At a workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Pre-cancer in the UK issues related to potentially malignant disorders of the oral cavity were discussed by an expert group. The consensus views of the Working Group are presented in a series of papers. In this report we review the literature on the epidemiology and natural history of potentially malignant disorders (PMD), detailing those characteristics of the patients and lesions thought to be associated with future development of oral squamous cell carcinoma (OSCC). Older patients, particularly females are more at risk than younger patients; the duration of PMD may be important. Those who have never used tobacco seem at greater risk than smokers. OSCC is more likely with PMD on the lateral and ventral tongue, floor of mouth and retromolar/soft palate complex than with those elsewhere. The vast majority of PMD in which OSCC develop are non-homogenous although 5% of homogenous PMD will develop carcinoma. Large lesions covering several intraoral subsites also appear more at risk.

Epidemiology of potentially malignant disorders

Incidence and prevalence

Studies into the incidence of oral PMD – new cases per year – are rare and most of those that have been performed have been carried out in India, a region of relatively high prevalence of OSCC and leukoplakia. In relatively short occupation-specific studies (2, 3), persons who used tobacco – smoked, chewed or both – develop most lesions, with an annual incidence rate ranging from 5.2/1000 to 30.2/1000 depending on pattern of use. Non-users of tobacco developed the fewest lesions ranging from 0.6/1000 to 5.8/1000 per year. In a 10-year follow-up study of over 30 000 individuals in three distinct geographic regions of India, selected because of the specific forms of tobacco habits practised there, annual incidence rates of 1.1–2.4/1000 were reported for males and 0.2–1.3/1000 for females (4). These lower incidence rates reflect differences in the study design – both adolescents and adults were examined and the study was based on a house-to-house survey, rather than on a specific occupational group. The authors of all these studies suggested that the causes of leukoplakia are closely related to the use of tobacco.

Key words: epidemiology; erythroplakia; oral leukoplakia; pre-cancer
somewhat higher to those reported from India (see above), the risk habits of the two groups being markedly different (5).

The prevalence of oral PMD, being the number of cases identified in a given population at any one time, has been examined worldwide, with most authorities agreeing to a prevalence rate of between 1% and 5% (6–8). Estimates provided by individual studies vary considerably depending on the country of origin, the nature of the population under investigation, the pattern of tobacco use and the clinical definition of leukoplakia. The largest studies have been conducted in the developing world. For example, in a house-to-house, village-by-village survey of 50 915 persons aged 15 years and over in four separate geographic regions of India, selected because of their different pattern of tobacco use, 1286 leukoplakias were identified in 881 patients, with a striking degree of regional variation in prevalence from 0.2% in Bihar state in the north to 4.9% in Andhra Pradesh in the east, apparently related to the pattern of tobacco use (9). A survey of 57 518 mill and allied textile workers aged 35 years plus in Gujarat state in western India found 6718 leukoplakias, as well as 35 lesions showing epithelial dysplasia, an overall prevalence of 11.7% (8), in contrast to the rate of 1.7% previously recorded for the same region (9). The highest prevalence was found in the older age groups: 14.6% for those aged 65 years and over compared with 9.6% for 35 to 39 year olds (8). Such dramatic differences between apparently similar study groups are almost certainly because of factors related to sample selection and variations in clinical criteria.

In the developed nations, most surveys have been based on hospital populations rather than communities. A community-based survey examined 20 333 Swedes aged 15 years and over from rural, suburban and urban areas and found white lesions in 24.8% overall (10). Divided on the basis of probable aetiology, idiopathic leukoplakia accounted for 0.7%, tobacco-associated leukoplakia (excluding the ‘smoker’s palate’) 2.9% and snuff dipper’s lesion 7.2% (10). An overall prevalence of ‘white keratotic lesions’ of 3.4% was reported in 23 616 Swedes aged 15 years and over (11). A 10-year follow-up study of 3674 Bombay policemen found that over 80% of lesions were 80% and 42%, respectively (9). No age group was spared; leukoplakias were identified even in those aged 15–24 years, although they were more frequent in older persons. This variation was attributed in part to the tobacco habit; in all areas, women were much more likely not to practise any form of tobacco use than men. Various forms of tobacco smoking and a mixture of both smoking and chewing were practised predominantly by men, except in Andhra Pradesh where reverse cigar smoking was largely seen amongst women, accounting for the more equal sex ratio seen there.

