**CANCER OF THE ORAL MUCOSA** **MEDICAL APPENDIX**

**With an addendum on the aetiology of cancer**

## DEFINITION

1. The oral mucosa can be considered to be a type of specialised skin and the most important tumour type is squamous cell carcinoma which is usually a well differentiated keratinizing tumour invading surrounding tissue. Poorly differentiated and anaplastic carcinomas are far less common especially where the lip is involved. More rare types are basal cell, spindle cell, adenoid, adenosquamous carcinomas and carcinoma in situ. About 1% of all malignant melanomas arise in the mouth and Kaposi's sarcoma can also occur on the gums or palate.

2. Lymphomas and leukaemic deposits may occur in the mouth, and so may tumours of the small salivary glands. These are best considered separately as manifestations of those diseases.

## CLINICAL MANIFESTATIONS

3. Carcinoma of the oral mucosa is the sixth most common cancer overall and accounts for about 2% of all cancers in Britain. The prevalence increases significantly after the age of 45 and more than twice as many men as women are affected. The incidence of oral cancer has been decreasing over the last four decades.

4. Any part of the mucosa may be involved but the lip (usually the lower lip) and tongue (usually its ventrolateral aspects) are the most common, each accounting for about 25% of oral cancers. The floor of the mouth, gums, cheeks, soft and hard palates, and oropharynx are involved in about 10% of cases. Although they are usually single tumours, oral cancers can sometimes be multiple. In a study of 210 cases, nearly 18% had more than one primary growth. Because tumours may grow over anatomical boundaries and are rare at some individual sub-sites, this appendix considers oral cancer in general. The exception is where specific aetiological factors for the sub-sites have been identified.

5. There are two main presenting features, a lump or an ulcer. In all sites the condition tends initially to be painless. The most frequent presenting complaint is of a swelling or ulcer that is resistant to healing and gradually enlarging, perhaps with some discomfort and a little bleeding. Carcinoma in situ presents as a diffuse, erythematous, somewhat velvety lesion, affecting the mucosa of one half of the soft palate or cheek. Its diagnosis is by biopsy.

6. Cancers of the oral mucosa are often not detected until they are well established, with obvious local invasion or spread to the submandibular, upper cervical or submental lymph nodes. There may be hypersalivation but often the mouth is dry. The hallmark of these tumours is induration at the base of the lesion. As well as soft tissue invasion, bone encroachment eventually occurs.

7. The **treatment** of these cancers is usually by surgical excision, which may be combined with radiotherapy. Radiotherapy alone is an alternative primary treatment and is commonly used in cancer of the lip, in inoperable cases, or with recurrent cancers. Newer forms of single-agent and combined chemotherapy are playing an increasing role.

8. The **prognosis** varies with the site of the cancer but is significantly better in the absence of lymph node involvement. With treatment, either by surgery or radiotherapy, the 5-year survival rate for cancer of the lip is about 80%. For cancer of the cheek it is about 40%, for the tongue or floor of the mouth it is about 30%, but only about 25% for the oropharynx, palate and gums.

**AETIOLOGY**

9. As with other malignancies the underlying cause of most cancers of the oral mucosa is unknown, but the involvement of certain factors is supported by epidemiological evidence. There is considerable geographical variation in its incidence. In the West, the condition is most frequently seen in the elderly male population.

10. Of the known carcinogenic factors, the two most commonly implicated are tobacco and alcohol. These independent risk factors also act synergistically. In Western societies, these cancers are very rare in non-smokers who do not drink alcohol. Overall, cigars, pipes, chewed tobacco and snuff (finely ground tobacco) rather than cigarettes, are the forms of tobacco more closely associated with oral cancer in most societies. Among Western societies there is a remarkably high incidence of cancer of the oral mucosa in some parts of France, especially Bas Rhin and Calvados, associated with high consumption of both alcohol and tobacco.

11. A number of lesions or medical conditions may be premalignant.

    11.1. Of the premalignant lesions, leukoplakia (including syphilitic leukoplakia), erythroplakia, sublingual keratosis and the palatal changes of reverse smoking (with the lighted end in the mouth) are recognised.

    11.2. Premalignant conditions include oral submucous fibrosis, iron deficiency anaemia with dysphagia, lichen planus, discoid lupus erythematosus, tylosis and xeroderma pigmentosa.

12. Leukoplakia is the best-known predisposing condition for cancer of the mouth. In about 5% of patients leukoplakia undergoes malignant transformation. In cases where epithelial atypia is present the figure is about 30%. Erythroplakia, particularly if erosive, carries an even higher risk.

