upper epithelium in histological sections of leukoplakia, more so in the mouth than pharynx or larynx [116], and this involvement is associated with a higher risk of malignant transformation [117]. The terms “candidal leukoplakia” and “hyperplastic candidiasis” have been used to describe such lesions.

It is now clear that high-risk HPV genotypes, particularly HPV 16 and 18, are important co-factors, especially in cancers of the tonsil and elsewhere in the oropharynx [118, 119]. The current state of knowledge is covered extensively in another chapter of the present volume.

The role of bacteria in the aetiology of UADT cancers is currently receiving more attention [120]. Endogenous production of acetaldehyde and reduction of nitrate to nitrites by oral flora is higher in drinkers with poor oral hygiene [121]. Understanding the role of the oral flora is certainly important in the management of the distressing mucositis associated with so much cancer therapy.

Air Pollution

Part of the urban/rural difference in the incidence of head and neck cancer has been related to atmospheric pollution. For example, mean sulphur dioxide and smoke concentrations in the atmosphere are positively correlated with squamous cancer of the larynx and, to a lesser extent, the pharynx in data collected some time ago from the West Midland region of England 1950–1990 [122].

Indoor air pollution resulting from the use of solid fuel such as wood, crop residue, animal dung and coal for cooking

and heating is a significant health problem in many developing countries, where a greater proportion of people use such fuels frequently in poorly ventilated areas. Many studies have been identified indoor air pollution as a risk factor for H&N cancer [123, 124] and a recent monograph by the International Agency for Research on Cancer has identified indoor air pollution from coal usage as a known human carcinogen, while that from biomass (primarily wood) as a probable human carcinogen [125]. Studies carried out in China and Brazil have reported exposure to wood smoke as a risk factor for oral cancer [126], nasopharyngeal cancer [127] and UADT cancer [128].

Solar Radiation

Prolonged exposure to sunlight represents an important risk factor for the development of squamous cell carcinoma of the lip in people with fair complexions, and those with outdoor occupations. Usually, the lower lip is involved because it receives considerably more direct sunlight than the upper lip [129]. Evidence comes from many countries, including those at latitudes with clean air through which ultraviolet light penetrates easily, such as Finland [130] or Sweden [131], and from countries closer to the equator with regular long hours of sunshine such as rural Greece where lip cancer can account for 60% of oral cancers [132] and in India, for example, in fishermen [6] – though some protection may exist in darker-skinned races or individuals. In Finland, the increased risk for lip cancer is confounded by smoking and social class, whereas that for oral cavity and pharynx is not; at these latter sites, alcohol was a much stronger confounder than tobacco [133]. A study from California shows that risk for women is strongly related to lifetime solar radiation exposure, but lipstick and other sunscreens are protective [134]. Although the observation goes back over a decade, there is a recent concern that modern cosmetic lip glosses may enhance UV damage to the lips, including increased risk of cancer [134].

Falls in the incidence of lip cancer have been interpreted as due to reduced occupational exposure to sunlight and to reduced pipe and cigar smoking [135, 136].

Global Scenario of Oral Potentially Malignant Disorders and Laryngeal Leukoplakia

The term Oral Potentially Malignant Disorders (OPMD) was recommended by an international Working Group convened by the WHO Collaborating Centre for Oral Cancer and Precancer in London in 2005 [135]. It conveys that not all

disorders described under this umbrella will transform to invasive cancer – at least not within the lifespan of the affected individual. Leukoplakia, Erythroplakia, Oral Submucous fibrosis, Lichen planus, Palatal lesions in reverse smokers, Actinic keratosis, Discoid lupus erythematosus, Dyskeratosis congenita, and Epidermolysis bullosa are described under the broad definition of OPMD [137, 138].

Global Prevalence of OPMD

Estimates of the global prevalence of OPMD range from 1 to 5% [139], although much higher prevalences are reported from Southeast Asia, usually with a male preponderance, for example, in Sri Lanka (11.3%) [50], Taiwan (12.7%) [140]

and Pacific countries like Papua New Guinea (11.7%) [141]. Wide geographical variations across countries and regions are mainly due to differences in socio-demographic characteristics, the type and pattern of tobacco use and clinical definitions of disease (see Table 1.4). In Western countries, the overall prevalence is low and a decreasing trend over time is observed.