PMD may be located on any part of the oral mucosa, most commonly the buccal mucosa, but involvement of multiple sites is frequent. Overall, the site of the leukoplakias seems to be attributable to a large extent to the type of tobacco habit. In Gujarat, where smoking is common, 43.9% leukoplakias were seen on the buccal mucosa and 35.4% at the commissures, with only 0.3% on the tongue and 0.8% on the palate. In Kerala, where chewing is practised, 64.8% of leukoplakias were found on the buccal mucosa, 24.3% at the commissures and 6.0% on the tongue, adjacent to the site of quid placement. In contrast, in Andhra Pradesh, with the widely practised reverse smoking habit, 71.3% of all leukoplakias were found on the palate, 8.1% at the commissures, 16.9% on the buccal mucosa and 2.7% on the tongue (9). A 10-year follow-up study of 3674 Bombay policemen found that over 80% of lesions were present on the buccal mucosa or commissures, with only 5% on the tongue (3).

In the Swedish study (10), white lesions were three times more common in males than in females. When proportioned according to probable aetiology, the male-to-female ratio for tobacco-related leukoplakia was 6:1 while for idiopathic leukoplakia it was 5:2. Lesions often affected multiple sites. Buccal mucosa or commissure was involved in almost 90% of cases, with only about
1% of lesions each on the tongue, palate and floor of mouth (10). In an extensive study of 670 Hungarian patients with leukoplakia followed for between 1 and 30 years the peak age incidence of leukoplakia was in the sixth decade, with a male-to-female ratio of 3.1:1 (16–20). The vast majority of lesions arose on the buccal mucosa and commissures (25.3% and 37.5%, respectively), with approximately 8% each on tongue, hard palate and alveolar ridge and 1.3% on the soft palate. In 125 male and 132 female Californian patients with leukoplakia followed for an average period of 7.2 years, approximately three-quarters of whom were smokers, leukoplakias were found on the buccal mucosa 46%, gum 40%, palate 27% tongue 26%, floor of mouth 22% and lip 11%. Multiple intraoral sites were involved in 70% of cases (21). Among 3783 lesions identified in a self-selected group of 23,616 predominantly white Americans who voluntarily attended health-screening clinics, there was a male-to-female ratio of 2:1 for the 789 oral white patches, with both sexes demonstrating an equal proportion (85%) of the 660 white lesions regarded as leukoplakias (11). Males presented mostly with lesions on the vermilion of the lower lip – almost certainly because of solar exposure. Females showed a higher incidence of lesions at intraoral sites; 25.5% of leukoplakias arose on the buccal mucosa in females with 24% on the lower gingiva, 13.5% on the tongue and 8.3% in the floor of mouth, the equivalent proportions for men being 22.6%, 16.9%, 6.5%, 5.1%, respectively (11). At an opportunistic screening system in Hungary (13), lesions were found most commonly on the tongue (36.5%), followed by the buccal mucosa (27.9%), alveolar ridge (13.6%) and commissures (12.5%). Buccal mucosa and commissures together accounted for 40.4% of lesions. Seventy percent of leukoplakias occurred in males, with 86.5% occurring in persons who were smokers, usually heavy smokers (13). A survey of 2023 Germans found leukoplakia almost twice as often in younger than in older patients. In patients aged 35–44 years, the lesions affected men more than two-and-a-half times as often as women but had an equal prevalence in men and women in patients aged 65–74 years (22). The location of lesions was the same in both the groups – buccal mucosa, tongue, labial mucosa and gingiva in descending order of frequency. In the Netherlands, the 90 female patients presented with leukoplakia most often in the sixth decade, while there was a bimodal distribution for the 76 males, peaking in the fifth and seventh decades (23). Tongue and floor of mouth were the most frequently affected sites – 54 cases affected the tongue only, 32 cases affected the floor of mouth only and 15 patients had multiple lesions involving the tongue and/or floor or mouth.

