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A Perspective of Oral Cancer

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Epidemiology and Etiology of Oral Cancer in Britain

Malignant neoplasms of the oral tissues are rare in the United Kingdom when compared with sites such as lung, stomach, colon, rectum, breast and uterus. They account for only 2% of the total malignant tumours. The vast majority (estimated at 90%) are squamous cell carcinomas, the remainder being predominantly malignant tumours of minor salivary gland tissue and, rarely, lymphomas, sarcomas and melanomas.

In round figures, 2400 new cases are registered each year in Britain – 2100 in England and Wales and 300 in Scotland. The number of deaths annually is half the number of new cases. So, although the incidence is small, it is a highly lethal disease and even curable cases may be severely mutilating.

Incidence and Mortality

The size of the clinical problem of oral cancer in England and Wales is shown in Table 1. The relationship between number of registrations and deaths has been reasonably constant for many years and it is interesting to compare the ratio (D/R) of the two. This provides an estimate of lethality or crude prognostic index for different sites. It can be seen from Table 1 that neoplasms arising in the tongue, rest of mouth and oral mesopharynx carry a much worse prognosis than lip cancers. The D/R ratio for intra-oral cancer is 0.6 whereas for lip it is only 0.1.

Lip and intra-oral cancer is more common in males than in females. Malignant neoplasms of lip are eight times as common in men as in women and intra-oral cancer twice as common.

There have, however, been changes in the last two decades. Male deaths have decreased from 1200 in 1950 to 550 in 1973 but female deaths have remained consistently around 300 per annum. The male/female ratio has therefore dropped from 4:1 to less than 2:1. This change in mortality figures has been reflected by a similar trend in incidence. Table 2 shows incidence and mortality rates in England and Wales from 1960 to 1970 and it can be seen that both lip and intra-oral cancer in men has been decreasing steadily over these ten years. This has not been the case in women where both registrations and mortality have remained remarkably constant. The D/R ratio has also remained constant, inferring little improvement in prognosis for either sex.

Oral cancer is very much an age-related disease. Ninety-eight per cent of cases are in persons over the age of 40. The overall incidence in the popu-

Table 1

Malignant neoplasms of buccal cavity and oral Mesopharynx. Average annual registrations (*R*) and deaths (*D*), 1962–1967, England and Wales

	Males			*Females*			*All persons*		
Site	*R*	*D*	*D/R ratio*	*R*	*D*	*D/R ratio*	*R*	*D*	*D/R ratio*
Lip	548	53	0.1	70	8	0.1	618	61	0.1
Intra-oral:									
Tongue	325	258	0.8	206	135	0.7	531	393	0.75
Mouth, other	430	201	0.5	225	100	0.4	655	301	0.5
Oral mesopharynx	196	130	0.7	72	52	0.7	268	182	0.7
Total intra-oral	951	589	0.6	503	287	0.6	1454	876	0.6

Table 2

Registrations (*R*) and Deaths (*D*). Oral Cancer in England and Wales 1960–1970. Rates per million

	1960–62 mean		*1963–67 mean*		*1968–70 mean*	
	R	*D*	*R*	*D*	*R*	*D*
Lip						
M	29	3	24	2	18	2
F	4	0	3	0	2	0
Intra-oral						
M	47	26	31	15	28	14
F	17	7	17	7	18	8

lation is 1 in 20 000 but this changes to 1 in 1100 in the 75 and over male population.

The lower lip is still the most common individual site for oral cancer, especially in Scotland and East Anglia. The most common intra-oral site is tongue, predominantly on the lateral border and ventral surface. The other important areas are floor of mouth, lower alveolar ridge and buccal mucosa. Other areas such as upper lip and palate are very rarely involved and when a malignant neoplasm does occur it is more likely to be of minor salivary gland origin than surface epithelium.

The incidence of intra-oral cancer is remarkably evenly distributed throughout the country. It is interesting to note, however, that although the incidence rates in Scotland and England & Wales are very similar, the mortality rate in Scotland is 40% higher.

