Evaluation of aspects of screening for oral cancer

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This thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Medicine
I declare that all the work within this thesis was carried out by myself whilst based at the Eastman Dental Institute. The neural network described in Chapter 5 was designed by Alan Elliott incorporating data gathered by myself.

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Abstract

Evidence suggests that early detection of oral cancer or precancer decreases both mortality and morbidity. Screening for oral cancer may be an effective health care intervention in view of the annual increase in new registrations of oral cancer and rising mortality rates. Oral cancer meets many of the criteria for a disease suitable for screening, however a need exists for research into the design of a screening programme and the validity of a screening test. Visual examination of the oral mucosa would appear to be a valid instrument for detecting oral cancer and precancer; in this study a selection of qualified dentists achieved this with a sensitivity and specificity of 0.74 and 0.99 respectively. Compliance from an invitational screening programme was disappointingly low (25.7%) compared to other similar programmes suggesting that targeting of high risk individuals may be more effective in detecting lesions. Data from the screened population was modified and used to train a computerised neural network, this was shown to be a useful tool for the identification of people at high risk from oral cancer and could detect lesions with sensitivity (0.80) and specificity (0.77), values comparable to dentists. Health care interventions such as screening programmes are assessed in terms of costs and benefits to the patient and public. Quality of life was compared in terms of utility values between patients treated for small oral cancers and those treated for more major cancers. Utility values for various stages of oral cancer were also obtained from a sample of the public since it is argued that they should play a part in health care decision making. Finally, the potential value of screening was determined using a decision model based on the results obtained from this study.
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Chapter 1

General Introduction
Oral cancer is generally defined as squamous cell carcinoma of the lip, tongue, gum, floor of the mouth, oropharynx and other unspecified parts and ill-defined sites of the mouth. These cancers are registered as ICD (International Classification of Diseases) 140, 141, 143, 144, 145, 146 and 149 and constitute over 90% of all malignant disease in the mouth. Malignant neoplasms of the salivary glands are generally excluded since their aetiology is completely different to that of oral squamous cell carcinoma (Pindborg, 1977). The remaining neoplasms are mainly sarcomas of the oral hard or soft tissues.

In the developed world oral cancer is the eighth most common malignancy (Parkin et al., 1993) and accounts for about 10% of all cancers. The incidence varies considerably throughout the World, accounting for up to 40% of all cancers in the Indian sub-continent, with similarly high rates in parts of Brazil, France and Canada (Johnson, 1991).

In the United Kingdom, oral cancer accounts for 1-2% of all cancers (Boyle et al., 1990). In England and Wales, in 1988 there were 2,337 new cases of oral cancer, which compared with 4,467 cases of cervical cancer, 26,702 cases of breast cancer and 3,881 cases of malignant melanoma. The incidence rate was about 4 cases per 100,000 per annum. The incidence is thought to be higher in the Indian immigrant population but there are no accurate records to prove this (Marmot et al., 1984). There is evidence that oral cancer is increasing in the United Kingdom (Johnson and
Wamakulasuriya, 1993; Hindle and Nally, 1991; Hindle et al, 1994) and similar increases have been reported in Denmark (Moller, 1989) and throughout Europe (La Vecchia et al, 1992). La Vecchia et al, in their analysis of trends in cancer mortality over the past thirty years found that there was an upward trend in oral cancer incidence in all European countries except in Scandinavia. This was especially so in the younger and middle-aged groups. However, unlike Hindle and Nally (1991), they found a decrease in mortality rate attributable to intra-oral cancer in British females. In Austria, Swoboda and Friedl (1994) found an increase in mouth/pharynx cancer in both females and males over the past thirty years and suggested that this was due to the increasing influence of alcohol. Macfarlane et al (1993) demonstrated a decrease in mortality from lip cancer in both females and males and thought that this was due to a reduction in overall incidence and an improvement in diagnosis and treatment. In the United States about thirty thousand people per year are diagnosed with oral cancer. The incidence appears to be increasing in certain groups such as older females and black males (National Cancer Institute, 1989). Over 8,000 deaths are attributable to oral cancer in the United States each year (American Cancer Society, 1992).

1.1.1 Age distribution

Oral cancer is essentially a disease of the elderly. The age specific incidence rate (males) in the United Kingdom rises to about 7 cases per 100,000 aged over 75 years compared to 4 per 100,000 for all age groups (Cancer Research Campaign, 1993). In the West, over 90% of cases are aged 40 years or over (Hindle and Nally, 1991).
However in areas of high prevalence many cases occur before the mid-thirties (Johnson, 1991). In England and Wales, Hindle and Nally found rising incidence rates of oral cancer in younger males over the past thirty years. In a recent study, Hindle et al (1995), analysed birth cohorts from archive OPCS data and showed that, although the overall incidence of oral cancer had reduced over the past century, the incidence and mortality had increased in younger males. They found that in the 35-64 year group mortality rates decreased up until 1966-70 (1.67 per 100 000) but increased in 1986-90 (2.91 per 100,000). These findings were not found in female cohorts. Sarkaria and Harari (1994) reported that although oral cancer is rare in those under 40 years of age, it is an aggressive disease and there appears to be a higher mortality in this age group, usually due to lack of control of the primary lesion.

1.1.2 Gender distribution

In the Western world there are almost twice as many cases of oral cancer in men compared with women (Johnson and Warnakulasuriya, 1993). Registration statistics in England and Wales show the disease to be twice as common in men than in women, 1,527 cases compared to 810 in women (OPCS, 1994). This distribution is thought to be due to the different smoking and drinking habits of the two groups (Moller, 1989; Doll, 1990). In a study in Connecticut, Chen et al (1991) documented an increase in female oral cancer and estimated that it was nearing that of males. This phenomenon was also highlighted by Hindle and Nally (1991) who found a 40% rise in mortality in younger British females. In areas of high prevalence men and woman
are affected almost equally.

1.1.3 **Socioeconomic factors**

Evidence suggests that the risk of oral cancer is lifestyle dependent (Day *et al*, 1993) and, like several other diseases, oral cancer appears to be more prevalent in the manual classes. In England and Wales, there are higher incidence rates of mouth cancer in the north of the country (Cancer Research Campaign, 1993). Greenberg *et al* (1991) investigated the influence of education, occupation and the number of years in work in relation to oral cancer risk and found that only the number of years in employment had an effect. They concluded that social instability was related to an increased risk of oral cancer. Bundgaard *et al* (1995) found divorced subjects had an odds ratio of 2.3 for oral cancer compared to those who were married. Pukkala *et al* (1994) investigated the incidence of oral and oropharyngeal cancer in different socioeconomic groups in Finland. They found lip cancer was five times more common in the lowest social class compared to the highest. However they found no clear correlation with social class and cancer of the oral cavity or pharynx.

1.1.4 **Ethnicity**

The prevalence of oral cancer is much greater in Southern Asia and this is attributable to cultural and social differences, for example, 'pan' chewing plays an important part in Asian life (Brownrigg, 1991). In a review of the use of tobacco and pan in the United Kingdom, over 95% of Bangladeshi women interviewed used pan with 62%
using additional tobacco (Summers et al, 1994). Since these customs have been carried to their new country and the Bangladeshi community has doubled between 1980-88, the prevalence of oral cancer in the United Kingdom may be influenced in the coming years. In the United States Blacks have a higher rate of oral cancer than Whites. Day et al (1993) investigated reasons for this disparity in a large case control study. They concluded that the higher incidence of oral cancer in Blacks was due to lifestyle since in the absence of alcohol and tobacco, they found that the risk of oral cancer for race was approximately equal.