In contrast, in an early study, Waldron and Shafer reported an equal sex ratio in their review of 3256 mucosal biopsy specimens reported over a 13-year period by two oral pathology laboratories (24), although this was after lesions on the vermilion of the lower lip, which predominated in men, were discounted. Leukoplakias were commonest in the fifth, sixth and seventh decades. Sites involved most frequently were the buccal mucosa, mandibular mucosa and mandibular sulcus, accounting for 47.1% of the cases, while tongue and floor of mouth were involved in only 15.4% of cases. Likewise, in a smaller study, there was an equal sex incidence in the 14 patients with oral leukoplakias from 1000 consecutive outpatient referrals to a Dutch dental school (12). Lesions were present on the lateral border of tongue and floor of mouth for six of the patients, although combinations of sites were involved in 3 out of the 14 patients. In 925 US veterans, all male, there were 130 white lesions in the 482 smokers (a prevalence of 22.8%) and 17 lesions in the 443 non-smokers (3.8%) (54). Lesions in both groups occurred most commonly on the cheek (72/130 smokers, 13/17 non-smokers), palate (45/130 smokers, 1/17 non-smokers) and tongue (9/130 smokers, 2/17 non-smokers). Floor of mouth involvement accounted for 1 of the 130 lesions in smokers and was not seen in non-smokers. The patterns of the lesions varied slightly depending on the particular smoking habits.

The systematic review by Petti (15) confirmed that oral PMD affects males at least three times as often as females (prevalence ratio 3.22:4.76) but there was no difference in prevalence between adults aged 50 years or over and those aged less than 50 years. Surprisingly, the review found no consistent geographic differences between North America/Europe and East Asia. This was attributed to the global use of tobacco and alcohol and although the type of product used varies markedly across the world, the pattern of consumption seems to be distributed uniformly on a global scale.

Aetiology of PMD

Tobacco use is the commonest pre-disposing factor for the development of an intraoral white lesion although a certain proportion of oral white patches have no known cause. In the developing world, tobacco use and areca nut use, either alone or in combination, account for the vast majority of leukoplakias. In Gujarat, 15% of 57,518 mill workers did not habitually use tobacco or areca nut and only 2% of the 16,210 persons who had a mucosal lesion did not have a tobacco-related habit (8). The 10-year leukoplakia review in India claimed that if there was no tobacco habit, there would be no leukoplakia (4).

In the developed world, the vast majority of oral leukoplakias are also associated with the use of tobacco (10, 14, 17, 21, 25–28). A survey of 20,333 Swedes, that found white patches in 24.8%, concluded that snuff dipping caused lesions in 7.2%, with pre-leukoplakia and tobacco-associated leukoplakia in 7.8% (10). Of 3131 Japanese subjects sampled in a screening survey, 75% of 77 patients with leukoplakia reported smoking while nearly 50% of persons without a lesion used tobacco (29). Large hospital-based surveys of leukoplakias in Hungary and Norway found tobacco to be the major risk factor associated with leukoplakia in 87% and 42% of their respective groups (18, 28). Information was available on tobacco use for 151 of the 166 patients in a series from the Netherlands (23): 93 patients (62%) were smokers.
The type of tobacco usage influences the distribution of the lesions: reverse cigar smoking causes lesions on the hard palate, chewing causes lesions at the site of quid placement and smoking of cheroots is associated with floor of mouth leukoplakias (30). Smoking causes changes at the buccal mucosa or commissures (4, 9). The frequency of tobacco use increases the likelihood of leukoplakias developing: heavy smokers are seven times more likely than non-smokers to have lesions (25). In a sample of unselected patients attending general dental practice in England, strong statistical associations were found between tobacco use and the detection of PMD or OSCC; patients smoking 20 or more cigarettes per day were almost 4 times more likely than non-smokers to have a mucosal lesion (14).

Support for the importance of tobacco in the aetiology of leukoplakia is given by the regression and/or disappearance of many lesions following abstinence. In a series of 138 Danes, it was noted that in those who abstained from smoking for 3 months, 56% of lesions regressed or disappeared while in those who quit permanently, 78% of lesions regressed or disappeared after a year (31). In Californians with leukoplakia, 50 patients stopped smoking following diagnosis of leukoplakia and 44% of lesions disappeared (21).

A significant number of leukoplakias have no obvious association with these aetiological factors. No cause could be attributed in 122 of the 705 patients with leukoplakia (17.3%) from Sweden (10). In the Hungarian series, 4.2% of leukoplakias had no known cause (17–20). Seventeen of 147 leukoplakias in US veterans were classified as idiopathic (11.6%) (54) and sixty-six of 157 Californian patients with leukoplakia (26%) had no obvious cause (50), with a similar proportion (27%) in the series in Norway (18). Others found that 13% of 104 leukoplakias had no associated risk factors (12). In a series from the Netherlands, 58 patients (38%) were non-smokers (23).