Stefano [154], conducted a meta-analysis of 23 primary studies on oral leukoplakia, from international data published between 1986 and 2002. The point-prevalence estimates were 1.49% (95% CI 1.42–1.56%) and 2.6% (random effect, 95% CI 1.72–2.74%). Leukoplakia was significantly more prevalent among males (prevalence ratio 3.22), but no difference was found between geographical areas and between younger and older adults. Using these data, they calculated that the crude annual oral cancer incidence rate attributable

Table 1.4 Summary of the prevalence of OPMD reported in the literature

References	Country (year)	Sampling method	F/M ratio	Age group	Disease entity	Definition used	Prevalence %
[50]	Sri Lanka (2008)	MSSC	0.6/1.0	≥30	OPMD	WHO 1994	11.3 weighted for gender and geographical location.
[142]	Taiwan (2005)	Random	0.9/1.0	≥15	OPMD Leukoplakia Erythroplakia Lichen planus OSF	Not given	12.7 7.4 1.9 2.9 1.6
[143]	USA (2003)	MSSC	0.9/1.0	≥20	Leukoplakia	Kramer 1978, Kramer 1980	0.5–0.3
[144]	Sri Lanka (2003)	Multi-stage stratified cluster (MSSC)	–	35–44 years and 65–74 years	OPMD Leukoplakia Erythroplakia OSF	WHO 1994	4.1 2.6 0.4
[145]	Spain (2002)	Stratified, random	0.8/1.0	≥30	Leukoplakia	WHO 1978, Axell, T et al. 1984	1.6
[146]	Germany (2000)	Stratified, random	1.0/1.0 0.7/1.0	35–44 year 65–74 year	Leukoplakia Leukoplakia	Axell 1976 Zain 1995 WHO-ICD-DA	1.6 1.0
[147]	Japan (2000)	All invited	0.4/1.0	m >40, f >20	Leukoplakia Lichen planus	WHO 1980	0.19 0.21
[148]	Malaysia (1997)	Stratified, random	0.7/1.0	≥25	Leukoplakia Erythroplakia OSF Lichen planus	WHO 1978 Axell, T et al. 1984	0.96 0.01 0.06 0.38
[149]	Netherland (1996)	Waiting room	0.9/1.0	13–93 year	Leukoplakia	Axell 1984 Axell 1996 Schepman 1995	0.6
[150]	Hungary (1991)	Random	0.7/1.0	All age groups	Leukoplakia Lichen planus	Axell 1984	1.3 0.1
[151]	Japan (1991)	Factory workers	0.5/1.0	18–63 years	Leukoplakia	Axell 1984	2.5
[152]	Sweden (1987)	Stratified random	Not found	≥15	Lichen planus	Axell 1976	1.9
[153]	Sweden (1987)	All-invited residents	0.9/1.0	≥15	Leukoplakia	Axell 1976	3.6

to leukoplakia would be between 6.2 and 29.1 per 100,000 thus suggesting that the global number of oral cancer cases is probably under-reported.

Age and Gender Distribution of OPMD

This varies considerably, mainly dependent on lifestyle and thus on ethnicity and geographical location. In the developed world, leukoplakia is usually found between the fourth and seventh decades of life, in the developing world some 5–10 years earlier [155]. Females are less commonly affected, largely reflecting greater use of relevant habits by men.

Malignant Transformation of OPMD

Risk of malignant transformation varies from site to site within the mouth, from population to population and from study to study [156–158]. A classic study conducted in the 1970s with follow-up over 7 years of more than 30,000 Indian villagers, showed transformation rates from 10 to 24 per 100,000 per year [157]. Another classic study from the early 1980s, a hospital-based study in Californian patients with oral leukoplakia, with a mean follow-up period 7.2 years, revealed a malignant transformation rate of 17.5% [158]. Rates for hospital-based studies are, unsurprisingly, consistently higher than community-based studies because of sampling bias.

Petti [154] has estimated a mean global prevalence of 2.6% for leukoplakia, and a mean global transformation rate of 1.36% per year (95% CI 0.69–2.03). Extrapolating from these figures suggests that considerably more OSCC should have been reported in recent times, a possible reason being under-reporting of cases of oral cancer in the developing world.