13. The precancerous condition of submucous fibrosis is found mainly in India and Sri Lanka. It is associated with eating chilis and with chewing quids of betel and lime (calcium hydroxide), either alone or mixed with tobacco. "Betel chewer's cancer" (although the quids do not always contain betel) tends to occur in the palate, buccal mucosa or tongue.

14. Cancer of the lip is causally associated with excessive exposure to ultraviolet light. Smoking, particularly pipes, increases the risk.

15. The Epstein-Barr virus is now thought to be a cause of hairy leukoplakia which is pre-malignant. Chronic candidal infection (often superimposed on leukoplakia), human papilloma virus, herpes simplex type 1 virus, syphilis (without leukoplakia) and chronic trauma have been cited as possible causal agents in oral cancer. The evidence is conflicting and there is no conclusive proof of a causal association with any of these. However, the fact that cancer of the alveolar ridge seldom arises in a dentate part compared with an edentulous ridge is highly suggestive that chronic trauma may be a significant factor in such cases.

16. Chronic low-grade mustard gas exposure, as in mustard gas manufacture, is associated with cancers inside the mouth, but not with cancer of the lip.

17. Cancer of the oral mucosa is not caused by climatic extremes, acute trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. Its progress is independent of external factors other than medical treatment.

**CONCLUSION**

18. Cancer of the oral mucosa is a malignant tumour. Constitutional and environmental factors play a part in the aetiology and a minority of oral tumours occur in relation to the premalignant states noted above. The course of the condition is unaffected by environmental factors other than those involved in its treatment.

## ADDENDUM on the aetiology of cancer

1. Clinical cancer is the end result of a multistage process involving initiating and promoting agents. If the carcinogen is an initiating agent, eg. asbestos - rather than a substance influencing a later stage nearer clinical manifestation, eg. cigarette smoking - cancer incidence in the population may continue to rise, albeit more slowly, for a considerable time after exposure to the carcinogen has ceased.

### Risk factors in individual cancers

2. The main factors that determine whether a particular individual develops cancer relate to constitution and exposure to environmental factors.

### Genetics

3. The close connection between certain chromosomal abnormalities associated with recognised clinical syndromes and subsequent tumour development, eg. polyposis coli and cancer of the large bowel and xeroderma pigmentosum and skin tumours, confirms that an individual's genetic make-up has an effect on his susceptibility to cancer.

4. Many studies have looked at cancer rate in the families of individuals with the disease. There appears to be no material tendency for cancer in general to cluster in families and no genes have been identified that increase the risk of cancer in all tissues. However, all common cancers do cluster in families to some extent – the risk of a sibling of a patient developing a tumour at the same site is twice normal. This might be due to genetic susceptibility but could equally well reflect lifestyle, eg. diet or hygiene or a common legacy of infections in early life.

### Environmental factors

5. Our knowledge of the environmental causes of cancer relies on animal laboratory investigation and human epidemiology with the two approaches complementing each other. Since there are features common to most cancers, there are factors which can cause cancer at all or many sites. Present evidence confirms the importance of life-style factors in cancer causation.

### Tobacco smoke

6. Cigarette smoking is thought to cause 30% of all cancer deaths and has been conclusively linked to cancer of the lung, upper respiratory tract, oesophagus, bladder, stomach, liver, kidney and chronic myeloid leukaemia. It may also contribute to cancers of the colon and rectum. Relevant factors include number of cigarettes smoked, tar content, age at smoking onset and duration of habit.

## Diet

7. There is good evidence that some common cancers would be less common if diet were modified. Animal fat consumption, particularly red meat, high salt intake and ingestion of very hot beverages and food have all been linked to specific cancers. Similarly what is **not** in the diet may be important. Low consumption of vegetables and fruit in the presence of high calorie intake is associated with several different tumour types, eg. childhood obesity and cancer of the breast and prostate, adult obesity and endometrial cancer. Consumption of alcohol (particularly along with cigarettes) increases the risk of cancer of the upper respiratory and digestive tracts. There is evidence that as little as two drinks a day may contribute to breast, colon and rectal cancer. In total, diet is considered to account for 30% of all cancer mortality in developed countries, alcohol for a further 3% and salt for 1%.

## Radiation

8. Radiation is difficult to avoid and, in total, radiation of all types causes 2% of all cancer deaths. Most of these deaths result from natural sources, particularly the UVB element in sunlight.

    - **UVB radiation** causes 90% of all skin cancers, including basal cell cancers, malignant melanoma and squamous cell carcinoma.