Although undoubtedly important in OSCC, there is uncertainty about the role of alcohol in the aetiology of PMD. In 15 811 participants of the 1988–1994 National Health and Nutrition Examination Survey in the USA, no independent role was found for alcohol in oral leukoplakia (32). In contrast, an oral cancer screening study in Kerala in south-western India found a significant statistical association with any form of alcohol use in 100 patients with erythroleukoplakia when compared with 47 773 oral disease-free controls; there was also a positive relationship with frequency and duration of alcohol consumption, independent of tobacco but with a synergistic effect (33).

Evidence for a role of Human Papillomavirus (HPV) in PMD is contradictory and an in-depth review is beyond the scope of this article. A recent cross-sectional study examining prevalence of HPV in oral lichen planus and leukoplakia compared with healthy control tissue using very sensitive techniques demonstrated HPV DNA in 12 of 68 oral leukoplakia samples (17.6%) and in 14 of 71 cases (19.7%) of lichen planus (34). While detected more frequently in homogenous (see Clinical Appearance below) than non-homogenous leukoplakia, there was no statistical association with the clinical subtype of leukoplakia; there was a positive correlation with tobacco use. Another recent study concentrated on one form of PMD, the so-called proliferative verrucous leukoplakia, and found no link with HPV (35).

Prognosis of potentially malignant disorders

Most authorities regard leukoplakia to be a dynamic rather than a static process, but this is usually in terms of its progression and the development of malignancy. Clearly the development of OSCC is the most feared complication but there are a number of other possibilities for a PMD in terms of its outcome: it may persist unchanged for the lifetime of the patient; it may enlarge to cover more of the oral mucosa; it may reduce in size or even disappear completely. The aetiology of leukoplakias and the effects of treatment must be taken into account when assessing the tendency to progress, reduce in size or regress. In Bombay in India, 42.5% of untreated leukoplakias disappeared in 5 years and 45.3% in 10 years, particularly in those who chewed tobacco, while 41.5% of lesions remained unchanged in 5 years and 31.6% in 10 years, particularly in smokers (3). In Gujarat 11% of the leukoplakias re-examined after 2 years had increased in size, 31.6% had decreased in size or disappeared and 57.3% had remained unchanged (36). Reduction in size or disappearance was recorded for 42% of leukoplakias in Kerala, 40% in Gujarat and 37% of non-palatal leukoplakias in Andhra Pradesh (4). Regression was more frequent amongst chews of tobacco and pipe smokers than in those who smoked cigarettes. The average duration of the leukoplakias in each region was calculated by dividing the prevalence by the incidence rate; leukoplakias persisted for 9 years on average in Kerala and 13 years on average in Gujarat (4).

In the developed world, in 214 Danes with leukoplakia followed for between 1 and 10 years, the lesions disappeared in 43 (20.1%), reduced in size in 38 (17.8%) and only increased in size in 7 patients (3.3%) (37). In 257 Californian patients with leukoplakia followed for an average of 7.2 years, lesions became smaller or disappeared in 49 patients (37%) of the 133 who were smokers and continued to smoke, in 22 patients (44%) of the 50 who had smoked prior to their diagnosis and then stopped, but in only 2 patients (3%) of the 74 non-smokers (21). In 138 Danish patients with leukoplakia, all of whom had either reduced or abstained from smoking following their diagnosis, a reduction in tobacco consumption by 50% or abstinence for 3 months, was associated with a reduction in size or disappearance of over half the lesions (56%) (30). After total abstinence for a year, approximately 80% of lesions reduced in size or disappeared.

In 520 Hungarian patients followed for between 1 and 25 years, attempted elimination of the causative factors resulted in lesions disappearing completely in 176 patients (33.8%), improving in 131 patients (25.3%), remaining unchanged in 135 patients (26%) and increasing in size in 47 patients (9%) (16). These
leukoplakias also changed in clinical pattern during follow-up; 19 leukoplakias (3.7%) progressed from a less worrying clinical type to a more worrying type and 47 leukoplakias (9%) changed from a more worrying clinical type to a less worrying type. Lesions containing red areas were more likely than the other types to increase in extent, although each of the clinical types of leukoplakia had the same tendency to reduce in extent (20). Lesions on the tongue and floor of mouth seemed much more likely to progress than to regress (4 of 41 progressed, none regressed), in contrast to those lesions on the buccal mucosa or commissures (12 of 253 progressed, 40 of 253 regressed).