Epidemiology of Laryngeal Leukoplakia

Epithelial precursor lesions of the larynx, clinically defined as leukoplakia and chronic laryngitis, are mostly seen in adults and affect men more often than women. This gender disparity is more pronounced after the sixth decade of life [159]. Epidemiological studies of laryngeal precursor lesions are scarce and the incidence differs worldwide and depends upon the amount, manner and types of exposure to relevant carcinogens. According to a recent review [160], 1,268 patients were clinically diagnosed as laryngeal leukoplakia and chronic laryngitis during the period from 1979 to 2004 in Slovenia. The incidence of patients, covering a region

with approximately 800,000 inhabitants or 40% of the population of Slovenia, varied for the benign group of precursor lesions (squamous hyperplasia and basal parabasal cell hyperplasia) from 0.84 to 4.62/100,000 inhabitants pa (mean value 2.61/100,000 inhabitants, SD=1.10). The incidence of patients for atypical hyperplasia ranged from 0.25 to 2.62/100,000 inhabitants pa (mean value 0.86/100,000 inhabitants, SD=0.49).

Aetiology of Laryngeal Leukoplakia

Laryngeal leukoplakic lesions are strongly associated with tobacco smoking and alcohol use, especially in combination [161–163]. Other risk factors are: industrial pollution, specific occupational exposures, nutritional deficiency, and hormonal disturbance [164–166]. A recent meta-analysis has shown a weak association between HPV-16 and laryngeal cancer [167]. Several authors have recently devoted much attention to the potential role of gastro-esophageal reflux disease, but the results are not conclusive [161, 168].

Salivary Gland Neoplasms

Epidemiology

Neoplasms arising in the salivary glands are relatively uncommon, yet they represent a wide variety of both benign and malignant histologic sub-types. The reported annual incidence, when all salivary gland tumours are considered, varies widely between countries and regions [169].

According to Globocan 2002, the world's highest incidence of salivary neoplasms was reported from the Northern Territory of Australia (though the number of cases in this thinly populated area was too small – only seven cases – to place credence on this value); the second highest from Croatia (Table 1.5). Within Japan, the highest rates are reported from the region of Nagasaki, regarded as long-term effects of the atomic bomb explosion in 1945. The estimated annual incidence in the USA is 1.5 cases per 100,000 population pa; here they constitute only about 6% of all head and neck neoplasms [170].

Site, Age and Sex Distribution

Nearly 80% of these tumours arise in parotid glands, 15% in submandibular glands, with the remainder distributed across the sublingual and minor salivary glands of the oral and

oropharyngeal mucosae [171]. In most series, benign neoplasms are the majority, representing 54–79% of cases described. Pleomorphic adenoma is by far the most common, accounting for about 50% of all salivary gland tumours. Warthin's tumour is second in frequency among benign neoplasms and, in most large studies, mucoepidermoid carcinoma is the most common malignancy [169].

Table 1.5 Incidence of salivary neoplasms: cases per 100,000 pa, standardised ASR(W)

Population	ASRW male	ASRW female
Australia, Northern territory	1.7	0.2
Croatia	1.6	0.6
Poland, Cracow	1.5	0.6
USA, District of Columbia white	1.4	0.4
USA, black	0.9	0.6
USA, white	1.1	0.8
UK, Oxford region	0.7	0.5
Canada	0.9	0.6
China, Hong Kong	0.7	0.5
India, Chennai	0.5	0.3
Japan, Nagasaki	0.7	0.5
France, Herault	0.8	0.7
Norway	0.7	0.6
Spain, Granada	0.6	0.5
Switzerland, Geneva	0.6	0.9

The average ages of patients with benign or malignant tumours are 46 and 47 years, respectively, with peak incidence of most of the specific types in the sixth and seventh decades. However, the highest incidence of pleomorphic adenomas, mucoepidermoid carcinomas and acinic cell carcinomas is significantly younger in the third and fourth decades. Salivary neoplasms are rare in young people and in patients under 17 years of age, a neoplasm of a major gland is as likely to be mesenchymal as epithelial in origin [172–175] (Figs. 1.26a, b).

Aetiology of Salivary Gland Neoplasms

The aetiology of salivary gland neoplasms is still poorly understood. Furthermore, especially with neoplasms that have mixed cellularity, notably pleomorphic adenomas and carcinomas arising therein, which show epithelial, myoepithelial and mesenchymal characteristics, controversy remains as to whether there is a single or more than one type of cancer stem cell [169].