1.1.5 **Site distribution**

Lip cancer is particularly common in fair skinned people especially those who work outdoors. Within the United Kingdom it is particularly common in Scotland (Macfarlane et al, 1993) and North West Ireland (Ormsby, 1993). According to OPCS statistics (OPCS, 1994), the most common registration for oral malignancy is cancer of the tongue (29%). In two studies documenting site distributions, cancer of the tongue was found to be the most common site for intra-oral cancer followed by the gingiva, floor of mouth and retromolar region (Langdon et al, 1977 (a); Jeppson et al, 1975). These areas are often referred to as the gutter zone. The hard palate and dorsum of the tongue are rarely affected. In Asia the site distribution is different and this is probably due to the difference in tobacco habits since the buccal mucosa and commissures are more commonly affected.
1.1.6 Staging systems for oral cancer

Oral cancer is staged in severity with regard to its size, degree of nodal involvement and metastasis (Table 1.1). The stage at which an oral cancer is detected is a major factor in determining an individual patient's survival. Langdon et al (1977b) developed another essentially similar system but with the site and pathology included in the staging (STNMP). Platz et al (1987) argue that the TNM staging system is not able to truly predict the prognosis of oral cancer since it only takes into account certain aspects of the disease. They suggest that more factors, such as the depth of the lesion, are required to assess long-term survival (Figure 1.1). Platz et al (1986) combine T1 and T2 in their comparisons between different stages when evaluating survival rates.
Table 1.1  International Union against cancer TNM staging system.

<table>
<thead>
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<th>Stage 0</th>
<th>T₀</th>
<th>N₀</th>
<th>M₀</th>
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<tr>
<td>Stage I</td>
<td>T₁</td>
<td>N₀</td>
<td>M₀</td>
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<tr>
<td>Stage II</td>
<td>T₂</td>
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<td>Any T</td>
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</table>

T represents any tumour size, where T₀: carcinoma in situ; T₁: 2 cm or less in diameter; T₂: Between 2-4cm in diameter; T₃: Greater than 4cm in diameter. N₀: no lymph nodes palpable; N₁: Clinically palpable nodes same side not fixed; N₂: clinically palpable nodes contra-lateral or both sides not fixed; N₃: clinically palpable nodes which are fixed. M₀ and M₁: absent or detected distant (blood-borne) metastases.
Factors influencing outcome of oral cancer excluding treatment variables (adapted from Platz et al, 1987)

Figure 1.1

- size
- degree of infiltration
- degree of histological differentiation
- mobility of site
- evidence of distant lymph nodes, clinical appearance, degree of fixation

age
sex
metastases
1.1.7 Clinical management

There is no agreed consensus on the management of patients with head and neck cancer although there is an increasing tendency towards less mutilating surgery. Surgery on the mouth usually results in loss of functions such as eating and drinking as well as alterations of facial appearance, whereas radiotherapy can result in long-term dryness of the mouth. Henk and Langdon (1993) demonstrated that a combination of brachytherapy and external beam radiation gave excellent results in treating floor of mouth and tongue cancers. Lefebvre et al (1994) found that brachytherapy was able to cure 82% of early oral cancers (T1 and T2 lesion) whereas surgery was more effective for T3 lesions. However reconstructive surgery has become more sophisticated with the advent of micro-vascular free flaps providing excellent restoration of function and improved appearance. The role of chemotherapy remains uncertain and its use has been limited to late stage disease. Some studies (Gupta et al, 1987; Merlano et al, 1992, South East Cooperative Group, 1986) have shown it to be of benefit, although Franchin et al (1995) interrupted their study of combined radiotherapy and chemotherapy due to the 'psycho-physical stress placed on the patients'. Photodynamic laser therapy is increasingly being used for the treatment of small lesions of oral cancer with excellent results (Grant et al, 1993). This treatment involves a photochemical reaction which causes the release of tissue damaging free radicals. The reaction is initiated by exposing a photosensitive drug to light of an appropriate wavelength. The destruction is contained within the tumour area since malignant cells may retain a higher concentration of the photosensitive drug than normal tissues (Henderson and Dougherty, 1992) and the laser can be accurately...
directed at the lesion.

**1.1.8 Survival and mortality**

Although oral cancer is not prevalent it is often fatal with over 60% of patients dying as a result of the disease (Platz et al., 1986; Speight and Morgan, 1993). The incidence to mortality ratio is 1.68 (tongue, female) compared to 2.1 for invasive cancer of the uterine cervix and 3.56 for malignant melanoma (female). Both these diseases have comparable incidence rates to oral cancer. Survival is dependent on the stage of disease at presentation with nodal involvement being an important predictor of prognosis (Tobias, 1994). Mortality from oral cancer has not changed over the past three decades (Stell and McCormick, 1985), despite advances in rehabilitation techniques. It varies according to stage and site of disease, for example, the five year survival rate for cancer of the gum is 40.7% (male) and 58.2% (female) compared to 26.3% (male) and 36.4% (female) for cancer of the oropharynx (Cancer Research Campaign, 1988). In a large European study, Platz et al (1986) found approximately four years difference in survival between those subjects with small oral cancers (those less than 4 cm) compared to those with large oral cancers (greater than 4 cm).

Jones (1994) found that survival fell with increasing T (size of lesion) and N (degree of nodal involvement) stages. This trend has previously been described by several other authors such as Henk and Langdon (1993), Easson and Palmer (1976) and Hibbert et al (1983). Also in those patients cured of the disease, there may be severe loss of function and disfigurement, thus stigmatising the patient (Binnie and Rankin, 1984).
1.2 Oral precancer

In the developed world most oral cancers appear to arise in apparently normal mucosa, however in South East Asia there is often a premalignant lesion present prior to the onset of cancer (Scully, 1993). The premalignant lesion is often a leukoplakia, erythroplakia or a combination of both these; a speckled leukoplakia. There are also several conditions of the oral mucosa which appear to have an increased incidence of oral cancer associated with them. These lesions and conditions are termed precancer and are described below. Precancer refers to 'a potentially malignant lesion or part of lesion'. In terms of oral cancer there are a number of precancerous lesions and conditions which have been defined by the World Health Organization (WHO 1978).

Precancerous lesion: is a morphologically altered lesion in which oral cancer is more likely to occur than in its apparently normal counterpart.

Precancerous condition: is a generalised state associated with a significantly increased risk of cancer. The following lesions and conditions have been identified as precancerous (Pindborg, 1980).

1.2.1 Leukoplakia

Leukoplakia is defined as a white patch or plaque which cannot be characterised clinically or histologically as any other disease (WHO, 1978). It is the most common oral premalignant lesion according to a study of over 23,000 Americans (Bouquot and
Gorlin, 1986). The histological features are those of keratosis and varying degrees of cytological atypia. Although the incidence of leukoplakia in the United Kingdom is unknown it has been demonstrated in other studies in the Western world as ranging between 2-4% (Bouquot and Gorlin, 1986; Hogewind and Van der Waal, 1988). Oral cancer has been noted as arising in areas of leukoplakia during follow-up and the histological features of some leukoplakias are those of oral cancer (Speight and Morgan, 1993). Banoczy and Csiba (1976) found epithelial dysplasia in 24% of leukoplakias and of 68 patients with dysplasias, nine developed oral cancer. In this study they also found that leukoplakia on the tongue had the highest incidence of malignant change. In other studies the malignant transformation rate varies from 3-28% (Pindborg, 1980; Bouquot, 1987). In the United Kingdom, Kramer et al (1978) showed a malignant transformation rate of 24% for sublingual keratosis. Leukoplakias are generally treated by surgical excision (Vedtofte et al, 1987) with close clinical follow-up depending on the severity of the lesion.

1.2.2 Erythroplakia

Erythroplakia is defined similarly to leukoplakia as a red patch that cannot be characterised clinically or histologically as due to any other condition (WHO, 1978). Its prevalence is unknown but it is much less prevalent than leukoplakia although areas of erythroplakia can arise in leukoplakia. Erythroplakia has the highest risk of developing cancer (Vedtofte et al, 1987). At least 90% of these lesions have features of carcinoma in situ or a degree of dysplasia (Shafer and Waldron, 1975; Mashberg, 1980). The malignant transformation rate has been estimated as 80% (Speight and
Morgan, 1993). Treatment is by surgical excision but the recurrence rate is high, possibly up to 40% according to Vedtofte et al (1987). One reason may be the difficulty in defining the margins at excisions. Like leukoplakia, erythroplakia is closely associated with tobacco smoking and alcohol abuse.

