ORAL CANCER: NEW INSIGHTS INTO AETIOLOGY AND BEYOND*

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Most oral cancer is squamous cell carcinoma, and is seen in older males. It is particularly common in the developing world. In all areas however, the aetiology appears to be multifactorial and strongly related to lifestyle, mainly habits and diet, though other factors such as infective agents are also implicated.

TOBACCO, ALCOHOL AND BETEL HABITS

Tobacco smoking[1] and alcohol use[2] are independent risk factors for mouth and tongue cancer. The combined effect of alcohol and tobacco is however greater than the sum of the two effects independently. Betel quid chewing and oral snuff are important risk factors[3] in specific geographic areas (eg betel chewing in South East Asia). Mouthwash use is a risk factor in a small sub-group of non-smoking, non-drinking women[4].

Recent studies of oral cancer have contributed greatly to the understanding of the role of these risk factors[5]. Two recent studies from India have confirmed the association between pan tobacco chewing and oral cancer[6] particularly cancer of the buccal and labial mucosa[7]. These, and other aspects of the epidemiology of oral cancer, are considered in a timely review which clearly establishes the priorities for preventing oral cancer in India[8].

A strong association between tobacco use and oral cancer risk was reported recently from China[9]. For all kinds of tobacco, combined into an index of lifetime cigarette-equivalent pack-years smoked, the risk among men rose from 1.0 in those who never smoked to 3.7 (95% CI(1.0, 7.4) in the highest group. Similar results were found among women. The risk of oral cancer was found to be higher for pipe smokers than for smokers of cigarettes. This study also found an independent effect associated with alcohol consumption: risk in the highest category of lifetime consumption was 2.3 (95% CI 1.2, 4.8) compared to non-drinkers. The combined effects of tobacco use and alcohol consumption were found to be multiplicative and the attributable risk for tobacco was estimated to be 34 per cent and for alcohol consumption was found to be 23 per cent.

A two centre study from Northern Italy[10] showed considerable risk increases associated with alcohol consumption and tobacco use. Compared to non-drinkers and non-smokers, the risk of oral (and pharyngeal) cancer was increased 80-fold in those with the highest levels of smoking and alcohol consumption.

The effects of different types of cigarettes smoked have also been examined[11], cigarettes being classified as "low/medium" if the tar-yield was below 22 mg and "high" if the tar yield was above 22 mg. Compared to non-smokers, the risk of oral cancer to smokers of low/medium cigarettes was 8.5 (3.7, 19.4) and for high tar cigarettes was greater at 16.4 (7.1, 38.2). A study of tongue cancer in Uruguay reported a four-fold greater effect of black than blond tobacco[12].

The previously mentioned case-control study in Northern Italy[13] has investigated the risk of oral cancer in an area where large quantities of wine are consumed. Among the heaviest drinkers (ie more than 84 drinks per week) the risk of oral cancer for those consuming wine only was 11.2; for those drinking wine and spirits the risk was 9.9 and for those drinking wine, spirits and beer the risk was lower at 4.1. It is apparent that it is not so much the

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particular source of alcohol which increases the risk of oral cancer but that alcoholic-containing beverages in general increase the risk.

DIET

A significant protective effect of diet against oral cancer has been generally shown in persons consuming carotene-rich vegetables and citric fruits[14, 15, 16]. A study from Northern Italy found milk, meat, cheese, carrots, green vegetables and fruit to be associated with a reduction in risk of oral cancer[17]. This effect persisted after adjustment for smoking and alcohol consumption, both of which were found to be associated with increased oral cancer risk. In a larger study from Northern Italy[18] the frequent consumption of pasta or rice, polenta, cheese, eggs and pulses increased the cancer risk but the frequent consumption of carrots, fresh tomatoes and green peppers reduced the risk and in a separate report from the same study[19] a high intake of maize was found to be associated with an increased (OR=3.2 95% CI (2.0, 5.4) but the effect seemed confined to individuals also reporting high consumption of alcoholic beverages.

More direct and precise measurements of diet constituents may be of more relevance to cancer risk. A study from Washington State in the United States examined oral cancer patients for pre-diagnostic concentrations of selenium and zinc by examining levels of these elements in toe-nails. Since the regeneration time for toe-nails is between 12 to 18 months in older individuals, it was felt that these levels would reflect body levels before cancer diagnosis. Men with oral cancer had lower nail selenium levels than did controls (OR-1.9) but women with oral cancer did not (OR=0.6). Individuals between the ages of 20 and 39, with oral cancer, were found to be more likely to have lower selenium levels than were controls (OR=16.4) and there was also a significant interaction between selenium and ascorbic acid levels which did not appear to be due to cigarette use. Subject with the greatest risk of oral cancer had low levels of both zinc and selenium (OR=3.8 for smokers and 5.7 for non-smokers)[20].