Viruses: Studies have shown a strong association between EBV and lymphoepithelial carcinomas [176, 177], with geographical variations, as this shows a preponderance for Asian

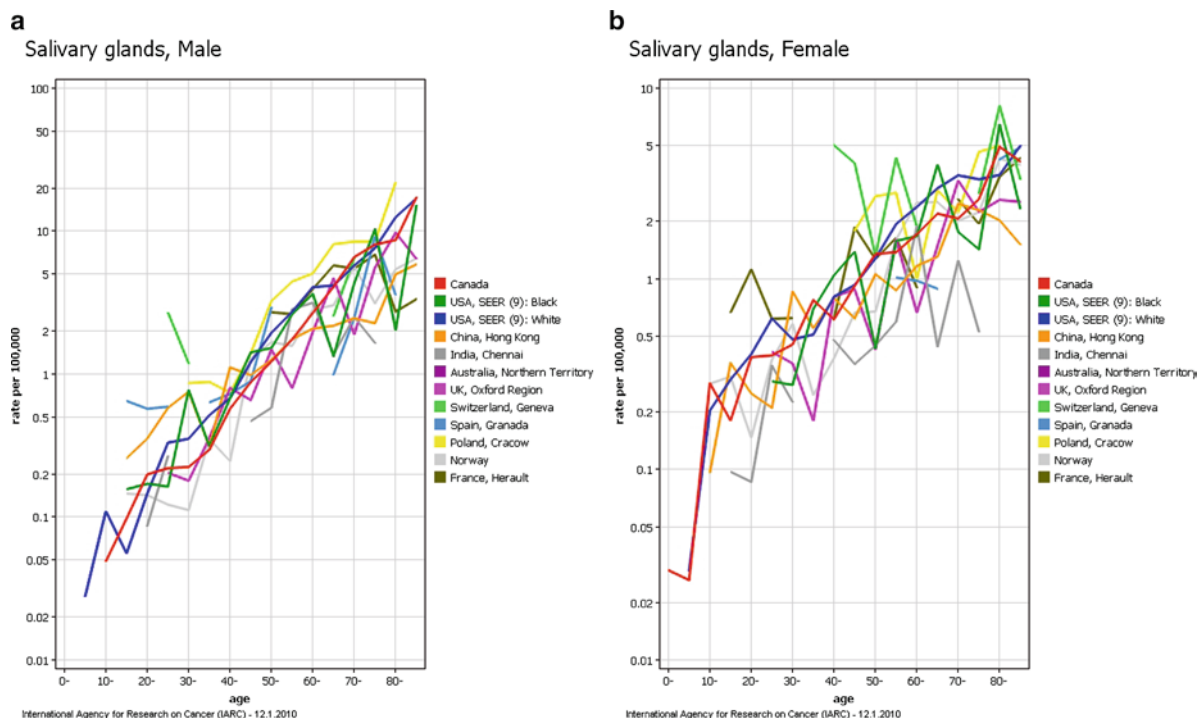


Fig. 1.26 The incidence of salivary gland neoplasms rises steadily, and linearly, with age. Data from selected countries are given in Fig. 1.26 (a, males; b, females). Note that the scales are, as usual with

such data presentations, logarithmic. Thus it is seen that across most of the life span there is no major sex predilection

patients [178] and Greenlandic Inuits [179]. Salivary tissue is an established reservoir for EBV, but a clear oncogenic role for EBV or for cytomegalovirus (CMV) has not been demonstrated in other salivary gland carcinomas or in benign parotid tumours [177]. SV40 sequences have been postulated in human pleomorphic adenomas [180], but there is no significant association between human salivary gland tumours and other viruses, including polyoma virus and papillomavirus (HPV).

Radiation: There is convincing evidence implicating exposure to ionising radiation and the development of salivary gland neoplasms. Long-term follow-up studies of the survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign, and 11 for malignant salivary neoplasms [181, 182]. The risk was directly related to the level of exposure to ionising radiation. There was a high frequency of both mucoepidermoid carcinoma and Warthin's tumours in these patients [183]. Therapeutic radiation, especially in the head and neck region, has been linked to significantly increased risk [184, 185]. Iodine 131, used in the treatment of thyroid disease, is thought to produce neoplasms, as the isotope is also concentrated in salivary glands [186].