Survival

Although comparison of D/R ratios in different sites provides an indication of the lethality of malignant neoplasms it does not provide an indication of how many people survive and for how long. This can be achieved by follow up of an initial sample of patients and can be illustrated graphically by recording the percentage still alive at various time intervals. A large sample was accumulated through the National Cancer Registry and survival curves for various sites are shown in Fig 1. It is immediately obvious that lip cancer has a much higher survival rate than any intra-oral site.

If this is analysed further by taking the stage of the disease at start of treatment into consideration (Fig 2) the early stage lesions (less than 4 cm diameter and localized) have a much better prognosis than late stage lesions (more than 4 cm in diameter and/or non-localized). Stage and site therefore are exceedingly important factors in chance of survival from oral cancer. An early cancer of lip has an 83% chance of surviving five years whereas a late stage intra-oral lesion has only a 17% chance.

Etiological Factors

One of the main purposes of epidemiology is to elicit causative factors of disease and many investigations have been carried out in an attempt to determine the cause of oral cancer. For many decades such factors as tobacco (smoking and

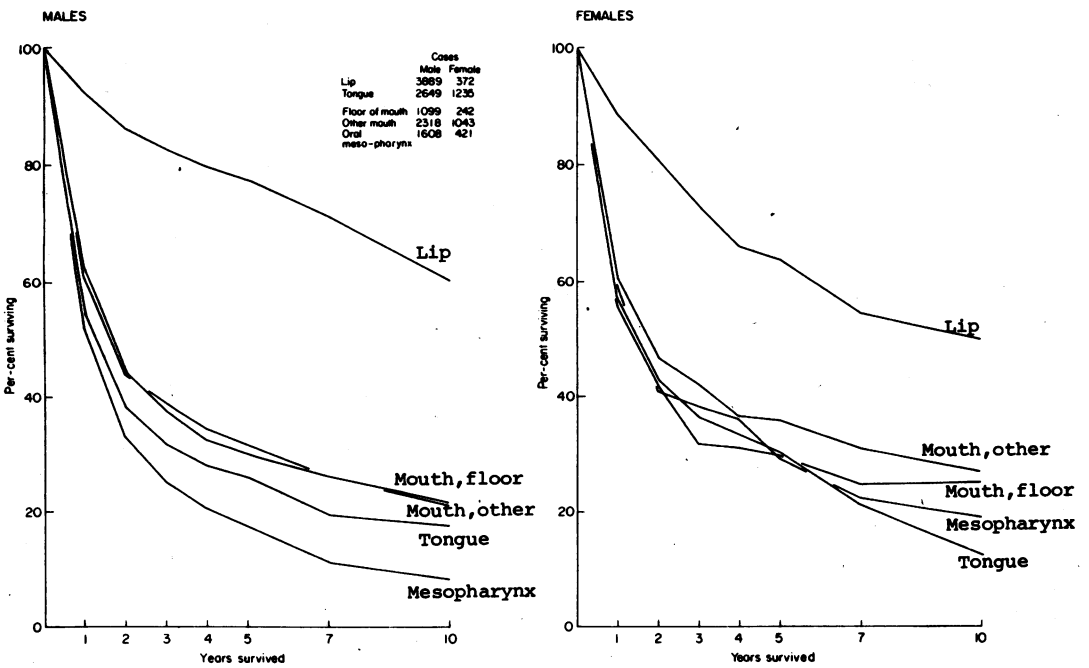

Fig 1 *Cancer of the buccal cavity. Corrected survival rates, all ages, all stages by site*