In a retrospective analysis of 175 PMD in 147 patients from the Netherlands treated conservatively, 81% of 149 homogenous lesions persisted unchanged, 1% became non-homogenous but 15% of lesions disappeared. In contrast, 10% of 21 non-homogenous lesions not treated by surgery persisted unchanged, 55% became homogenous in type and 20% disappeared (23). No significant differences in outcome were found between the surgically treated group compared with a 'wait and see' group.

**Development of OSCC**

Estimates of the so-called malignant transformation rates of PMD in the literature vary enormously, from site to site within the mouth, from population to population and from study to study (reviewed in 39, 40). In the large-scale community-based surveys with long follow-up periods, which have mostly been performed in the developing nations like India, estimates of the rate of malignant transformation of PMD range from 0.13% to 2.2% per year. One death from oral cancer arising in a leukoplakia was recorded amongst 117 Bombay policemen with leukoplakia, providing a rate of 0.9% over 10 years (0.9/1000 year) (3). The 7-year follow-up findings on over 30 000 Indian villagers in a long-term prospective study covering four separate areas of the country found no cases of OSCC in Bihar and only one case in Gujarat (41). It identified five cases of OSCC in 948 patients with mucosal alterations in Andhra Pradesh in eastern India and 14 cases in 431 patients with a variety of mucosal lesions from Kerala in southern India over the 7-year period, giving transformation rates of 10/100 000 year (0.1/1000 year) and 24/100 000 year (0.24/1000 year), respectively (41). In a further, more comprehensive report on the same sample after 10 years of follow-up, 13 cases of OSCC were identified in Andhra Pradesh from a total of 1240 leukoplakias and 11 cases of oral cancer in Kerala from 4105 leukoplakias, equivalent to transformation rates of 0.6/1000 year and 4.4/1000 year, respectively (4). All these cancers were noted to arise in abnormal areas of mucosa. After only 2 years follow-up, a study based in Gujarat state found 6 cases of OSCC arising from 4762 industrial workers with leukoplakia, a rate of 0.13% or 0.63/1000 year (36). The variation in rates from study to study are attributed to differences in follow-up times, study group selection and tobacco habits; in Andhra Pradesh, most of the cancers arose in the palate associated with reverse cigar smoking, while in Kerala chewing was the major form of tobacco use, with most cancers arising in the buccal mucosa or lip. In contrast, in a study based in a cancer hospital in Bombay that recorded the progress of 626 patients with oral leukoplakia over follow-up times ranging from 3 months to 23 years, 63 patients developed intraoral carcinoma (10%), although the site of the carcinoma and leukoplakia differed in 14 cases (22%) (42).