Several studies have suggested that exposure to routine dental radiographs may be associated with an increased risk of salivary neoplasms, though the evidence is inconclusive [187, 188]. Exposure to ultraviolet radiation has also been implicated [189–191], though this seems biologically improbable. There appears to be no excess risk in those exposed to radon [192], or the microwaves of cellular telephones [193, 194].

Occupation: There is a literature relating salivary gland neoplasms to occupation. Suggested risks include rubber manufacturing [195], exposure to metal in the plumbing industry [196] and nickel compounds [195], woodworking in the automobile industry [197] and employment in hairdressing and beauty shops [198, 199]. An increased risk of salivary gland cancers was reported in people living in certain Quebec countries where asbestos was mined, and this risk was inversely proportional to distance from the mines [200].

Lifestyle and nutrition: Tobacco and alcohol, which are highly associated with head and neck squamous cell carcinoma, have not been shown to play a major role in the development of salivary malignancies [201]. However, tobacco smoking has been associated with the development of Warthin's tumour. Exposure to silica dust and kerosene as a cooking fluid increased the risk of salivary neoplasms in a Chinese population [202], and an increased risk of parotid neoplasms was associated with exposure to nickel, chromium, asbestos and cement dust [203]. An elevated level of risk has been described in those with a high cholesterol intake [204].

Hormones: Oestrogen activity or upregulation of oestrogen receptors have been described in pleomorphic adenomas in

some studies [205], but were absent in another [206]. Progesterone and androgen receptors are present in some salivary neoplasms [205, 207] and binding of hormones to these may influence tumour progression.

Other Important Cancers of the Head and Neck: Malignant Melanoma and Kaposi's Sarcoma (KS)

Malignant melanoma is recorded by cancer registries separately from mucosal and other cancers (Table 1.6). These data represent all skin sites but the management of melanoma often falls into the hands of head and neck clinicians, so the data are of interest. DNA damage from ultraviolet light, especially acute sunburn and especially early in life, is the major risk factor. This explains the high incidence rates in Australia, New Zealand, northern Europe and among white South Africans: for head and neck melanoma the risks associated with ultraviolet light are most marked at low altitudes [208]. Melanoma of UADT mucosa is a serious, usually fatal, disease: global epidemiological data will be "buried" in the graphs and tables above. Such data as available have been reviewed recently by van der Waal et al. [209].

Table 1.6 World standardised incidence rate per 100,000. Accessed from <http://www-dep.iarc.fr/> in December 2009

Country	Melanoma skin (C43)		Kaposi sarcoma (C46)	
	Male	Female	Male	Female
World	2.8	2.6	0.0	0.0
More developed	8.3	7.5	0.0	0.0
Less developed	0.7	0.7	0.0	0.0
Eastern Africa	1.2	2.3	23.0	9.5
Middle Africa	2.2	2.1	30.0	8.6
Northern Africa	0.7	0.5	0.3	0.1
Southern Africa	5.4	4.1	13.2	5.7
Western Africa	1.1	0.9	4.6	1.4
Caribbean	1.0	1.1	0.0	0.0
Central America	1.3	1.7	0.0	0.0
South America	2.4	2.3	0.0	0.0
Northern America	16.4	11.7	0.0	0.0
Eastern Asia	0.3	0.2	0.0	0.0
Southeastern Asia	0.5	0.5	0.0	0.0
South Central Asia	0.5	0.4	0.0	0.0
Western Asia	1.6	1.5	0.0	0.0
Eastern Europe	3.3	3.8	0.0	0.0
Northern Europe	8.4	10.0	0.0	0.0
Southern Europe	6.0	5.5	0.0	0.0
Western Europe	7.3	10.3	0.0	0.0
Australia	38.5	29.5	0.0	0.0
New Zealand	33.8	29.2	0.0	0.0
Melanesia	4.8	2.9	0.0	0.0
Micronesia	1.2	0.7	0.0	0.0
Polynesia	5.1	0.0	0.0	0.0

Kaposi's sarcoma (all sites) is an AIDS-defining lesion and is thus most common where HIV-disease is most rampant: it is a major problem in sub-Saharan Africa, in many countries of which KS is the most frequently diagnosed cancer [210]. In our series of 710 head and neck cancers in northern Nigeria, KS was the most common HIV-associated malignancy [211]. KS is seen less commonly in the current era of highly active anti-retroviral therapy in populations where such therapy is widely available. Many of the zero numbers in these tables reflect absence of data – or situations where KS is not separately registered.