The following are considered to be precancerous conditions:

1.2.3  **Lichen Planus**

Lichen planus is a relatively common mucocutaneous disease which involves the skin and/or mucous membranes. It was first described in 1869 by Wilson and an association with malignant transformation was suggested at the turn of the century (Hallopeau, 1910). Lichen planus has a classic appearance of bilateral white lesions (papular or reticular) on the buccal mucosa and tongue. Other types of lichen planus include atrophic, ulcerative or bullous lesions. Its prevalence is approximately 1% (Scully and El-Kom, 1985; Kaplan, 1991) and it predominantly affects those aged 30-70 years of age, especially women.

Evidence from retrospective studies suggests that there is a 'small but clinically important premalignant potential' for lichen planus (Barnard et al, 1993). Most cases of oral carcinoma arising in patients with lichen planus appear to do so in those with atrophic lesions (Fulling, 1973; Silverman and Griffiths, 1974). The incidence of neoplastic transformation in lichen planus has been documented as ranging from 0.4% to 5.6% (Murti et al, 1986; Silverman et al, 1985; Holmstrup et al, 1988). Even if
the transformation rate is low it will mean that a patient with lichen planus will be at greater risk than one without. One of the reasons for the controversy existing over the premalignant status of lichen planus is that there are lesions not having the clinical appearance of lichen planus but having lichenoid features histologically as well as lesions resembling clinical lichen planus but with dysplasia or atypia histologically (Eisenberg and Krutchkoff, 1992). Diagnosis by biopsy is not universal practice (Barnard et al, 1993), and this may explain the malignant change which occurs in some cases of 'lichen planus'. Eisenberg and Krutchkoff described a lesion with features of lichen planus and with cytological atypia, as 'lichenoid dysplasia'. Eversole (1992) concluded that precancerous lesions with lichenoid features may exist separately to oral lichen planus, although lichen planus may also have a slight tendency to undergo malignant transformation.

1.2.4 Syphilis

In the past syphilitic leukoplakia of the dorsum of the tongue was considered an important precancerous condition, however it is now decreasing in incidence. Banoczy (1977) found that 3% of leukoplakia patients had syphilis and of those patients who subsequently developed oral cancer 10% had syphilis. Hobaek (1946) proposed that the atrophy of the tongue epithelium caused by syphilis may allow an increased effect by aetiological factors such as smoking and alcohol.
1.2.5 Sideropenic dysphagia (Patterson-Kelly syndrome, Plummer Vinson syndrome)

Alhbom (1936) first pointed out the relationship between sideropenic dysphagia and oral cancer. This association was demonstrated by Wynder et al (1957). Sideropenic dysphagia is a collection of symptoms including low serum iron, diminished iron stores, chronic dysphagia and atrophy of the mucosa of the upper gastrointestinal tract in middle aged women. Rennie et al (1982) stated that many disease states were associated with iron deficiency. Rennie and Macdonald (1984) demonstrated an increased cell turnover in atrophic epithelium in iron-depleted hamsters. Prime et al (1986) however failed to show any difference in the severity of epithelial dysplasia in experimental iron sufficient and deficient rats. It is generally accepted that iron deficiency may be related to loss of epithelial integrity and this may cause the epithelium to be more susceptible to chemical carcinogens.

1.2.6 Oral submucous fibrosis

This chronic disease of the oral mucosa occurs almost exclusively in Indians and is due to the local action of areca catechu nut. The inflammatory reaction produced is thought to destroy the underlying connective tissue which then heals by deposition of thick collagen bands. This thicker underlying connective tissue leads to a reduced blood supply resulting in atrophy of the overlying epithelium. There is a 13-14% frequency of dysplasia in this condition (Pindborg, 1980) and it was found to be present in 40% of Indian patients with oral cancer (Pindborg et al 1967).
1.2.7 *Lupus erythematous*

This is a systemic auto-immune disease. Its presentation in the mouth is similar to that of lichen planus. Andreasen (1964) reported a 0.5% malignant transformation rate in patients with skin discoid lupus erythematosus. All cases have been associated with the lower lip and tend to be more common in men.

1.2.8 *Actinic keratosis*

This is a condition which effects the lower lip and tends to be more common in men. It is thought to be due to excessive sun exposure and ultra-violet light. About 10% of all actinic keratoses undergo malignant transformation. (Lynch *et al*, 1984).

1.3 *Risk Factors*

In the West, excess tobacco and alcohol consumption are probably the most important risk factors for head and neck cancer (Blot *et al*, 1988; Austoker, 1994a; Doll *et al*, 1994 a & b) with strong evidence that they act synergistically (McCoy and Wynder, 1979). Dietary factors are increasingly being considered as important influences.

1.3.1 *Tobacco*

There are several studies demonstrating the relationship between tobacco and oral cancer (IARC, 1986; Doll *et al*, 1994a). The main type of tobacco consumption in
the West is cigarette, cigar and pipe smoking. Since 1919 cigarettes have become the most popular type of smoking (Wald and Nicolaides Bouman, 1991). In one study 80% of oral cancer patients were found to use cigarettes and a six-fold increase in risk of developing oral cancer was found compared to non-smokers (Baric et al, 1982). Smokeless tobacco, although popular in Nordic countries and in the United States in particular, is not widely used in the United Kingdom and although it is known to be associated with an increased risk of leukoplakias (Kaugars et al, 1991) there is some dispute as to its role in progression of leukoplakias to oral cancer (Greer and Poulsen, 1983). Gupta et al (1984) estimated that up to 75% of cancers in the upper aero-digestive system, in Southern Asia, were attributable to separate and combined habits of tobacco and betel quid 'pan' chewing. Pan is a combination of betel leaf, areca nut and lime with tobacco often added (Summers et al, 1994). The high incidence of oral cancer in Bangladesh is thought to be due to a combination of pan and tobacco habits.

Brugere et al (1986) found no significant difference in location of cancer from the type of tobacco used except in those with cancer of the lip. Jovanovic et al (1993) found that the relative risk associated with tobacco smoking was highest for oral cancer in the retromolar region. Barasch et al (1994) found that smoking was more closely associated with cancer of the floor of the mouth than the tongue and gingiva.

There is evidence to suggest that smokers who have stopped smoking for over 10 years reduce their risk to that of non-smokers (Blot et al, 1988) and the effect of stopping reduces the risk of a second primary oral cancer comparable to those who
have never smoked (Silverman and Griffiths, 1972). Gupta et al (1992) found that a reduction in tobacco use led to a reduced incidence of leukoplakia and thus a lower risk of oral cancer. However, Spitz et al (1990) found that oral cancer patients were more likely to continue to smoke than patients with other cancers of the upper aerodigestive system.

### 1.3.2 Alcohol

It is thought that the increasing incidence of oral cancer is related to increased consumption of alcohol (Moller, 1989; Doll, 1990; Hindle and Nally, 1991). Studies of abstentious religious groups such as Mormons have found that the incidence of oral cancer is much lower than that of the general population. However it must also be remembered that religious groups tend to differ from the rest of the general population with respect to cigarette smoking and diet which may modify the risk of oral cancer (Kato and Nomura, 1994). Franceschi et al (1990) found a strong dose response effect depending on the number of drinks consumed in a week although the association for oral cancer was lower than that for oesophageal cancer. Doll et al (1994b) found that the risk of death from alcohol-augmented causes including mouth cancer was dose dependent. McCoy and Wynder (1979) postulated that the solubilising effect of alcohol on other carcinogens such as tobacco may be the cause of the increased risk of oral cancer.