    - **Electromagnetic radiation** as a cause of cancer has been the subject of several recent studies. The results are confusing and inconsistent and reported associations may not be causal. It is of two main types:

        I. **Extremely low frequency fields**, eg. power lines and household appliances. Basic science confirms that these radiations are of too low frequency to initiate cancer causing genetic mutation as they are of insufficient energy to ionise molecules.

        II. **Radiofrequency electromagnetic radiation**, eg. cellular telephones, microwaves and living creatures. Although more energetic than i., they are still unable to cause molecular ionisation.

    In conclusion, at this date there is no good scientific evidence that electromagnetic radiation causes cancer. Any possible association remains hypothesis.

    - **Ionising radiation** can penetrate animal tissues and damage DNA and theoretically has the power to produce cancer in most tissues. The actual risk due to exposure to ionising radiation may, however, be different. It is often overestimated and not evidence-based. Amongst Japanese residents of Hiroshima and Nagasaki who survived more than a year after detonation, only 1% have died of tumours.

Studies of humans exposed to high dosage of ionising radiation, eg. the Japanese atomic bomb survivors or individuals medically irradiated for tumours, have shown an increased incidence of cancer due to that exposure. There is, however, no firm evidence from human low-dose epidemiological studies which unequivocally demonstrates an increase in cancer incidence. This may be due to the very large size of study population which would be needed to demonstrate an increased incidence.

For radiation protection purposes it is, therefore, accepted that there is no threshold level below which no carcinogenic effect is produced, and the risk of a cancer developing is extrapolated on a dose-proportional basis from high to low doses and dose rates.

All humans are constantly exposed to ionising radiation from both the natural environment and man-made products. The natural sources include cosmic radiation from space, radiation from the ground, and from inhaled and ingested materials. Air travel and mining both increase exposure to background radiation. Radiation originating in the body comes mainly from potassium, while lungs are exposed through radon in inhaled air. Man-made radiation comes from medical uses, past atomic tests, man-made products and radioactive waste.

Natural radiation differs depending on location. In the UK the average annual dose is less than 2,000 microsieverts. There is, however, a considerable range; it may rise to 8,000 microsieverts in some areas and to 100,000 in some homes. The UK average annual dose from man-made sources in total is less than 300 microsieverts and, again, there may be variation.

From 1952 to 1958 the UK carried out 21 atmospheric nuclear tests in the Pacific Ocean. The locations were chosen because of their isolation and low natural radiation level. On average the Christmas Island annual background radiation is less than 700 microsieverts.

**Radiation dose**

9. The effects of ionising radiation depend on the exposure size of the accumulated dose.

**Therapeutic drugs**

10. About 20 agents, not all of which are in current use, are known to cause cancer. Potential carcinogens may still be used if the hazard is judged to be less than the chance of saving a life, eg. certain cancer drugs. Close scrutiny is kept on drug hazards and the position of oestrogens in hormone replacement therapy (HRT), known to cause endometrial cancer, and of the oral contraceptive pills, which have been associated with carcinoma of the cervix, breast and hepatoma, is closely monitored. Together, prescribed drugs are held responsible for less than 1% of all fatal cancers.

## Occupation

11. Historically, study of occupational exposures has identified many important carcinogens. Material or process modification and, latterly, health and safety statute have removed many potential hazards in the developed world. However, the long latent period of cancer means that a considerable time will be required for the effects of industrial carcinogens to be eliminated and, equally, new hazards may remain unsuspected for a long time. At present overall, occupation is considered responsible for 2-3% of all fatal cancers in developed countries. Particularly important occupational carcinogens are asbestos dust exposure, exposure to combustion products of fossil fuels and ionising radiation.

## Pollution

12. Investigation of the relation between environmental pollution – air, soil and water – and cancer is difficult because of the widespread nature of pollution and similar risk to people over a wide geographical area. It is generally accepted that, in the UK at the beginning of the last century, air pollution via combustion may have contributed to a few percent of lung cancers. Over the last 30 years with increasing statute on pollution reduction this has become much less common. Advances in chemical analysis have allowed recent interest in pollution of soil and water as possible cancer risks.

13. Another complicating factor in accurately attributing risk of cancer to individual external agents is **interaction**. Some carcinogenic agents act together to produce effects much greater than the sum of the separate individual effects, eg. smoking and asbestos in relation to cancer of the lung: smoking, alcohol in relation to carcinoma of the oesophagus, and aflatoxin and hepatitis B infection in cancer of the liver.

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