These figures are much lower than those derived from studies in the developed nations, which tend to represent more selected hospital-based samples, derived from patients referred to specialist units by primary health care workers. Estimates of the malignant transformation rate of PMD in the studies range widely between 1.1% and 17.5%. At a cancer hospital in Sweden, 782 patients with a clinical diagnosis of oral or lip leukoplakia were followed for between 1 and 44 years; of 650 (83%) patients who used tobacco, 0.2% developed OSCC in 2 years and 0.4% in 5 years, whilst the non-tobacco users (17%) had transformation rates of 1.1% and 3.1% at 2 years and 5 years, respectively (27). The progress of 214 Danish patients with leukoplakia was recorded for periods of between 3 months and 10 years and a maximum transformation rate of 4.4% per annum was calculated, based on death registrations for those lost to follow-up (three patients) and the observed cancer incidence, although only four patients developed OSCC between 1 and 5 years of follow-up (1.9%) (37). A study of 105 unselected patients in California, with a diagnosis of oral leukoplakia, recorded OSCC in 7 patients (6%) over follow-up periods ranging from 1 to 11 years (43). However, this group included nine patients who had been previously treated for intraoral tumours, three of whom developed further intraoral malignancy. A study of 235 English patients with intraoral white patches identified 187 with leukoplakia of whom nine developed OSCC, a 4.8% transformation rate (44). An annual transformation rate of 0.8% was calculated for 331 Danish patients with oral leukoplakia based on an average follow-up period of 4.3 years; 3 of the 12 OSCC did not develop in the areas of leukoplakia (45). Forty of 670 Hungarian patients with oral leukoplakia with between 1 and 30 years follow-up developed OSCC, a rate of 5.9%, mostly within the first 5 years after diagnosis (17). A retrospective study of 63 English patients with leukoplakia in the floor of mouth/sublingual region found that 17 had invasive malignancy identified either at presentation or within a period of 3 months (46). Of the remaining 46 patients, seven went on to develop OSCC, a rate of 15.2%. Indeed, the authors suggested that this form of leukoplakia was particularly sinister, and termed it 'sublingual keratosis'. In a similar retrospective study on 19 English patients with sublingual keratosis, three cases of OSCC occurred, a rate of 16% (47). Forty-five of 257 Californians patients with oral leukoplakia with a mean follow-up period of 7.2 years developed OSCC, a transformation rate of 17.5% (21). A combined retrospective/prospect-ive follow-up study of 157 patients in Oslo noted that 11 patients developed OSCC in the first 10 years of the
The precise location within the mouth seems to have a profound influence on the risk of malignant transformation. Most leukoplakias occur on the buccal mucosa, yet those on the floor of the mouth and lateral border of the tongue, sites where OSCC are frequently seen, seem disproportionately associated with the subsequent development of cancer. Of nine OSCC arising from leukoplakias in Denmark, four occurred on the tongue (44%), although there were only five leukoplakias (1.7%) present on the tongue (45). In Hungary, 8.2% of leukoplakias arose on the tongue, but these accounted for 37.5% of those undergoing malignant transformation; in other words, malignancy occurred in 27% of all tongue leukoplakias (17). Similarly, the floor of mouth seemed a high-risk site for transformation; 13% of floor
of mouth leukoplakias developed OSCC. In contrast, although most of the leukoplakias (63%) were found on the buccal mucosa or buccal commissures, only 2.9% and 1.1%, respectively, of these lesions progressed to OSCC (17). In England, the floor of mouth was thought to be particularly at risk; 24% of leukoplakias at this site became malignant eventually (46). The tendency of tongue leukoplakias to become malignant has also been emphasized in the Californian study (21). Sixty-seven of 440 leukoplakias (26%) occurred on the tongue, but 13 of the 45 (29%) OSCC arising in those leukoplakias were found on the tongue. In addition, leukoplakias on the gingiva were also proportionally over-represented in terms of malignant transformation: 102 of the 440 leukoplakias (40%) were seen on the gingiva, while 11 of the 45 OSCC (25%) occurred at this site. Floor of mouth was the third commonest site for carcinoma to develop from leukoplakia (21).

In contrast, no definite association between the precise intraoral location and the risk of transformation was identified in patients in the Netherlands (23). Although 15 patients from 101 with lesions on the tongue or floor of mouth developed OSCC, compared with 5 from the 65 whose lesions were located elsewhere, the figures did not reach statistical significance. Further follow-up supported this impression; while most of their patients with PMD on the tongue and floor of mouth underwent surgical excision, in patients who were managed conservatively an equal proportion of lesions at other sites developed OSCC as at these so-called ‘high-risk’ sites (38).

Considering the issue from a slightly different viewpoint, Mashberg and Meyers (49) found that of 222 asymptomatic small OSCC in 161 heavy smoking and drinking North American patients, 201 (90%) were located in the floor of mouth (101 of 222), the soft palate complex (64 of 222) or on the ventral or lateral aspects of the tongue (36 of 222). In a cross-sectional study of dysplastic lesions and OSCC in the USA, the highest prevalence of severe dysplasia or carcinoma in situ was in the floor of mouth (13.5%) and tongue (5%), emphasizing the apparent high-risk nature of lesions at these sites (24).

Clinical appearance
Oral leukoplakia can show a variety of clinical appearances. Some will be uniformly white, flat or slightly wrinkled, containing many fine cracks or fissures (termed ‘homogenous leukoplakia’) while others will be non-homogenous with a warty or nodular appearance, perhaps predominantly white with red areas or largely red with white speckles (‘erythroleukoplakia’). Those containing nodular or red areas have been shown to run a greater risk of malignant transformation than the uniformly white ones. In Denmark, speckled leukoplakias accounted for 57% of those which became malignant (4 of 7 leukoplakias in which OSCC developed were speckled) (37), and 9% of leukoplakias that developed a malignancy were speckled in type in contrast to all other types, which had a rate of 1.3% (45). Dividing Hungarian leukoplakias into ‘leukoplakia simplex’ (265 of 520), ‘leukoplakia verrucosa’ (173 of 520) and ‘leukoplakia erosiva’ (82 of 520), OSCC arose in eight of the group of leukoplakia verrucosa (4.6%), in 23 of the leukoplakia erosiva (28%) and in none of the leukoplakia simplex (16). Expressing this data in a different way; 74% of those leukoplakias in which OSCC eventually developed were of the ‘erosiva’ type, while 26% were of the ‘ verrucosa’ type (16). Extended study reinforced this finding; 10 OSCC arose from the group of 183 ‘leukoplakia verrucosa’ (5.5%) and 30 from the group of 116 ‘leukoplakia erosiva’ (24%).