The aetiology of KS was described in 1994 and is now clearly established as infection with Human Herpes Virus Type 8 (HHV-8, also known as Kaposi Sarcoma Herpes Virus – KSHV). It is a multifocal malignancy of lymphatic endothelial cells. Endemic KS in HIV-negative subjects still exists, especially in the Mediterranean where it has long been regarded as having an ethnic predilection – for certain Jewish groups. There is a puzzle with HIV/AIDS-related KS, however; the head and neck, especially the mouth, is a common site for KS in HIV-positive subjects; the oropharynx is the primary reservoir, and saliva/oral fluids are the major vehicle of transmission [212]. Transmission occurs via oral-genital contact and is more common in men who have sex with men. In India, which is currently the single nation of the world with the highest number of HIV infections, KS is almost never seen. Whether this is because of different social practices, differences in the strains of KS circulating in that country – with different pathogenicity – or differences in host response, remains unknown [213] (Table 1.7).

The Death to Registration Ratio (D/R) for melanoma can be readily calculated here. For ANZ this ranges from 0.09 to 0.18, whereas in northern Europe, the average approaches double this, viz 0.16 for women and 0.26 for men. Women do better all over the world, possibly because they seek treatment earlier. Note that these outcomes are substantially better than for oral cancer. In ANZ, there are highly effective public education campaigns regarding protection against sun damage, and many screening and treatment facilities. In spite of this, the comparatively poor outcomes perhaps reflect a degree of complacency towards the very common sun-induced lesions, many of which are benign.

Primary Neoplasms of the Jaws and Facial Bones

While to a large extent, these lesions constitute the “bread and butter” for many oral/maxillofacial pathologists and surgeons, such lesions are comparatively rare: they do not represent anything like the major public health problem of epithelial tumours of the head and neck. They are not, therefore,

Table 1.7 World standardised mortality rate per 100,000. Accessed from <http://www-dep.iarc.fr/> in December 2009

Country	Melanoma skin (C43)		Kaposi sarcoma (C46)	
	Male	Female	Male	Female
World	0.8	0.6	0.0	0.0
More developed	1.8	1.2	0.0	0.0
Less developed	0.3	0.3	0.0	0.0
Eastern Africa	0.7	1.3	20.8	8.8
Middle Africa	1.3	1.3	25.3	7.8
Northern Africa	0.4	0.3	0.2	0.1
Southern Africa	2.9	2.2	12.4	5.4
Western Africa	0.7	0.5	4.0	1.3
Caribbean	0.4	0.3	0.0	0.0
Central America	0.6	0.5	0.0	0.0
South America	0.9	0.6	0.0	0.0
Northern America	2.5	1.3	0.0	0.0
Eastern Asia	0.1	0.1	0.0	0.0
Southeastern Asia	0.3	0.3	0.0	0.0
South Central Asia	0.3	0.2	0.0	0.0
Western Asia	0.7	0.6	0.0	0.0
Eastern Europe	1.6	1.2	0.0	0.0
Northern Europe	2.2	1.6	0.0	0.0
Southern Europe	1.6	1.1	0.0	0.0
Western Europe	1.8	1.3	0.0	0.0
Australia	5.1	2.6	0.0	0.0
New Zealand	6.1	3.6	0.0	0.0
Melanesia	2.5	1.5	0.0	0.0
Micronesia	0.6	0.3	0.0	0.0
Polynesia	2.5	0.0	0.0	0.0

a major thrust of this volume, but have excellent coverage in other modern textbooks including those referred to in the “Introduction” of this chapter.

It is not appropriate here to indulge in the favourite pastime of oral pathologists to debate the classification of such lesions, uniformity of which would be essential to the comparability of international epidemiological data. Furthermore, it is extremely difficult to mine international and national databases for detailed histological typing, so that the incidence and mortality associated with bone and odontogenic tumours might be reliably quantified. Recourse has to be made to case series and, while these are valuable, significant regional differences in epidemiology and risk factors are hard to quantify. A concise summary of the situation with odontogenic tumours is in the WHO “Blue Book” of 2005 [169].