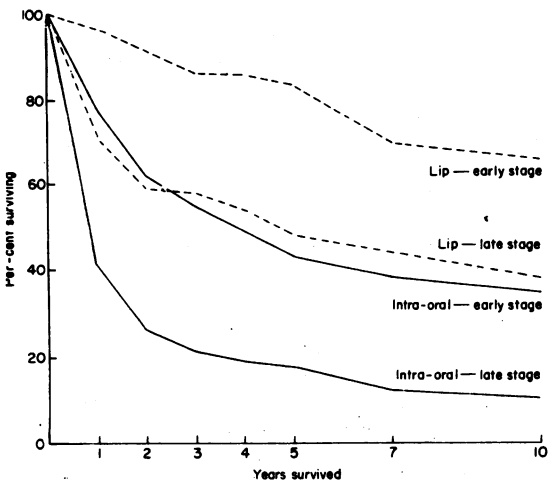

Fig 2 *Lip and intra-oral cancer. Corrected survival. Both sexes, all ages by stage*

chewing), alcohol, syphilis, dental sepsis and iron deficiency have been examined and by and large the findings have been equivocal as far as intra-oral cancer is concerned. There is a definitive relationship between squamous cell carcinoma of the lower lip and actinic radiation and it is generally agreed that pipe smoking is related also (Levin *et al.* 1950, Wynder *et al.* 1957).

It is beyond the scope of this paper to review the voluminous evidence implicating or rejecting the above factors. They have been comprehensively discussed elsewhere (Clemmeson 1965, Binnie 1975).

Some points, however, are worthy of comment regarding intra-oral cancer.

There would appear to be a positive association between pipe and cigar smoking and mouth cancer, but a negative one with cigarette smoking. Oral cancer has been steadily decreasing over the last twenty years and so has non-cigarette tobacco consumption. Cigarette consumption on the other hand has been increasing steadily until very recently.

Data on tobacco chewing are not available in Britain since no specific tobacco for chewing is manufactured. According to Waldron (1970), however, tobacco chewing is a contributory factor to the production of leukoplakia and verrucous carcinoma in the United States. Recently, however, this has been refuted by Smith (1975) in a large, long-term prospective study.

There is also conflicting evidence about the association between alcohol and oral cancer. Wynder *et al.* (1957) showed an association with frequent, heavy drinking, especially of whisky (American). In France, Schwartz *et al.* (1962) showed a strong association between alcohol consumption and cancer of various sites, especially pharynx, œsophagus and probably buccal cavity. In France, deaths from oral and œsophageal cancer parallel one another very closely and both are rising alarmingly. L Massé, in a lecture given in the University of London (1972, unpublished), linked the increase in œsophageal cancer to the alcohol consumption especially in Brittany and Normandy of crude, pot-still, 'Calvados'. It is tempting to suggest that the relationship applies to oral cancer also. In Britain, however, the increase in alcohol consumption corresponds with the downward trend in oral cancer. One wonders if this contrast between Britain on the one hand and the United States and France on the other could be due to the fact that prohibition in the United Kingdom of unmatured pot-still spirits containing toxic by-products has been a preventive measure in oral carcinogenesis.

Since Paterson and Brown Kelly independently described the association of chronic dysphagia and mucosal atrophy of the upper gastrointestinal tract in 1919 to the Section of Laryngology of the Royal Society of Medicine, a definitive association has emerged with sideropenia (Waldenstrom & Kjellberg 1939) and the supervention of carcinoma. This has been well documented in Swedish women (Ahlbom 1936, 1937). It would be interesting to know how many patients with oral cancer in the United Kingdom have chronically low serum and marrow iron levels.

Cawson (1969) and Pindborg (1971) have drawn attention to the possible relationship between chronic hyperplastic candidiasis, 'speckled leukoplakia' and the development of oral cancer. Higgs & Wells (1972) have shown that many patients with chronic oral mucocutaneous candidiasis are sideropenic.

Lastly, it is tempting to link the decrease in oral cancer with an improvement in oral hygiene. I think it is fair to say that there is not the degree of extreme dental sepsis that was present, say, twenty years ago. Many cancer therapists, while admitting they have no statistical evidence, feel that this is the single most important factor in the reduction of oral cancer. This is therefore speculative, but there is also no evidence to disprove the association.