Looking for clues to help predict which of 63 floor of mouth leukoplakias might eventually transform, it was noted that 4 of 7 lesions (57.1%) which progressed to OSCC were nodular, in comparison to only 3 of 22 lesions (13.6%) which did not (46). In Californian patients, only 23 of 440 leukoplakias (5.3%) had a red area, in contrast to 37 of 45 (82%) which eventually developed malignancy (21). In a series of Norwegian patients, 157 leukoplakias were divided into four groups; homogenous (60 of 157), verrucous (41 of 157), erosive (28 of 157) and nodular (28 of 157) (28). It was noted that a single case in the homogenous group developed OSCC, two in the verrucous group, three in the erosive group and eight in the nodular group. In the Netherlands, a stronger statistical association was found between the non-homogenous PMD and the development of OSCC amounting to a sevenfold increased risk when compared with homogenous lesions (38).

Size
A few studies have considered the size of PMD to be important. From a total of 331 Danish PMD followed for more than 1 year, eight of nine leukoplakias that developed OSCC were greater than the mean lesion size of 5.5 cm² (45). In a series of 111 Japanese patients with oral leukoplakias, 12 patients had ‘large and widely spread’ lesions rather than ‘localized’ white patches and three of these 12 later developed OSCC compared with five of the 99 localized lesions (50). In a study of 50 patients from Northern Ireland (51), multivariate survival analysis underlined the link between the clinical extent of PMD and the eventual development of OSCC. Although statistically significant on their own, neither duration nor clinical appearance was associated with development of OSCC when the variables were considered simultaneously. The risk of malignant progression was noted to be approximately six times greater in patients with large confluent PMD and approximately four times greater in those with PMD affecting a single anatomical site than in those with multiple lesions. A five-times increased risk of future OSCC was identified for larger PMD for 236 patients from the Netherlands (area greater than 200 mm²), in spite of attempts to control the more worrying-looking lesions with surgery (38).

In recent years, some workers have highlighted a group of patients with leukoplakia that have quite a different clinical behaviour, regarded by some as a unique from of PMD. The term ‘proliferative verrucous leukoplakia’ (PVL) was used to describe 30 patients who had a
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persistent relentless multifocal leukoplakia, many of which progressed from flat lesions through increasing degrees of thickening, fissuring and warty proliferation, until the eventual development of OSCC (52). Twelve patients died with OSCC that arose from the leukoplakia, 14 were alive but still with evidence of disease and only three were alive and free of disease. Others have reinforced the high probability of OSCC occurring in patients with PVL in spite of multiple surgical interventions, the proportion of cases developing tumour ranging from 60% to 100% (53–55).

Idiopathic leukoplakias

Leukoplakias where there is no obvious aetiological factor have been noted to have a significantly increased risk of malignant transformation in comparison with leukoplakias where there are associated causative agents. While tobacco is the most important risk factor associated with leukoplakia, lesions in non-tobacco users seem to be at increased risk of developing OSCC. In a Swedish study, an increased cumulative frequency of cancer was recorded in the group who did not use tobacco (1.1% over 2 years, 3.1% over 5 years) in comparison with the smokers (0.4% over 2 years, 0.4% over 5 years) (27). A similar trend was observed in Denmark; five of 45 leukoplakias in non-tobacco users became malignant (11.1%) in comparison with 6 of 283 lesions in tobacco users (2.1%) (45). In Hungary, the proportion of smokers in the group of leukoplakias that developed tumour (78%) was less than in the group that was not complicated by OSCC (87%). The difference was attributed to a greater propensity for malignant transformation in leukoplakias not associated with tobacco (16, 17). Of 74 non-smokers in a group of 257 Californian leukoplakia patients, 18 patients developed OSCC (24%). In contrast, 21 carcinomas arose in the 133 individuals who continued to smoke after diagnosis (16%) and only six OSCC arose in the 50 individuals who stopped smoking after diagnosis of the leukoplakia (12%) (21). In the series of 46 leukoplakias with follow-up in the Netherlands (71), the only three patients who developed OSCC were non-smokers. In an extended study, non-smoking female patients with leukoplakia were found to be at a statistically significant risk of malignant transformation compared with women who smoked while no such relationship could be determined for the men (23). Multifactorial statistical analysis was unable to demonstrate an association between tobacco use and OSCC from PMD (38).