Difficulties also arise because some databases/case series include benign neoplasms – and with odontogenic lesions, there are frequently grey areas regarding the behaviour of a particular diagnostic category or individual lesion. Strictly speaking, cancer registries should only record malignancy. Hamartomatous and benign lesions are very much more common than malignant odontogenic tumours [214]: Differences emerge between case series based on dental/oral-maxillofacial departments which are more likely to include the former, whereas cases handled in broader general hospitals or cancer hospitals will select for malignancies.

Ameloblastoma is clearly the most common malignant odontogenic tumour worldwide. An extensive series of 1,642 cases from Sichuan University [215] found that benign tumours comprised 97% of cases: ameloblastoma was the most common malignancy, followed by odontogenic keratocystic tumour. In a series of 1,088 cases from northern California [216], 76% were (benign) odontomas: ameloblastomas comprised 12% – a surprisingly high figure perhaps reflecting the specialised nature of this laboratory. This paper also tabulates data from case series all over the world describing the frequencies of the various types of odontogenic “tumour”.

There has long been an impression that odontogenic tumours are more common in Africa – perhaps because so many advanced lesions come late to diagnosis. A thoughtful analysis of the literature up to the early 1990s is given by Smith, [217]. In a more recent series, of 308 odontogenic tumours in Lagos, southern Nigeria, 97% of the tumours were benign and only 3.4% malignant; ameloblastoma with predilection for the mandible was the most frequent [218].

Among primary malignant bone tumours [219], most case series around the world contain very small numbers of patients, but indicate various types of osteo[genic] sarcoma to be most common. Osteosarcomas of all sites account for 40–60% of primary malignant bone tumours and ~10% of these occur in the head and neck, mostly in the jaws. These tend to be diagnosed approximately two decades later than their long bone counterparts, which have a peak incidence between 10 and 14 years. Head and neck osteosarcomas metastasise less frequently than those in long bones, and have a better 5-year survival rate, reported between 27 and 84%. The experience of one USA centre has recently been described [220], with a helpful review of the literature. Out of 2,830 biopsies of oral and jaw lesions diagnosed 1983–2003, in Lagos, 59 (2.08%) were primary malignant bone tumours, osteosarcoma again being most frequent (28.8%). Interestingly the mean age at presentation (27 ± 14 years) was lower than reports from other parts of the world.

Cancer Metastatic to the Head and Neck

Tumours metastatic to the H&N from distant sites are comparatively rare, representing about 1% of oral tumours. Most lesions are found in patients between the fifth and seventh decades of life. They affect the jaws more commonly than soft tissues in a ratio of 2:1 [221]. The most common primary tumours metastatic to the jaws are breast (20%), lung (13%), kidney (8%), adrenal (8%), bone (7%), colorectal (6%), prostate (5%), and liver (5%).

A review of cases revealed that 54% of the 218 metastatic tumours to oral soft tissues were located on the attached gingiva,

followed by 22% on the tongue: The role of inflammation in the attraction of metastatic cells to the gingiva has been suggested [222].

The Future of Head and Cancer Epidemiology

As with many aspects of life, global inequalities are increasing in the incidence rates of head and neck cancers, in the provision and quality of prevention and screening programmes, and in access to and quality of patient care. The drivers of these inequalities are socio-political: war, poverty, pestilence, climate change, lack of food and water security [223]. The problems do not derive primarily from ignorance of causes and mechanisms of disease, but from ineffective or absent implementation of the right policies, and from lack of resources to implement them. As scientists and clinicians devoted to head and neck oncology we all have a moral responsibility to contribute to these wider social and political challenges. The knowledge to apply world best practice is within the pages of this book. The leadership of many local and national bodies is acknowledged: these activities need to be in dialogue and synergy with global leadership through agencies such as the World Health Organisation, the International Agency for Research on Cancer, the UICC/International Union against Cancer, the International Federation of Head and Neck Oncologic Societies, the International Academy of Oral Oncology and others. The International Association for Dental Research launched an initiative in 2010 seeking to reduce global inequalities in oral cancer (and in other oro-facial diseases and disorders).

It is a truism that however sophisticated and effective our diagnostic and treatment armamentarium becomes, head and neck cancer rates around the world will never be reduced by such interventions – though, of course, hundreds of thousands of lives may be saved or improved. The emphasis must be on primary and secondary prevention, on the implementation of policies that work to these ends and on their continued evaluation and improvement.

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