In a study of United States war veterans, the strongest association with alcohol was found to be cancer of the anterior tonsillar pillar followed by the floor of the mouth.
and tongue (Mashberg et al, 1993). Jovanovic et al (1993) also found that the floor of the mouth had an increased relative risk due to alcohol drinking compared with other sites in the mouth. Brugere et al (1986) found that patients with cancer of the floor of the mouth had the highest consumption of alcohol.

Some groups have demonstrated that beer and spirits are more important than wine in the risk of oral cancer (Blot et al, 1988) whereas others have found the reverse (Franceschi et al, 1990). Mashberg et al (1993) found no difference in oral cancer risk between different types of drinks. Since the type of alcohol used varies throughout the world it is difficult to separate the effects of different types of drink. However since the association with total alcohol consumption has been consistent, this is probably more important than the type of beverage (Kato and Nomura, 1994).

1.3.3 Viruses

There is increasing evidence that viruses may contribute to the causation of oral cancer. Infection with the Epstein-Barr virus is clearly associated with nasopharyngeal cancer, Burkitts lymphoma and other types of lymphoma in immunosuppressed patients. DNA from the human papilloma virus has been detected in head and neck cancer (Woods et al, 1993). Tobias (1994) postulated that the dormancy of these possible carcinogens may explain the high rate of second primary malignancy in oral cancers.
1.3.4 *Fungal infections*

It is still unknown whether candida is an opportunistic invader or initiator of oral cancer (Arendorf *et al.*, 1983; Holmstrup and Besserman, 1983) however oral dysplastic lesions with candidal infection have a greater risk of malignant transformation (Johnson, 1991).

1.3.5 *Diet and Nutrition*

Nutritional deficiency is considered to produce atrophy of mucous membranes and it is possible that this makes them more permeable to local carcinogens. The importance of vitamin A and C has been highlighted by Franceschi *et al.* (1990). Use of β-carotene and retinoids has been used to reverse premalignant leukoplakia (Stich *et al.*, 1988). Gridley *et al.* (1992) found that users of supplements of vitamins A, B, C and E were at lower risk of oral and oro-pharyngeal cancer (after controlling for other risk factors). After adjusting for all the vitamin supplements it was found that vitamin E was the only one associated with a significantly reduced cancer risk. The effect of iron deficiency is discussed in another section (sideropenic dysphagia). Hebert *et al.* (1993) found, after accounting for other aetiological factors, a protective effect against oral cancer from milk or dairy products and cabbage consumption but an increased risk from vegetable oil and excess animal fat consumption. La Vecchia *et al.* (1991) found that the strongest protection from oral cancer was from frequent fruit consumption.
1.3.6 Mouthrinses and dental hygiene

Winn et al (1991) demonstrated a significant increase in oral and oro-pharyngeal cancer associated with regular use of a mouthwash. This risk was increased by 40% in males and 60% in females after adjustment for smoking and alcohol intake. The risk appeared to be in proportion to dose, frequency of use and the alcohol concentration of the mouthwash. Llewelyn (1994) expressed his concern at deregulation of mouthwashes in the United Kingdom, in that continual use for plaque removal may increase the risk of oral carcinoma, and called for warning labels on these products. A recent study by Maier et al (1993) demonstrated a relationship between poor oral hygiene and an increased risk of oral cancer in a matched case control study. Poor oral hygiene is related to social status and oral cancer is more common in social classes IV and V, so this finding is probably coincidental since cancers rarely arise in areas of oral sepsis (Cancer Research Campaign, 1993).

1.4 Screening

1.4.1 Principles of screening

Screening as a method of preventive medicine arose from the concept that treatment of diseases early in their development offered the best chance of cure or prevention of progression. Screening is defined as the application of a test or tests to people who are apparently free of the disease in question in order to sort out those who probably have the disease from those who probably do not. A screening test is not intended to
be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment (Wilson & Jungner, 1968). There are several situations in which individuals are screened:

1. Early diagnosis of a disease or 'pre-symptomatic screening'. The objective of this type of screening is to detect a disease (usually a cancer) more frequently at a pre-invasive phase or at an earlier stage of invasive disease than is usual in clinical practice (Shapiro, 1992). This should therefore interrupt the natural history of the disease and prevent progression to advanced disease and death (Chamberlain, 1993).

2 Protection of the public from infectious diseases, for example by the routine screening of immigrants.

3 Prior to entry into an organisation, for example train drivers with eye defects.

4 Protection of a work force, for example, protection against radiation in hospital radiographers by monitoring radiation badges.

5 Life insurance, by assessing those individuals who are more at risk of a disease by medical screening.

1.4.2 History of screening.

In Britain screening has been practised for the past 80 years in the regular
examination of children of school age and in routine post-natal care. Screening for endemic industrial diseases such as silicosis by chest x rays was also implemented around that time. Screening for pulmonary tuberculosis was introduced in 1943 and enabled treatment to be commenced at an earlier stage as well as removing the affected person from the community.

Screening for communicable disease became less important with the widespread use of antibiotics and increased medical knowledge, so that more emphasis was placed on non-communicable diseases such as cancer and heart disease. Screening for phenylketonuria was developed within the NHS in the mid 1950s, cervical cancer screening in the 1960s and trials for breast cancer screening commenced in the mid 1980s. The success of a screening programme is judged in terms of its cost-effectiveness and overall reduction in mortality and morbidity by prevention of the disease. For example, screening for phenylketonuria although uncommon (one in 20,000) was found to be cost effective since the cost of prevention was less than the cost of treating the established disease (Butler, 1993).

Screening for cervical cancer has been widely established throughout the United Kingdom and although overall time trends in mortality did not initially appear to be effected by screening, detailed analyses showed that 'in the absence of screening, an increase in mortality would have occurred' (Hakama, 1990). They stated that screening in the United Kingdom may have resulted in 'a 20-30 per cent reduction in risk of and mortality from cervical cancer'. The main problem is that 60% of women who develop cervical cancer have never been screened despite financial incentives by
the Government (Williams, 1992). Hakama (1990) stated that the reduction in risk is closely related to the organisation of the programme. This is certainly true in Finland where a population based, well organised programme with a wide target age range was established which resulted in a reduction of 60% in cervical cancer incidence. Breast cancer screening has been examined after 10 years of follow-up and it was found that although the reduction in mortality was 14-21% in those screened, the results were not statistically significant. In the screened population the number of patients with locally advanced disease and metastasis was found to be much lower (Alexander et al, 1994).

Targeting cancer may provide benefit to the whole population in terms of reduced health care costs but it is more likely that the benefit is at the individual level in terms of increasing that individual’s quantity and quality of life. In a review of screening Holland (1974) gave three reasons for screening; for preventing or treating a disease and equally important but often overlooked alleviating a disease which is beyond cure or prevention, for example, providing glasses or hearing aids.

1.4.3 Ethical and psychological problems associated with screening

It is generally accepted that if a screening programme is implemented there is an ethical obligation to ensure that it does more good than harm to the participant and that the adverse psychological effects are negligible (Flynn, 1991; Austoker, 1994b).

For example the lung cancer screening programme in the United Kingdom was
abandoned since it failed to show any benefits between the screened and unscreened populations in terms of cumulative mortality rates (Fontana, 1985).

Although the theoretical ideal of screening is justifiably beneficial there have been criticisms levelled from other health professionals (Mant & Fowler, 1990) who claim that 'screening has the potential to do more harm than good'. Marteau (1989) demonstrated high levels of anxiety in patients participating in screening programmes. She suggested that screening-related anxiety could be reduced by explaining why a particular patient had been selected and the benefits to that individual of being screened. Edwards and Hall (1992) stated that an individual should be able to provide informed consent prior to being screened.

