

An Overview of the Prevention of Oral Cancer and Diagnostic Markers of Malignant Change: I. Prevention

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Abstract: The incidence of oral cancer appears to be on the increase, with patients presenting at an earlier age. An overview of the prevention of this important condition is given in this article, and diagnostic markers will be discussed in a later presentation. Greater awareness of the aetiological agents involved in the development of oral cancer and their avoidance, should help reduce the number of cases. General dental practitioners have an important role to play in advising patients on healthier lifestyles (primary prevention), the detection of potentially malignant disease before it becomes malignant (secondary prevention) and screening for field changes in patients with a history of oral cancer. The role of chemoprevention (defined here as tertiary prevention) is also considered.

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Clinical Relevance: General dental practitioners may play a significant role in prevention of oral cancer.

Oral cancer is probably the most serious condition that the general dental practitioner (GDP) is likely to encounter. There is no way of accurately predicting the number of cancers that the GDP may see throughout his or her practising life because of variations in hours worked, patients seen, specialist practice, cases presenting to doctors, etc.—and failure of almost half of the population of the UK to attend a dental surgeon regularly. Approximately 2000 new cases of oral cancer are registered per year in the UK. Each year, approximately half that number die from or with the disease. The incidence

(particularly in Scotland and in younger patients) is apparently increasing. Although it may not be as common as some of the more 'high-profile' cancers (e.g. breast and lung), oral cancer warrants our attention because of the relatively high mortality rate and because it is largely a preventable disease. Many patients who develop mouth cancer smoke and drink excessive amounts of alcohol. The GDP may be well placed to monitor at-risk individuals, either through lifestyle advice (primary prevention) or identification of high-risk lesions (defined here as secondary prevention).

This report will consider the prevention of squamous cell carcinoma—the most common (greater than 90%) oral cancer—summarized in Table 1. The following discussion provides an overview of the known aetiological factors for oral cancer and lesions that may be indicative of future

malignant change. Tertiary prevention has been defined here as that which is available for preventing recurrence or development of a second malignant tumour in patients who have already been diagnosed with mouth cancer.

PRIMARY PREVENTION

Primary prevention focuses on avoidance of known aetiological factors and alterations in lifestyle to prevent cancer developing in the first place. This is particularly important because oral cancer is one of the few cancers with a high potential for prevention. The main aetiological factors implicated in oral cancer are:

- tobacco use;
- alcohol consumption;
- sunlight;
- diet and nutritional status;
- chronic candidal infection;
- viral infection; and
- immune deficiency.

Tobacco Use

It was only in the late 1950s that one of the main aetiological factors in the development of oral cancer was 'discovered'. Smoking (cigarettes, cigars, pipes), reverse smoking and tobacco chewing are all associated with oral cancer in those patients who are susceptible to the carcinogens contained in tobacco. The risk of developing mouth cancer rises with increasing

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Primary prevention:

- Advise on stopping or reducing smoking
- Advise moderation of alcohol intake
- Dietary advice (especially encouraging intake of fresh fruit and vegetables)

Secondary prevention (potentially malignant lesions):

- Always screen entire oral mucosa
- Recognize abnormalities (e.g. change of colour)
- If candidal infection present, identify cause and treat
- Refer any suspicious lesion to specialist, especially if there is no improvement within three weeks of treatment (or removal of probably causative factors)

Tertiary prevention (prevention of recurrence):

- Importance of routine extraoral and intraoral examination
- Regular review
- Low threshold for re-referral
- Dietary advice (fresh fruit, vegetables)
- Chemoprevention may play some role

Table 1. Summary of methods for the prevention of oral cancer.

intake, although there is great variation between reports on how intake affects the relative risk. One estimate puts the risk of a person who smokes more than 20 cigarettes a day of developing the disease at 10 times that of a non-smoker. The difficulty of accurately assessing daily use of tobacco over a number of years and the honesty (or memory) of the individual may blur the issue. However, oral cancer is not common amongst non-users of tobacco.

Some patients may ask ‘is it worth stopping since I’ve smoked for so many years?’ It would seem that the risk for those that quit smoking for ten years or more is no greater than that of the non-smoker. However, these people may be the ones who would not have developed oral cancer even if they had continued smoking (i.e. they have a genetic resistance anyway).

Alcohol Consumption

An independent causative role for alcohol is less clear, mainly due to the fact that most heavy drinkers also smoke. There is a definite synergistic effect between alcohol and tobacco (increasing the risk³²⁴), which is much

greater than the risk of alcohol alone (3 2.5) or tobacco alone (3 10). This is thought to be due in part to alcohol acting as a solvent for the carcinogens in tobacco. Religious groups that do not take alcohol or tobacco show a decreased risk of developing oral cancer.