MOUTHWASH USE

A major United States study[21] based on 866 cases and 1,249 controls from four areas of the United States, adjusting for tobacco and alcohol usage, recently found the risk of oral cancer among users of mouthwashes increased by 40 per cent in men and 60 per cent in women, but the increased risk was only apparent for use of mouthwashes of a high alcohol content, (defined in this study as 25 per cent or higher). Thus, it appears as if the effect of alcohol from mouthwash is similar to that of alcohol used for drinking, although in terms of attributable risk the contribution of mouthwash use to oral cancer must be very small[22, 23]

ORAL HEALTH

A case control study from China in which every oral cancer case prior to surgery and every control at time of interview had a structured oral examination[24] found denture-wearing per se not to be a risk factor, although among males there was an increased risk associated with wearing dentures made from metal (OR=5.5). "Poor dentition", as reflected by missing teeth, emerged as a strong risk factor independently of other established risk factors: the odds ratio for those who had lost between 15 and 32 teeth compared to those who had lost none was 5.3 for men and 7.3 for women and there was also a trend towards increasing risk of oral cancer with increasing numbers of teeth lost. Those who reported that they did not brush their teeth were also found to have an increased cancer risk (OR= 6.9 in men and 2.5 in women) over those who brushed.

Generally similar findings were reported from a case control study in Brazil with, after adjustment, the risk among those reported teeth brushing to be 'infrequent' 2.6 95% CI (1.7, 4.0) compared to those who brushed their teeth daily[14]. Thus poor oral hygiene appears to be associated with increased risk of oral cancer, independent of any effect of tobacco, alcohol, or other well proven risk factors. Further studies are required.

The association between lichen planus and oral cancer risk remains controversial. Such an association received some support among the findings from Chinese study described above[24]: there were substantial risks reported for those who had leukoplakia and lichen planus on examination compared to those without such lesions.

SOCIOECONOMIC STATUS

Another interesting study was that reported concerning the relationship between socioeconomic status and oral cancer risk[25]. Three indicators of socioeconomic status were considered (education, occupational status, and percentage of potential working life in employment) and, after adjustment for established risk factors, only lack of employment was found to have an independent association with oral cancer risk. Though the authors concluded that their findings were consistent with the hypothesis that behaviours leading to social instability, and/or social instability itself, are linked to an increased risk of oral cancer, there may be other explanations such as habits, oral health, diet and nutrition etc.

INFECTIVE AGENTS

Candida albicans and viruses such as herpesviruses and papillomaviruses may be

implicated in at least some cases, and the extensive literature has recently been reviewed[26, 27, 28]

TOWARDS PREVENTION

Understanding risk factors for a disease is a large step, but only the first step towards prevention. The impact on oral cancer of smoking avoidance is well-known and there is very important information emerging recently from epidemiological studies that there appears to be a marked decline in oral cancer risk within five years of smoking cessation[5] However, tobacco control is a difficult objective to achieve since smokers find the habit very pleasant and addictive. Similarly, restriction of alcohol consumption is difficult to achieve for similar reasons. Thus, it is difficult at the present time to see what could be achieved quickly by intervening directly on the most important risk factors for oral cancer.

Perhaps diet holds more prospects for prevention particularly if the protective effects found to be associated with fruit and vegetable consumption could be translated into an association with a specific vitamin or mineral or micro-nutrient which could be then given to well individuals as a supplement. Since the mouth is such an accessible site and that the group of compounds including vitamin A, beta-carotene and other retinoids are recognised as being essential for orderly cell differentiation, there may be hopes that chemoprevention for oral cancer is feasible[29]. The major drawback at the present time is the side effects of the known active retinoids are too great to take into general use: there is a recognised need for less toxic compounds.

Chemoprevention is not an objective simply for the developed countries: in fact, the developing world have perhaps been showing the way on this topic. A recent primary prevention trial in Uzbekistan (former USSR) was carried out on a random sample of men aged 50 to 69 years chosen because they lived in a high risk region where the habit of nass use was very common. A significant decrease in the prevalence odds ratio (OR) of oral leukoplakia was observed after 6 months of treatment in men receiving retinol, beta-carotene and vitamin E (OR = 0.62, 95% CI (0.39, 0.98). A reduction in the prevalence of oral leukoplakia was also confirmed in men who were in the medium or high category regarding blood concentrations of beta-carotene after 20 months of treatment[30].

Thus, it appears that chemoprevention for oral cancer is emerging as a very strong alternative to conventional approaches to primary prevention and treatment. More studies are needed in areas of different risk and progress would be made much quicker if there was a greater measure of coordination and collaboration in any such on-going trials. At a time when oral cancer risk is rising again in many western countries, the case for prevention trials is becoming stronger.

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