Marteau (1990) also recommended that informing the screened individual of their screening result would reduce any adverse psychological effects. Lerman and Rimer (1993) found that the distress associated with receiving abnormal cancer screening results may interfere with participation in subsequent screening and diagnostic follow-up. They concluded that no screening programme should be initiated without planning how the communication of an abnormal result and its follow-up were to be dealt with. However a study, in which the psychological reactions to a melanoma screening programme were measured, showed no increase in psychosomatic problems, anxiety or false sense of security, but an increased subjective susceptibility to melanoma was demonstrated (Brandberg et al, 1993). In a study to investigate the adverse effects of mammographic screening the most significant effect was in those subjects who were recalled for a suspicious lesion and the authors called for accurate reading of all
mammographs in order to reduce recall for false positives. However no long-term
effects were found (Cockburn et al, 1994).

1.4.4 Screening for cancer

'Screening is now regarded as a cost-effective and clinically useful approach for the
eyearly diagnosis of several malignancies especially such diseases as breast and cervical
cancer.' (Miller et al, 1991).

Breast cancer screening

Mammography is the most effective method of screening for breast cancer. An
interval of 1-3 years is recommended and has been found to substantially reduce
breast cancer mortality in women aged 50 to 70 years of age. It has been found to be
cost-effective. In women less than 50 there appears to be minimal benefit. The aim
of the British Government is to reduce the rate of breast cancer deaths among women
invited for screening by at least 25% (from 95.1 per 100,000 to 71.3 per 100,000)
by the year 2000 (Department of Health, 1992).

Cervical cancer

Screening for cancer of the cervix by cytology has been found to be effective in
reducing the incidence and mortality of the disease (Hakama, 1990; Parkin et al,
1985; Adami et al, 1994). The ideal programme is one which is organised with
women entering at 25 years of age, with a screening interval of 3-5 years up to the age of 60. The aim of the British Government is to reduce the incidence of invasive cervical cancer by at least 20% (from 15 per 100,000 population to no more than 12 per 100,000) by the year 2000 (Department of Health, 1992).

Colorectal cancer

It is not yet determined whether removal of adenomas (possible precursors to colorectal cancer) has an effect on cancer incidence and mortality. Much work is being done in the field of faecal occult blood tests to assess their sensitivity and specificity. Targeting of high risk individuals (close relatives) is generally thought to be effective.

Ovarian cancer

There is little data on the effect of screening for ovarian cancer on mortality. However the five year survival rate is greater than 95% in patients whose cancer is limited to the ovary (Dembo et al, 1990) compared to approximately 10% in advanced disease (Kottmeier, 1982). Unfortunately like oral cancer the majority of patients (60%) present with advanced disease. There is a concerted effort to develop a screening system to diagnose ovarian cancer at a pre-clinical stage thus decreasing incidence and mortality.
**Malignant melanoma**

Screening for malignant melanoma is still at an early stage of development although it is gaining in momentum in countries such as Australia and New Zealand. When melanomas are detected at an early stage there is a high cure rate. The incidence is rising in the United Kingdom and there is a call for increased public awareness. The aim of the British Government is to halt the year on year increase of skin cancer by the year 2005 (Department of Health, 1992).

**Prostate cancer**

Screening is at a developmental stage since there are arguments about the sensitivity and specificity of the tests available (Denis *et al.*, 1995). Another problem is that it is a disease which effects the elderly and therefore may not be cost effective, however much research is needed to evaluate this fully.

1.5 **Screening for oral cancer**

A renewed interest in screening for oral cancer has been expressed in recent years, by the dental media and profession since it may be a simple and effective method of controlling a disease of high morbidity and mortality. Maloof (1984) listed several reasons why oral cancer is a lesion which is ideal for screening. The main consideration is that it is easy to detect at all stages of development and that early diagnosis results in simple treatment, better cosmetics and survival. In 1991, a UK
working group was organised to assess the possibility of screening for oral cancer and this resulted in a publication outlining the overall advantages and disadvantages (Speight et al., 1993). There have been several communications in the dental media highlighting the year on year increase in new registrations of oral cancer (Boyle et al., 1993; Renson, 1990; Hindle and Nally, 1991) and concern has been expressed at the large percentage of patients who present late for treatment. Hutchison (1994) lists the reasons for late referral as lack of knowledge by patients and professionals and the increased charges for dental treatment which deter people in high risk groups from attending for regular examinations.

Many groups have measured the prevalence of oral mucosal disease (Hogewind and van der Waal, 1988; Jorge et al., 1991; Ikeda et al., 1995a; Dombi et al., 1994; Kleinmann et al., 1993) but few studies have investigated screening for oral cancer. Few of these have assessed the validity of screening with some exceptions (Ikeda et al., 1988, Warnakulasuriya and Pindborg, 1990). A need exists therefore to assess screening in terms of its effectiveness and accuracy in detecting oral cancer at an earlier stage than would occur in normal clinical practice.

1.5.1 Screening tests for oral cancer

There are several methods to examine the mouth for oral cancer or precancer. It is important that the screening test is simple, cheap and acceptable. The three main methods described in the literature are discussed below. There are more advances being made in the field of genetic testing but this is still very developmental.
Visual examination

This method of screening for oral cancer is simple and involves a systematic examination of the oral soft tissues (Mock, 1985; British Postgraduate Medical Federation, 1991). The following procedure is recommended by the World Health Organisation (1980) for a thorough methodical examination of the mouth, using two mouth mirrors and a good light source.

Lips: examined when open and closed. Any variation in texture, colour or irregularities in the vermilion border are noted.

Lower and upper labial sulci and mucosa: examined with the mouth partially open noting any swellings or changes in colour of the oral mucosa.

Labial commissures, buccal mucosa, buccal sulci (upper and lower): the mouth mirrors are used as retractors and the mouth is wide open. The entire buccal mucosa is examined from the commissures to the anterior pillar of the fauces. Any changes in colour or mobility are noted and it must be ensured that the mirrors do not cover the commissures when retracting the buccal mucosa.

Alveolar ridges and gingiva: are checked both lingually and buccally.

Tongue: is examined initially at rest with the mouth partially open. The dorsum of the tongue is examined for any swelling, ulceration or changes in colour or texture.
of the surface and papillae. The tongue is then protruded and any abnormal mobility
is noted. The ventral surface is then examined similarly.

Floor of mouth: with the tongue elevated this area is examined for any changes in
colour or presence of ulcers.

Hard and soft palate: with the mouth wide open and the tongue depressed to allow
examination of the hard palate and soft palate.

The facial tissues should also be examined and the sub-mandibular and cervical nodes
palpated.

This technique should take about 3 minutes to complete. Roed-Petersen and Renstrup
(1969) designed a map of the oral mucosa to record any abnormalities detected by
clinical examination. In other studies the examiners indicated the area of abnormality
on a checklist (Downer et al, 1995).

_Toluidine Blue Dye_

Toluidine Blue is a member of the thiazine group of metachromatic dyes, which is
soluble in both water and alcohol (Strong et al, 1968). It primarily stains nucleic
acids which are present in large quantities in malignant, pre-malignant, ulcerated
and inflamed tissues. The technique was initially described by Rickart (1963) and has
been widely used to detect neoplastic areas on the cervix.
Several groups (Shedd et al, 1967; Myers, 1970; Mashberg, 1984) have suggested that toluidine blue can be used as an adjunct to oral cancer screening because of its ability to stain potentially malignant areas of the mouth. The toluidine blue dye can either be applied directly using a cotton wool tip to the suspicious area or used as a rinse. Mashberg (1984) quotes a sensitivity of 89.9% and specificity of 90.8% using a technique which involves two applications of the dye 10 to 14 days apart. Between applications, all possible irritants to the oral mucosa are removed to reduce false positives due to traumatic lesions. However another study (Miller et al, 1988) staining malignant and premalignant lesions in the hamster cheek pouch reported a false negative rate of 27.8% in detecting carcinomas and 95.2% in detecting carcinoma in situ and dysplasia.

It is possible that toluidine blue dye does have a place in detecting malignant and premalignant lesions of the mouth in patients following radiotherapy to detect possible recurrence or field changes but it is not considered to be a substitute for biopsy or close visual examination (Myers, 1970).

