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Editorial

Where next in oral cancer prevention and control?

Although of low frequency in industrialised countries, squamous cell carcinoma of the oral cavity and adjacent structures has high morbidity and mortality. In the Indian sub-continent, the mouth ranks among the most frequent sites where cancer occurs. As far as the United Kingdom is concerned, there are over 3,000 new cases of oral and oropharyngeal cancer per year and about 60% of patients will die of their disease within five years. Despite many advances in surgical techniques and rehabilitation there have been no improvements in survival of oral cancer patients for decades. Whilst oral cancer incidence showed an overall reduction during the last century from a peak which occurred at around 1920, from the mid sixties significant increases in incidence and mortality were observed in males aged 35-64 years in particular (Hindle *et al*., 1996).

Oral precancer

Although oral cancer often apparently arises *de novo*, there are also a number of precursor lesions which constitute a detectable pre-clinical phase. The most important are leukoplakia, erythroplakia and erosive lichen planus. Mucosal disorders associated with heightened risk may be present in up to 5% of the population over 40 years of age in industrialised countries (Kleinman *et al.*, 1991). A wide range of overall malignant transformation rates for precancerous lesions from 4% (Speight and Morgan, 1993) to as high as 36% Lee *et al.* (2000) have been reported depending on the degree of dysplasia and length of follow up. Because of the potentially lethal nature of precancerous lesions, which are generally without pain or discomfort, it is important that apparently healthy people with disease are identified and kept under continuous clinical supervision.

Risk factors for oral cancer

Apart from well documented substantial geographic variations, there are clear differences in oral cancer incidence and mortality between population groups according to ethnicity and socio-economic status. These suggest differential exposures to specific risk factors. It has been postulated that tobacco smoking and alcohol consumption (reviewed by Arens, 1999), moderated by the protection afforded by fresh fruit and vegetables (Pavia *et al*., 2006), explain a high proportion of intraoral cancer cases in the Western world.

Prevention and control of oral cancer

Poor survival is at least in part due to failure to detect small lesions and potentially malignant lesions early. The majority of patients first seek professional advice only when a tumour is already well advanced. The reasons for patient delay in reporting oral cancer are not well understood (Scott *et al*., 2006). It would seem that the key to better quality and length of survival is more effective detection of disease at a premalignant stage or when the invasive lesion is small. This supposition combined with our knowledge of the risk factors for oral cancer, and the consequent possibilities for health promotion and education, has major public health implications.

Primary prevention

With such well-known factors as tobacco and alcohol (carrying an attributable risk of 75-95%) it is theoretically possible to prevent a substantial proportion of oral cancers (Cancer Research Campaign, 1993). Even in individuals who already have precancerous lesions there is evidence from a large intervention trial in India that the chance of these undergoing malignant change is reduced if patients can be persuaded to curtail their dependence on tobacco (Gupta *et al*., 1992). Clearly, increasing the level of public knowledge about oral cancer and its risk factors is an essential prerequisite for facilitating desired changes in lifestyle. In support of this, at the World Health Assembly in May 2003 the member states of the World Health Organization ratified a groundbreaking public health treaty to control tobacco supply and consumption (Petersen, 2003). Yet research suggests that current levels of public awareness about oral cancer and its correlates are disappointingly low (Bhatti *et al*., 1995; Warnakulasuriya *et al*., 1999). Moreover, general evidence of the effectiveness of health promotion aimed at improving oral health, apart possibly from one to one counselling, is not encouraging (Kay and Locker, 1998). In this connection it is reassuring to note that a recent systematic review has confirmed that professional counselling on smoking cessation can have a positive effect (Carr and Ebbert, 2007). It would seem incumbent upon all engaged in public health and personal health services to promote smoking cessation and moderation in drinking habits vigorously.