Conclusions

Oral cancer, though diminishing, is still a highly lethal and distressing disease. The factors causing intra-oral cancer are still very speculative and it is hoped that a study in progress by Professor Cawson for the Department of Health and Social Security will shed light on some of the etiological problems. In the meantime, since we have no practical way of reducing the incidence we must attempt to reduce mortality by earlier diagnosis and institution of treatment.

Most of the statistical information in this paper is from three sources:

(1) **Binnie W H, Cawson R A, Hill G B & Soaper A E** (1972) Oral Cancer in England and Wales: A national study of moribidity, mortality, curability and related factors. Office of Population Censuses and Surveys: *Studies on Medical and Population Subjects* No. 23, HMSO, London

(2) Registrar General's Statistical Review of England and Wales. Part 1 – Tables Medical (Published annually) HMSO, London

(3) Registrar General's Statistical Review of England and Wales. Supplement on Cancer HMSO, London (1968–70)

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The Role of Histopathology in Diagnosis and Prognosis of Oral Squamous Cell Carcinoma

There can be little argument that histopathology plays a key role in cancer diagnosis, particularly in the mouth where access for biopsy is so easy. Techniques such as exfoliative cytology are notoriously unreliable, particularly when dealing with keratinized mucosa, and will not be discussed further (for example, Folsom *et al.* 1972, Reddy *et al.* 1975).

In spite of a somewhat variable clinical appearance, which may lead to doubt as to whether or not a suspicious lesion is really neoplastic, the majority of squamous cell carcinomas of the oral mucosa are readily diagnosable by conventional criteria on routine microscopic preparations: most are overtly invasive squamous cell carcinomas at presentation and the histopathologist can readily recognize them as such.

Major difficulties do arise, however, in determining what are truly 'premalignant' lesions. There occur in the oral mucosa, as in other mucosæ, a range of keratotic lesions, some of which are clearly benign, others of which certainly presage invasive neoplasia. These are the range of conditions commonly and loosely known as oral leukoplakia – a word which has so many shades of meaning that it may be wise to abandon its use altogether. Whilst the chances of a patient with a keratotic lesion developing a carcinoma are much higher than in patients without such lesions, it must be remembered that the minority of oral cancers develop in pre-existing white patches – perhaps of the order of 20% (*see* MacDonald 1975). Indeed, so-called leukoplakia is a much over-valued clinical sign of malignancy, and features such as erythroplakia, chronic ulceration and induration are much more sinister.

Microscopically these white patches reveal a range from perfectly benign hyperkeratoses, through lesions showing variable degrees of epithelial atypia, to so-called 'carcinoma-in-situ', to 'micro-invasive carcinoma', to truly invasive neoplasms. This is the traditional battleground of the early diagnosis of oral cancer, but emphasis on it has acted for many years to the detriment of detailed study of the variability of frank malignancies. This paper therefore reviews two major areas: (1) Methods for improving the accuracy and objectivity of diagnosis of the borderline case. (2) A consideration of the variability of overt invasive carcinomas, of prognostic features detectable therein, and of the value of these in the planning of patient management.

Methods for Improving the Objectivity and Accuracy of Diagnosis of Premalignant Lesions

At the cellular level squamous cell carcinomas show disturbances in the homeostatic mechanisms controlling cell division, cell maturation and cell aggregation. To these must be added evidence of host response seen in the tumour stroma, and the whole question of epithelial-mesenchymal interaction. Features attributable to each of these processes are listed in Table 1; some, of course, reflect disturbances in more than one of the fundamental control processes.

Most attempts at measuring the degree of epithelial atypia in oral premalignant lesions relate to these signs, or to combinations of them, and some recent studies which have attempted to put this type of analysis on a more objective and quantitative basis are reviewed below.

(1) *Multifactoral analysis:* Two studies deserve mention here. The first (Smith & Pindborg 1969) scores features objectively, but subjectively weights their importance. The second (Kramer *et al.* 1970, Kramer *et al.* 1974), whilst involving more subjective scoring, calculates weighting factors in an entirely objective fashion.