*Oral exfoliative cytology*

Oral exfoliative cytology is a method of obtaining a sample of epithelial cells either by scraping or rinsing the oral mucosa. Since Cahn (1965) found that malignant epithelial cells are less cohesive that normal epithelial cells, the presence of disease is easy to determine since malignant cells will be abundant in the exfoliate. Folsom et al (1972) demonstrated a false negative rate of 31% (sensitivity 69%) from oral
cytological scraping of any lesions detected on dental examination and concluded that although useful as an adjunct for diagnosis its limitations should be acknowledged. However Nicholls et al (1991) found that the sensitivity and specificity for brush cytology was high with low inter-observer variability and concluded that it may have a place as an aid to identifying clinically unsuspected cancers or precancers especially those with field cancerization. Vaillant et al (1994) demonstrated a 96% reliability with cytological smears. Ogden et al (1994) have developed sophisticated analysis techniques in analysing smears achieving a sensitivity of 0.70 (DNA profile) and 0.90 (keratin markers) and it is possible that it has a place in reviewing patients for field changes or possible secondary oral cancers. However the widespread opinion is that oral exfoliative cytology is unreliable since dysplastic epithelium is rarely superficial enough to provide an adequate cytological scrape (Scully, 1993).

1.5.2 Criteria for screening

Prior to the implementation of a screening programme several accepted criteria should be met (Wilson & Jungner, 1968). Interestingly these criteria fail to take into account any changes in quality of life which may arise from screening (Denis et al, 1995). The criteria are listed below and the arguments for oral cancer discussed.

The condition sought should be an important health problem.

The disease must be measured in terms of importance to both the individual and the community. Although oral cancer is a relatively uncommon disease in the United
Kingdom, with an incidence rate of 4 per 100,000 and 2,337 new registrations (OPCS, 1994), the consequences to the individual and the state in terms of morbidity and mortality are high. Communication from the Department of Health estimated inpatient stay for treatment of oral cancer cost over £8 million for 1990-91. This is probably a gross under-estimate since it excluded aspects unique to oral cancer such as speech therapy, dietician advice and rehabilitation post surgery. The overall five year survival rate, approximately 60% (Cancer Research Campaign, 1988) has remained unchanged for over 30 years despite advances in surgical rehabilitation (Stell and McCormick, 1985).

_There should be an accepted treatment for the screen detected lesion_

This is probably one of the most important aspects to be fulfilled since the patient will not benefit from the knowledge of having a disease for which there is no treatment. It is also essential that early detection of a disease actually affects the prognosis and outcome. There is evidence from a large European study of cancer of the head and neck that the prognosis of a small oral cancer is better than that of a large oral cancer (Platz et al, 1986). Evidence from another study (Silverman 1988) indicated that small lesions had a better prognosis. A problem encountered with oral cancer is lack of available information on the progression of precancerous lesions to oral cancer and this has led to wide divergence in modes of treatment of these lesions.
There should be adequate facilities for diagnosis and treatment

A pre-requisite of any screening programme is that there must be an established highly efficient mechanism already in place to deal with subjects who are screened positive. Oral cancer cases are usually referred to oral surgeons, ear nose and throat specialists, or plastic and general surgeons depending on the area and the referring practitioner. Over 60% of patients are referred by general dental practitioners with the remainder being referred by doctors (Scully et al, 1986). These centres of excellence are equipped to deal with oral cancer or precancer. There is a variety of investigations which referred patients may undergo to determine a definitive diagnosis. The accepted method is a biopsy but other tests may be used depending on the unit. It is generally accepted that a red, white patch or an ulcer which has been present for longer than three weeks should be biopsied (Hutchison, 1994; Scully, 1993).

There should be a recognisable latent stage or early asymptomatic stage

In order to be able to detect a disease at an early stage of its development there must be an asymptomatic or pre-cancerous phase. This is illustrated in figure 1.2. The ideal time to detect oral cancer would be at the latest point at which further progression could be prevented by treatment (Chamberlain, 1993) or by removal of risk factors such as tobacco (Gupta et al, 1986). This point of transformation is not yet known for oral cancer. However it is recognised that some oral cancer cases are preceded by a precancerous lesion and that this may make oral cancer amenable for
early detection. (Pindborg et al, 1991)

There should be a suitable test or examination

Screening is generally considered to be a filtering mechanism to identify any individuals at higher risk of a disease. Any screened subjects found to be positive are referred for follow-up for a diagnostic test. Screening must therefore be cheap, simple to use and valid in terms of sensitivity and specificity so that few patients are referred for unnecessary and expensive follow-up (Mock, 1985). For example, the screening test for colorectal cancer is relatively cheap but if a patient has a positive screen the diagnostic test (a colonoscopy) is usually in the region of a thousand dollars (Gordis, 1994).
Natural History of a cancer

Figure 1.2

- Biological onset of disease
- Symptoms
- Diagnosis
- Therapy
- Outcome

- Detectable preclinical phase
- Clinical
The test should be acceptable to the general population

The type of test offered to the population may effect uptake if it is perceived to be unpleasant or unsafe. It is also important that there is a public awareness of the disease in question so that the potential benefits of being screened are apparent. For example the treatment and adverse effects of breast cancer have a high profile in womens' magazines and breast cancer screening by self-examination and mammography is positively encouraged. Examining the mouth is generally accepted since almost everyone in the developed world will probably have had their teeth examined at some point in their lives. It is probably not regarded as an invasive technique compared to other screening tests. An oral examination is generally accepted as being neither unpleasant nor unsafe.

The natural history of the condition should be adequately understood

It is considered that the earlier oral cancer is detected the better the outcome in terms of morbidity and mortality. It is not always possible to detect cancer in its initial stages but there appears to exist a phase described by Miller (1985) as the detectable preclinical phase. He defines this as the point in time where a sensitive test will detect a disease before a patient would normally have developed symptoms, so called 'clinical surfacing' (Eddy, 1980). The more sensitive a test, the more likely it is to detect a disease closer to its initiation. In terms of oral cancer there are several states of precancer as described in section 1.3. The problem in the United Kingdom is that most cancers appear to arise de novo and the detectable preclinical phase may be
either microscopic, requiring sophisticated techniques to detect or a small cancerous lesion. Another problem is the unknown rate of progression from the precancerous state to the cancerous state. Speight and Morgan (1993) estimated that it may take up to 15 years for some white patches to develop into oral cancer. Detecting a white patch in a seventy year old may be of interest, but not of consequence, since treatment could not be justified either in terms of prevention or possible cost saving. This is an obvious problem in detecting oral cancer but with the incidence increasing in younger age groups, the argument for early diagnosis and treatment becomes stronger.

The aim of screening, as mentioned previously, is to detect cancer early. Treatment of small lesions of oral cancer results in five year survival rates in the region of 80% (Evans et al, 1982) and evidence from Platz et al (1986) shows a discernable difference in years gained from having a small cancer compared to a large one. The aim of screening in the United Kingdom is therefore to increase public knowledge and to detect oral cancer when it is small and can be successfully treated.

There should be an agreed policy on whom to treat as patients

Kleinmann et al (1991) called for an internationally agreed consensus on what should be considered a precancerous or cancerous lesion since this would allow for comparisons between different studies and countries. The World Health Organisation (1978) have defined a number of precancerous lesions and conditions related to oral cancer.
The cost of screening should be evaluated

There are no documented studies within the United Kingdom of the cost for oral cancer screening versus treatment of lesions. Downer and Speight (1993) described a method based on that formulated by Eddy (1986) which compares the effects of primary and secondary intervention in oral cancer in Sri Lanka.

The screening programme should be continued to allow full evaluation.

Once a screening programme has been implemented it is important to continue follow-up. Obviously the number of interval cancer cases will be less than at the initial screening but to fully assess a screening programme all cases must be taken into account to assess any reduction in mortality gained by screening.

1.6 Advantages of screening

Reduction in mortality

'The objective of screening is to reduce the risk of death from the disease being screened for' (Hakama, 1990).