Secondary prevention

As regards secondary prevention, population screening for oral cancer is clearly an option worth exploring. Screening is predicated on the supposition that early detection will increase survival and quality of life. If, for example, the proportion of patients presenting with tumours of greater than 2cm diameter could be moderated from 60% to 40%, with a commensurate increase in the number of cases detected with premalignant or small lesions before this advanced stage is reached, then material health gains might be achieved. Oral cancer

and precancer fulfil many of the criteria of a disease suitable for a population screening programme (Wilson and Jungner, 1968; Speight *et al.*, 2006).

- The disease is an important public health problem.
- There is an accepted treatment.
- Facilities for diagnosis and treatment - at least in industrialised countries – are available.
- There is a recognised early symptomatic stage.
- There is a suitable test or examination (systematic clinical examination of the oral mucosa).
- The test is non-invasive and should be acceptable to the population.

Additionally:

- There should be an agreed policy on whom to treat.
- The programme should be a continuous process.
- The natural history of the disease should be known and fully understood.

Meeting these two latter criteria would be a matter for policy makers. However, optimally two further requirements should also be met and here the position of oral cancer as a candidate disease is more problematic:

- The programme should be cost-effective.

These are issues where research has not yet provided full answers, nevertheless, on balance, there appear to be good arguments for pursuing the possibilities of screening in one form or another as a strategy for reducing the burden from these diseases (Speight *et al.*, 2006).

Three types of screening programme for oral cancer and precancer have been investigated in recent years:

1) Invitational programmes where people on some official list, or located in some form of institution, are contacted (Downer *et al*., 1995; Ikeda *et al*., 1995).
2) Opportunistic programmes where, for example, individuals attending a dental or medical practice for reasons unrelated to oral cancer are invited to have an oral mucosal examination (Jullien *et al*., 1995a; Lim *et al*., 2003).
3) Case finding programmes where house-to-house calls are made in order to contact and examine eligible residents in a specific locality.

A number of programmes of this latter type have been implemented in areas of high oral cancer incidence and mortality in the Indian sub-continent using trained health workers as screeners (Mehta *et al*., 1986; Warnakulasuriya and Pindborg, 1990; Warnakulasuriya and Nanayakkara, 1991; Mathew *et al*., 1997). Invitational screening programmes for oral cancer and precancer tend to be impaired by poor uptake; typically around 15-25% (Ikeda *et al*., 1995; Jullien *et al*., 1995b), unless conducted among people in a discrete environment such as a commercial company (Downer *et al*., 1995). Obviously, the response rate to invitation is a major measure of success in any screening programme. Compliance to follow up for full diagnostic investigation in a secondary care facility by individuals screened positive is also of prime importance. Rates of attendance among those referred were shown to vary considerably in a review by Moles *et al.* (2002) with less than 30% compliance being recorded in one study (Fernandez Garrote *et al*., 1995).

Despite considerable clinical heterogeneity with respect to type of programme, location, target population, type of personnel involved and their level of training, and other confounding variables, screeners have been shown to perform systematic clinical examination of the oral mucosa, for malignant and premalignant lesions, with a generally acceptable degree of accuracy and consistency. In a review of validation studies of test performance, with 'gold standard' verification involving independent clinical examination by an expert, a global estimate for reported sensitivity of the order of 0.80 was calculated in a Summary Receiver Operator Characteristic (SROC) curve analysis (Moles *et al*., 2002; Downer *et al*., 2004). The corresponding global estimate of specificity was in excess of 0.95. The lowest specificity reported was for Sri Lankan health workers. Whilst false positive screening outcomes are liable to cause considerable anxiety and distress for those misclassified, an emphasis on sensitivity at the expense of some loss of specificity , as occurred in the Sri Lankan programmes, is probably acceptable in the case of a life-threatening disease.