The exact mechanism by which alcohol exerts its effect is unknown. The bulk of alcohol is metabolized in the liver, although extrahepatic metabolism (including in the oral mucosa) is known. Normally alcohol is metabolized to acetaldehyde, which has been shown to be mutagenic (although pure ethanol has not). Variation between individuals in isoenzymes responsible for the metabolism of alcohol may explain differences in susceptibility to cancer. The various mechanisms by which alcohol may affect the oral mucosa are reviewed elsewhere.

Sunlight (Actinic Radiation)

The incidence of lower lip cancer is higher in Caucasians in sunnier climates, and fair-skinned people are advised to wear sunscreen to prevent actinic damage.

Diet and Nutritional Status

There have been numerous studies indicating a relationship between chronically low vitamin A or beta-carotene plasma levels and oral cancer. Other epidemiological studies suggest that micronutrients such as selenium may also protect against cancer. Studies on diet and nutritional state are difficult because few centres regularly assess these factors in their patients with oral cancer. Some studies have found that eating fresh fruit and vegetables lowers the risk; however, the daily amount required to confer protection is not known. The antioxidants vitamin C, beta-carotene and vitamin E may be protective factors. Although some vegetables may be high in nitrates and nitrites (which have been associated with upper aerodigestive tract cancers), the overall effect of increased intake is to reduce susceptibility.

Dietary iron may play a role in maintaining epithelial thickness. Deficiency of iron is said to lead to upper aerodigestive tract cancers (Plummer-Vinson or Brown Kelly Patterson syndrome: a rare combination, particularly affecting northern European women, of glossitis, dysphagia and hypochromic anaemia, in which post-cricoid carcinoma develops). World-wide, anaemia is common and yet, in the absence of any other obvious aetiological agent, this is not a high-incidence cancer, which suggests that other factors are also responsible for the syndrome. Recent case-controlled studies have found an increased risk for head and neck cancers in patients with high fat and red meat intake.

Chronic Candidal Infection

Infection with *Candida* species can give rise to chronic hyperplastic candidiasis (sometimes referred to as candidal leukoplakia—see below). Chronic candidal infection may disturb epithelial cellular activity and give rise to neoplastic change. For example, chick embryo ectoderm undergoes squamous metaplasia and hyperplasia when infected with *Candida albicans*. Candidal leukoplakia has a higher malignant transformation rate than leukoplakia, suggesting that the infection is the cause of the lesion and not merely superimposed upon it.

Viral Infections

Despite various candidate viruses (e.g. Epstein-Barr virus, cytomegalovirus, herpes virus) there is no strong evidence for an important association between oral cancer and viral infection. Although in one study RNA complementary to herpes virus DNA was found in oral cancer (and not the normal mucosa), it may still be a ‘passenger’ and not active. Indeed, oral cancers do not commonly arise in the intra-oral sites of previous herpetic infection. Oncogenic human papilloma viruses (HPV) have been detected in oral cancer (usually HPV6, HPV16 and HPV18) but these viruses may also be found in normal oral



Figure 1. Extensive leukoplakic patch affecting the left floor of the mouth.

mucosa. HPV may help promote cancer by blocking tumour suppressor gene function (see Part 2).

However, the fact that a virus cannot be detected does not necessarily exclude its role, as it may have exerted an influence previously (the ‘hit and run’ theory).

Immune Deficiency

A defective immune response may predispose to carcinogenesis via a number of mechanisms. However in HIV infection, such immunodeficiency does not appear to increase the risk for squamous cell cancer, although lymphoma and Kaposi’s sarcoma are not infrequently found.

Other Factors

Chronic irritation has been implicated but this may be coincidental.

The use of mouthwash has also been suggested due to the ethanol content (which may range up to 27%) but this association could simply reflect use to combat the symptoms of the disease.

Stress is known to impair the immune system, and may be an adverse influence. Studies have shown a high level of depressive symptomatology in patients with oral cancer, both before and after treatment.