Adami et al (1994) compared the survival rates from invasive cervical cancer between 1960-64 (pre-screening) and 1980-84 in Sweden. They found that screening reduced mortality by more than half in women less than 40 years of age. In older women
(where screening was less extensive) there was only a slight improvement between 1960-4 and 1980-84. They concluded that although there may be other explanations for the better five year survival rates over the 20 years the most obvious explanation appeared to be that screening reduced mortality by earlier diagnosis of invasive disease.

Blamey et al (1994) stated that mortality can be reduced up to 40% in women who attend for screening and that the overall reduction in breast cancer mortality in Sweden over a 12 year follow-up period was 29% in women greater than 50 and 13% in women less than 50 years of age. Early results from the UK Trial of Early Detection of Breast Cancer Group (1988) found that screening could achieve a 'worthwhile mortality reduction'.

In the field of colo-rectal cancer Smart (1992) stated that mortality could be reduced by 30% by screening with faecal occult blood tests. Eddy (1985) in a review of the value of screening for cancer in adults concluded that the evidence that screening reduced mortality was strongest for breast cancer, suggestive for cancer of the cervix and colon and theoretical for cancer of the endometrium and oral cavity.

Humphrey (1989) predicted that prevention and early detection programmes could double the survival rate from some cancers. Certainly this would be true for oral and ovarian cancer.
Reduction in the incidence of invasive cancers

Parkin et al (1985) investigated the impact of screening on the incidence of cervical cancer in England and Wales and found that there was a substantial reduction in cases in women aged 35-64 attributable to screening. As mentioned previously, population screening in several Nordic countries has reduced the incidence of invasive cervical cancer (Miller, 1985). Adami et al (1994) concluded that cytology screening improved prognosis of patients with cervical cancer and suggested that further research was required as to whether it was due to diagnosis of preclinical disease or earlier diagnosis of symptomatic disease.

In the field of breast cancer screening the screen detected cancers tend to be smaller and non-invasive compared to the symptomatic cancers (Blamey et al, 1994).

Other advantages

Screening enables the identification of high risk individuals thus providing opportunities for early intervention. For example, changing the tobacco habits of a patient with oral leukoplakia may result in resolution of the lesion (Roed-Petersen, 1982; Gupta et al, 1995).

By reducing the incidence of invasive cancers the prognosis of individual patients should improve not only in terms of mortality but also morbidity. Most small cancers require less surgery leading to a more successful and rapid recovery compared to
large cancers. Less invasive treatment will also be cheaper. However, the obvious benefits from screening and earlier diagnosis and successful treatment can be assessed not only in terms of financial cost but in also terms of the benefits of restoring a person back to normal family and working life, which are probably immeasurable.

1.7 Disadvantages of screening

Selection bias

The more health aware an individual is the more likely they are to attend a screening programme. This may influence the outcome of the screening programme. This phenomenon is favourable for screening for breast cancer since this is more commonly found in patients of social classes I and II and this group are more likely to seek preventive care. In screening for cervical cancer the uptake is low since it is more prevalent in the lower social classes (Williams, 1992). Oral cancer occurs up to three times more frequently in social class V compared to social class I (Townsend et al, 1988).

Length bias

This is related to the natural history of the disease which may be unique to each individual patient. For example, a disease with a short preclinical phase is more likely to have a short clinical phase. A screening programme is more likely to detect disease with a long preclinical phase. It is thought that diseases which have a long
preclinical phase have a long clinical phase and therefore have a better prognosis. It is possible therefore that in these cases, screening may have little benefit. This is a problem in screening for neuroblastoma. There is a variety of different types of neuroblastoma. Some have a good prognosis and may regress spontaneously, therefore screening offers no benefit. Conversely there are types which are aggressive with short preclinical phases which are less likely to be detected by screening (Gordis, 1994).

Lead time bias

This argument relates to the benefit that a patient may derive by being diagnosed at an earlier stage of their disease so that the actual survival time may appear to be longer than if the patient had clinically surfaced by self presentation (Eddy, 1980). One may argue that time spent in ignorance of the disease and free of medication may have been deprived by screening. Therefore in order for this bias to be minimised it is important that there is a noticeable increase in survival and quality of life by detecting a disease early.

Over-diagnosis bias

This bias is introduced by assuming that all lesions detected require treatment. Since rates of progression of cervical cancer are not known most screen detected lesions are treated, but it is thought that some premalignant states may regress spontaneously meaning that treatment was not required.
In the case of oral cancer, at least 15% of oral leukoplakias regress spontaneously but the reasons for regression are not known. It would be considered negligent to leave a leukoplakia untreated assuming it to be one of the 15% which may regress. A major problem in screening for any type of cancer is the lack of absolute knowledge of progression and regression rates for precancerous lesions (Speight and Morgan, 1993). It could be argued that these lesions must be treated, since a 'wait and see' policy would defeat the objective of early detection if a lesion were allowed to progress. Further studies of disease progression are therefore essential in order to truly assess the value of detecting and treating precancerous lesions.
Chapter 2

Aims
2.1 Summary of aims

The overall aim of this study was to evaluate the possible benefits of screening for oral cancer. When assessing the outcomes of screening there are certain aspects which must be assessed and since these had not been previously been measured in a Western population the following aims were set:

1. To obtain values for the sensitivity and specificity of an oral cancer screening test.

2. To assess the uptake rate of an invitational screening programme

3. To evaluate a potential training method for screeners.

4. To investigate methods of selective screening from high risk habits.

5. To compare patients treated for small and large cancers to determine whether there is an advantage in detecting cancers at an earlier stage.

6. To investigate the general public's perception of oral cancer.

7. To investigate the potential benefits of screening by construction of a decision pathway using the data gathered from the above projects
Chapter 3

Evaluation of a screening test

for oral cancer
3.1: Introduction

3.1.1 A screening test for oral cancer

'Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment' (Wilson and Jungner, 1968).

There are essentially three methods of screening for oral cancer, looking (visual examination), scraping (exfoliative cytology) or staining (Toluidine blue). These three methods have been discussed in Chapter 1. In evaluating a screening programme it is important that the screening test is simple and able to detect cancer at an earlier stage than would be usual in clinical practice (Shapiro, 1992). When deciding which method to use for this project, the advantages and disadvantages of each were considered.

The general consensus of opinion on oral exfoliative cytology is that the smears taken may not provide a true representation of the oral mucosa since they tend to be too superficial. In a screening programme this would result in a large number of false negatives. Also the decision on which areas to smear in clinically normal mucosa would be impossible. Ogden et al (1991) quantified the cytoplasmic and nuclear areas of cells from oral cancer and normal mucosa and concluded that cytology may have a place in detecting secondary oral cancers. However they found that there were
no changes in these measurements associated with tobacco or alcohol use which would have been useful in identifying individuals at high risk of oral cancer.

Ogden et al (1993) demonstrated a difference in the keratin profiles in smears taken from malignant and normal sites in the mouth. This is an immunocytochemical staining technique which thus incurs extra cost to an otherwise cheap process. For these reasons it was decided not to use oral exfoliative cytology for this screening programme.

Toluidine blue or other staining methods (Lugol’s iodine) would appear to offer a more promising screening test. Although there have been several studies measuring the sensitivity and specificity of toluidine blue in detecting oral precancer and cancer, there appears to be much variation (Reddy et al, 1973; Mashberg, 1981; Silverman et al, 1984). The main problems anticipated in this study were that the use of toluidine Blue is technique sensitive, expensive and time consuming. However, with experience these problems would be reduced but the cost element would still persist. Epstein et al (1992) concluded that the routine use of toluidine blue could not be recommended despite the high sensitivity (0.93) and specificity (0.63) demonstrated in their study. This reasoning was based on the low incidence of oral cancer and precancer in the general population and the problems that false positive screens may present in terms of increased work-load and psychological trauma to subjects (Marteau, 1990).