Future directions in oral cancer and precancer screening

Many general dental practitioners nowadays undertake a systematic clinical examination of the oral mucosa as part of a patient's routine dental check up and, certainly in the UK, continuing education and training courses on the differential diagnosis of soft tissue lesions and patient counselling are available. It has been suggested that opportunistic screening for oral cancer and precancer in general dental or medical practices of patients aged over 30-40 years, and probably in other categories of heightened risk, is likely to be the most effective screening strategy (Speight *et al.*, 1995; 2006). On the other hand it has also been argued that people in the higher risk categories are among those least likely to attend for regular dental checks. The results of a demonstration study of screening in dental practices (Lim *et al*., 2003) contradicted this view and showed that the prevalence of suspicious lesions among adults attending these practices was around 4.2% and therefore close to the predicted rate. Elsewhere a 5.5% prevalence of potentially malignant lesions was found among predominantly white collar staff of a company headquarters, 53% of whom attended a pilot in-house invitational programme (Downer *et al*., 1995). Yet advantageous as the initiatives of individual practitioners may be, they do not constitute a formal, fully evaluated, national screening programme.

The highest form of evidence of the efficacy of a clinical intervention is from a prospective randomised controlled trial (RCT) and the final report of such a trial, ongoing in Kerala, India since 1995, has been published (Sankaranarayanan *et al*., 2005). The study showed encouraging results. After 10 years, in male users of

tobacco or alcohol, or both, the reduced mortality rates in the intervention (screened) group compared with the control were statistically significant. However, the cost and logistical difficulties of organising and managing such an operation in an industrialised country with relatively low disease incidence would be formidable. Very large numbers of subjects would have to be followed over a long time period in order to measure significant changes in incidence and mortality.

In the shorter term there are a number of interim, or surrogate, measures that could give early indications of the possible effectiveness of an oral cancer and precancer screening programme (Chamberlain, 1993; Downer *et al*., 2006). As well as the basic measures of quality already alluded to – acceptable levels of sensitivity and specificity of the test, a satisfactory uptake of the programme and a high level of compliance in referral to secondary care among 'positives' – an increase in the numbers of previously undisclosed premalignant lesions identified would be an important interim marker of effectiveness. Initially an increase in the yield of new cases registered with patients presenting at an earlier stage should also be observed whilst in later years, the incidence of late stage cancer should fall. Yet while these interim measures are necessary findings in a successful programme, they are not sufficient to prove the value of screening. The matter is also complicated by the existence of at least three possible types of bias – self-selection, lead time and length - any one of which can give rise to false optimism over the likely benefits of a screening programme.

Next steps in evaluating oral cancer screening

Ultimately it is essential to know whether a screening programme is cost-effective. It is possible to gain some insight into the likelihood of this through the technique of computer simulation modelling. Using a Markov statistical approach, a hypothetical RCT can be modelled in which, for instance, a notional population, subject to a screening programme, is compared with a similar unscreened population. In other words the outcome of the programme in terms of health gain, usually expressed as quality adjusted life years (QALY), is compared with the outcome under the *status quo* or 'do nothing' scenario. Comprehensive costings of both screening and secondary care are required to inform the model. Modelling a health care process can provide only general insight and understanding and not definitive answers. Nevertheless, although they cannot replace the RCT, probabilistic models have an important place both in health care planning and in aiding clinical judgement. They can enable a variety of different strategies (e.g., invitational versus opportunistic screening programmes) to be compared rapidly and relatively cheaply in sensitivity analyses and would appear to constitute an indispensable preliminary phase in the evaluation of a population screening proposal: probabilistic modelling could indicate the most promising approach to test subsequently in a RCT. A relatively crude simulation modelling exercise (Downer *et al*., 1997a; 1997b; 1998) suggested that opportunistic screening of preselected patients in high risk groups could be a promising strategy and should be subject to formal economic appraisal. Such an appraisal has since been undertaken and supports the supposition (Speight *et al*., 2006). Further empirical confirmation, and gaining a more profound understanding of the natural history of oral cancer and the benefit of early intervention, are signposts for the next stages of research into the prevention and control of this major disease.

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