SECONDARY PREVENTION

Little is known of the natural history of oral cancer, its velocity of growth and whether an ideal therapeutic time point exists. Some clinically detectable

lesions may regress over time, which may be related to changes in high-risk habits. Furthermore, we do not know what proportion of oral cancers arise from a clinically detectable pre-existing lesion: potentially malignant lesions and conditions have been identified for years but may still be largely undetected, ignored or mistreated. It is essential that practitioners are aware of, and feel confident to diagnose clinically, potentially malignant oral lesions early. In one study, 90% of asymptomatic oral cancers presented as either a red or speckled lesion, which highlights the potential role of the GDP in early detection.¹

Thorough examination of the mucosal surfaces, in good light, is essential if these lesions are to be identified early. Extra-oral examination should also be performed to check for nodal involvement, which may significantly affect the prognosis.

Potentially Malignant Lesions or Conditions

These include:

- erythroplakia;
- leukoplakia;
- speckled leukoplakia;
- candidal leukoplakia;
- submucous fibrosis;
- sublingual keratosis;
- actinic keratosis;
- lichen planus; and
- discoid lupus erythematosus.

The term ‘potentially malignant’ is



Figure 2. An extensive erythroplakic patch affecting the edentulous maxillary ridge (note the squamous cell carcinoma in the buccal sulcus).



Figure 3. Speckled leukoerythroplakic patch of the left floor of the mouth.

preferred to ‘precancerous lesion’ because not all precancerous lesions become cancerous: some may regress and some stay the same if untreated. These lesions are reviewed in detail elsewhere (see Further Reading).

Leukoplakia

Leukoplakia (Figure 1) is defined as a white lesion that cannot be characterized as any other definable lesion. Between 4 and 18% of oral leukoplakias will transform into cancer; some 15% will spontaneously regress. Site plays a role: sublingual lesions are said to have a higher risk of malignant transformation (up to 40%).

Erythroplakia

This is a red patch that cannot be characterized clinically or histologically as due to any other condition (Figure 2). Erythroplakia is associated with a much higher malignant transformation rate than leukoplakia (80% and above).

Speckled leukoplakia

These lesions (Figure 3), as the name suggests, contain areas of red and white and carry a much higher malignant transformation rate than leukoplakia alone.

Oral Submucous Fibrosis

Epidemiological studies suggest that this condition (Figure 4) is induced by chewing areca nut. It is particularly common in Asia and rarely seen in those who do not have this habit. Symptoms include burning sensation, pain, altered salivation and reduced mouth opening. There may be ‘blanching’ of the



Figure 4. Pigmentary changes in a patient with oral submucous fibrosis who had restricted mouth opening.

mucosa, and fibrous ‘bands’ may be evident. The pathogenesis is unclear, although raised levels of copper due to areca nut chewing may lead to deposition and cross-linking of collagen by upregulation of lysyl oxidase, and thus increased fibrosis and DNA damage. There may also be a genetic predisposition (e.g. HLA antigens, autoantibodies).

Patients with this condition have a risk of also developing squamous cell carcinoma (up to 10% over 10 to 15 years).

Lichen Planus

Patients with the erosive forms of lichen planus (Figure 5) are more likely to develop a cancer, especially of the tongue: studies cite a malignant transformation rate of around 1.2%. In particular, there is evidence of change from white papules or striations to areas of atrophy or ulceration, some of which may be associated with drug therapy. The patient’s drug history should be checked and changes discussed with the prescribing clinician. Lichenoid drug reaction is common in patients with hypoglycaemia or hypotension.

Discoid Lupus Erythematosus

As many as 20% of patients with this condition develop oral atrophic lesions with striated keratotic halos, but only a few cases of carcinoma have been reported.

Infection

Candidal leukoplakias (Figure 6) can have a premalignant potential but they regress after antifungal treatment (e.g. fluconazole). To develop cancer three factors are required:

1. Genetic predisposition.
2. Oral carriage of *Candida*.
3. Tobacco usage.

Tertiary syphilis, once thought to be an important precancerous condition, is now very rare due to early treatment—and it has been suggested that it was the drugs used to treat the infection (such as arsenic) that actually helped to induce malignancy.

TERTIARY PREVENTION

For those who have already been treated for cancer, the prevention of either recurrence or a second malignant tumour is defined here as the third line in prevention.

This group of patients is at greater risk of developing multiple primary tumours despite adequate clearance of the surgical margins. Of those that develop recurrence, 90% do so in the first two years. Patients are also at risk of developing other aerodigestive tract tumours. In view of this, these patients should be reviewed regularly for life, initially in a dedicated clinic but thereafter by their GDP.

Extra-oral examination for clinically detectable enlarged lymph nodes and intra-oral inspection of the entire oral mucosa is essential at each visit.

The systemic administration of



Figure 5. Lichen planus affecting the left buccal mucosa.