Summary and critique

The literature on the natural history of PMD is vast and varied and consists mostly of prevalence and progression studies, non-randomized trials and reports of series or single cases. Some of the best publications in this field (now often ignored) come from the large Indian studies in the 1970s and 1980s. Many recent studies have repeated these seminal works with little further advancement in knowledge. It is ironic however, that case reports and series based on experienced clinical observation provide much of the valuable clues as to the natural history of this disease.

Definitions of leukoplakia and erythroplakia are well accepted, most authors adopting those proposed by Axell et al. (56). The first paper from this series critically evaluated and updated these definitions (1). Although they are diagnoses of exclusion (and hence dependent on the vigour and rigour with which other explanations of red/white oral lesions have been sought), uniform use of terminology has helped and must be regarded as essential when managing patients and conducting research. However, we feel that the distinction between potentially malignant lesions and conditions is neither so clear-cut nor clinically useful as once perceived. The implications with the term potentially malignant lesion are that it is more localized in the mouth, has no associated generalized/systemic component, has a higher risk of OSCC development and that if OSCC does occur, the tumour develops within the altered area of mucosa. Unfortunately, these tenets do not always hold: leukoplakias can be ill defined clinically, merging imperceptibly with more normal (or rather, less abnormal) adjacent mucosa (38); tobacco use, the main risk factor of leukoplakia, has significant systemic effects; in a proportion of cases the OSCC develops in mucosa at a site distant to the leukoplakia (45, 51, 57). Furthermore, with the exception of oral lichen planus and oral submucous fibrosis, development of OSCC in the other so-called potentially malignant conditions is so uncommon and unlikely that they cannot contribute significantly to either OSCC or ‘mucosal white patch’ burdens. That some patients with lichen planus should develop OSCC is not surprising but again such an event is so uncommon, even by the best estimates, that it may devalue the designation ‘potentially malignant’ and run the risk of overburdening clinicians and causing concern to patients with lichen planus unnecessarily. Similarly, while the risk of future OSCC in patients with oral submucous fibrosis is greater than for lichen planus, it seems unnecessary to assign it to the separate category of potentially malignant condition, and it probably should be regarded as a lesion or disorder. The precise nature of proliferative verrucous leukoplakia requires further study. This diagnosis is often ascribed retrospectively and while many of the cases described seem to have features in common (52–55) it is not clear whether it represents a unique variant of PMD or one form of clinical outcome.

Estimates of the prevalence of PMD vary depending on the populations studied, selection criteria, methods of data collection but the best guess suggests a global prevalence of 2–3%. While studies from different parts of the world may not be directly comparable, it is interesting to note that the systematic review by Petti (15) did not establish a statistically significant difference in prevalence between developing and developed nations, probably because of the global use of tobacco. The vast majority of lesions are associated with tobacco use, previous or current, although around 10% of lesions appear to have no known cause; the roles of alcohol and HPV infection are unclear at present. In
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The proportion of PMD that will develop OSCC is uncertain but low; best estimates suggest a rate of less than 2% per annum. Factors apparently associated with an increased likelihood of development of OSCC in PMD can be divided into those related to the patient and those related to the lesion. Older patients, particularly females (who may have lesions of longer duration) are more at risk than young patients while those who never used tobacco are paradoxically at greater risk than smokers. Factors related to the lesion include the anatomical site, the clinical appearance and the presence of epithelial dysplasia (40, 41). PMD on the tongue, floor of mouth and retromolar/soft palate complex appear to be twice as likely to develop OSCC as those on the buccal mucosa, palate or gingiva. The vast majority of PMD in which OSCC eventually developed are the non-homogenous type although 5% or so of the homogenous form will develop carcinoma; larger lesions covering several intraoral subsites also appear more at risk. The duration of the lesion may be an important but unquantifiable factor. Which of these factors – age of patient/duration of lesion, site, clinical type appearance and size – is/are the most important is not certain but they seem to be interdependent, at least to some degree.

In spite of the prolonged and detailed study of PMD, accurately predicting which patients or lesions will develop OSCC is impossible at present. Our hope rests in the realms of molecular developments that might identify those at higher risk of OSCC but robust clinical data in terms of epidemiological surveys and carefully conducted randomized trials must form the cornerstone upon which these tests need to be based and interpreted.

References