Figure 6. Chronic hyperplastic candidiasis at the commissure of the mouth.

retinoids can reduce the recurrence rate for oral cancer. Other antioxidants, such as carotenoids, alpha tocopherol and glutathione, have shown promise as cancer prevention agents. Whether a diet rich in fresh vegetables and fruits (which naturally contain some of these agents) can prevent recurrence is unclear, as patients rarely show a dramatic change in nutritional intake.

Retinoids (including vitamin A, beta-carotene and 13-*cis* retinoic acid) are the most frequently used chemopreventive agents. Although results have been conflicting and the exact mechanism of their action is unclear, it would seem that they may be of value in preventing malignant change in potentially malignant conditions and preventing second malignant tumours from arising. Unfortunately their use can be complicated by side-effects such as raised lipid and cholesterol levels or exfoliative cheilitis, and the duration of any protective effect following cessation of treatment is unknown.

SUMMARY OF PREVENTIVE METHODS

Although the incidence of oral cancer would appear to be increasing, particularly in younger people (under 40 years) and sometimes with no obvious aetiology, the fact remains that most oral cancers occur in patients who smoke tobacco and drink excessive amounts of alcohol.

GDPs have regular contact with a large proportion of the general population, which provides an opportunity to give advice on risk

factors. It should not be forgotten that prevention of smoking has more health gain than merely reducing the risk of developing mouth cancer. The GDP may have an important role to play in educating their patients about smoking and sensible levels of alcohol intake. The Royal Colleges of Psychiatry and General Medical Practitioners advise that low-risk levels are <21 units/week for men and <14 units/week for women (one unit equals half a pint of beer, one glass of wine or one measure of spirits). Men who drink more than 50 units/week and women who take more than 35 units/week are at a much greater risk of developing oral cancer (and other disorders) than those whose intake is more moderate.

GDPs are also in an ideal position to advise on the benefits of increased dietary intake of fresh fruit and vegetables.

Even if individuals only present to their GDP for symptomatic relief of dental disease, a limited opportunity for

screening of the oral cavity exists. Few people will have performed self examination of the mouth—perhaps this should be encouraged.

Vital staining can help to identify malignant disease in suspicious lesions. Toluidine blue is one method claimed to stain malignant lesions. It is thought that the dye is taken up by the nuclei of malignant cells, in which there is increased DNA synthesis. However, both false positives and false negatives can arise, so great caution is advised in the clinical use and interpretation of toluidine blue staining.

On identification of a potentially malignant lesion, obvious traumatic factors should be eliminated, deficiency states treated—and if candidal leukoplakia is suspected, appropriate antifungals prescribed. If the lesion does not improve within a short time, the patient should be referred for biopsy and histological diagnosis.

The second article will review the

diagnostic markers that have been studied in association with oral cancer

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BOOK REVIEW

Periodontics: A synopsis. By W. M. M. Jenkins and C. J. Allan Wright. Butterworth Heinemann, Oxford, 1999. (184pp, £16.99).

This excellent book continues to go from strength to strength. Previously entitled 'Guide to Periodontics' it has been renamed and the number of pages reduced. Although it incorporates much of the text and many of the illustrations of its predecessor, this new edition is designed to be more concise and provides a more incisive comment. Some chapters from the earlier editions have been removed and chapters added on 'Periodontal Regeneration', 'Early-onset Periodontitis', and 'Chemical Antimicrobial Pocket Therapy'. This last chapter is a timely addition given the current interest in subgingival antimicrobial therapy. The section on dental implants has been expanded, reflecting the increase in the number of implants placed and the importance of proper aftercare. An excellent addition

is a section detailing further reading and lists a number of pertinent reviews. The book is well laid out, easy to follow and very readable. The black and white illustrations and photographs are good and, although a little bit smaller than before, there is no loss of clarity. There are new, and much welcome, illustrations covering the range of furcation treatments described and also the possible techniques that can be used in mucogingival surgery. The authors have tried to be as concise as possible and yet be as comprehensive as possible: a difficult task in a small book but done in sufficient detail for undergraduate students. I feel that perhaps some more could have been said about the effect of smoking on periodontal disease and the response to treatment in smokers. A great number of refractory periodontitis patients are smokers and smoking has a deleterious effect on all forms of periodontal therapy, especially surgical, GTR and implants. The case presentation at the end is still too short. It would have been better if a number of cases could have

been illustrated rather than just the one. These points aside, this is an excellent book. Aimed at the undergraduate student, mainly in the final year, this book more than fulfils its aims. It is also an excellent book for those wanting to brush up on their knowledge, such as general dental practitioners or those beginning postgraduate courses.

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