In the present study it was therefore decided to evaluate visual examination as a method to screen the mouth (WHO, 1980). It is cheap and simple in that materials
and time used are minimal. A selection of dentists volunteered to act as screeners. This provided the opportunity to evaluate current best practice in oral examination and the potential screening potential of general dental practitioners since no additional training was provided. It is also important that the test is acceptable to the screened population and most people will have had their mouths dentally examined at some point in their lives. Few studies have attempted to evaluate the effectiveness of oral cancer screening (using a visual examination as the screening test) in terms of sensitivity (proportion of true positives) and specificity (proportion of true negatives). Sensitivity and specificity are expressions of the validity of the test (Appendix I). Other studies of oral mucosal conditions have tended to establish the prevalence of oral cancer and precancer (Bouquot and Gorlin, 1986; Hogewind and van der Waal, 1988; Kleinmann et al, 1991, Dombi et al, 1994) and the effects of primary intervention (Gupta et al, 1986) rather than screening per se. Recently several industrial firms have taken the initiative and are promoting screening programmes for their employees (Downer et al, 1994; Feaver, 1990) and the possibility of mouth self examination is also being evaluated (Mathew et al, 1995).

3.1.2 Methods of recruitment

With increasing emphasis on preventive medicine there is much interest in the most effective methods of recruiting participants into screening programmes. Subjects can be recruited either by an invitational or opportunistic approach.

Opportunistic screening within general medical and dental practices where patients are
invited to be screened during a routine consultation has been advocated as a low cost intervention. The potential would seem to be great given that over 90% of patients consult their doctor at least every five years (Fowler and Mant, 1990) and that 60% of people over 35 years in England and Wales are registered with a dentist (Dental Practice Board, 1994). However a recent study in the United States revealed that only 14.3% of respondents in a survey of over 12 000 people had been examined for oral cancer by their dentist, physician or hygienist (Anonymous, Morbidity, Mortality Weekly report, 1994). Reasons for opportunistic screening not being effective in medical practice and to some extent dental practice may be due to lack of time and the patient being too ill to participate. Heywood et al (1994), found that very few patients actually at risk of cancer were offered preventive intervention by their doctor.

Invitational screening is a more active approach in which the subject is invited to attend for screening usually by letter or telephone. This method of recruitment is considered to cover a wider spectrum of people and not just the 'worried well' and regular attenders of medical or dental practices. In this study it was decided to investigate the uptake from an invitational method of recruitment since no previous studies in the United Kingdom have been undertaken. An opportunistic method of screening was used within the hospital group but it would not have been possible to accurately measure compliance.
3.1.3 Classification of social class

There is much evidence to suggest that participation in preventative programmes, including screening, is poor in the lower socioeconomic groups (Champion, 1992; Roetzheim et al, 1993; Nicoll et al, 1991; Koh et al, 1991a; Mills et al, 1994). Early presentation for treatment of cancer is also unusual in the uneducated and lower social groups (Mandelblatt et al, 1991; Richardson et al, 1992; Kogevinas et al, 1991; Vineis et al, 1993). Most cancers exhibit a positive social class gradient with higher incidence in manual workers compared to professionals. Exceptions include breast cancer and malignant melanoma which are more common in professional classes and, not surprisingly, attendance in breast and skin screening programmes is high (Ross et al, 1994; Koh et al, 1991a).

Greenberg et al (1991) related social instability to an increased risk of oral cancer, whilst Reichard et al (1993) found that late diagnosis and poor prognosis for tongue cancer was related to the low socioeconomic status of their patients. Townsend et al (1988) stated that men in Social Class V are more than three times more likely to die from lip, oral or pharyngeal cancer than those in Social Class I. Poor nutritional status (found in lower socioeconomic groups) is considered to a contributory factor for oral cancer and this may explain the association (La Vecchia et al, 1991). As part of this study an attempt was made to investigate the influence of socioeconomic groups on attendance for screening for oral cancer in the absence of any other similar studies.

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There are a number of generally accepted methods for analysing the social profile of a group of individuals and some of these are described below:

3.1.3.1 Registrar General’s classification of social class

This system was developed at the turn of the century and classifies individuals (and their dependants) on the basis of their present occupation or previous one in the case of unemployed people. It was originally introduced to analyse variations in demographic statistics, in particular infant mortality. There are five social classes: professional (I), intermediate (II), non-manual and manual (III), semi-skilled (IV) and unskilled manual (V). It is easy to use since it only depends on occupation rather than asking about income or education. It is widely employed in the United Kingdom in surveys such as the General Household Surveys (OPCS, 1990). However it ignores such factors as ethnicity and the partner’s occupation.

3.1.3.2 ACORN: A classification of residential neighbourhoods

This system was originally developed for market research by CACI Ltd. It applies census statistics and classifies geographical areas of households into 38 different neighbourhood types, which have been refined into six large groups identifying different patterns of consumer behaviour. Its main advantages are that it only requires postcodes for usage and it depends on a large number of variables rather than just the occupation of the head of the household. It is only as up to date as the current census,
which could be up to ten years old.

3.1.3.3 The Jarman Index

This index was developed by Jarman (1983) from questioning general practitioners in London and organisations connected with the health service about their workload. He then derived eight factors for his index which would indicate urban deprivation. Like ACORN, it is only as current as the last census and since the areas used are electoral wards, the sizes can vary considerably. It has been used for measuring general medical practitioners workload and for planning health care.

In this study ACORN was used to determine the socioeconomic group of each patient registered with the medical practice targeted in the oral cancer screening programme. ACORN has been used in other studies to relate dental health to social class (Elley and Langford, 1993). In this study it was used to relate social class to compliance. The ACORN data were compared with OPCS data on the distribution of social classes within the wards covered by the medical practice. The OPCS data are based on the Registrar General's classification of social class.

3.1.4 Statistical evaluation of screening

Since the aim of screening is to determine those who probably have disease from those who probably do not, it is important to evaluate the ability of the screening test to detect abnormalities. Wilson and Jungner (1968) discuss several criteria which need
to considered when evaluating a screening test. These are discussed below.

3.1.4.1 Validity

The validity is defined as the ability of a test to separate out those with the disease from those without. By applying a screening test to a sample of people, a subject can be categorised as follows:

True positive: with disease and with positive test
True negative: without disease and with a negative test
False positive: without disease and with positive test
False negative: with disease and with a negative test

If the screening test was ideal it would be able to correctly identify all those people with disease and those without. However no screening test which relies on an element of judgement is ideal and this introduces the concept of sensitivity and specificity.

3.1.4.2 Sensitivity and Specificity of the test

This is a standard approach by which to measure the proportions of patients who are correctly categorised by the test. The proportions are known as the sensitivity and specificity of a test and are expressions of its validity (Downer, 1994; Altman and Bland, 1994a) (see Appendix I).
Sensitivity can be defined as the proportion of true positives correctly diagnosed by the test or as a measure of the probability of correctly diagnosing a case. Sensitivity is often referred to as the detection rate of the test (Wald, 1994). This is not necessarily synonymous with the detection rate of a screening programme since many individuals in the target population may not come forward for screening.

Specificity can be defined as the proportion of true negatives correctly identified by the test, or as a measure of the probability of correctly identifying a non-diseased person. The false positive rate is the proportion of unaffected individuals with positive results and is often used to express the specificity. It is calculated as 1 - specificity and expressed as a proportion or a probability of false-positive registration.

Since all these measures are expressed as proportions it is possible to calculate confidence intervals for them (Altman, 1991) and hence undertake hypothesis testing and statistical comparison. The sensitivity and specificity of a test will alter if the criteria by which a subject is defined as negative or positive is changed. Another aspect which will effect the success of a screening test is its reliability which is dependent on both variation in the implementation of the test and the person performing the test. In this study the screening test was easy to apply and not particularly technique sensitive which meant that any changes in reliability would probably be observer related.
3.1.4.3 Positive and negative predictive values

It is also important to know the probability that the test will give a correct diagnosis (Altman and Bland, 1994b) and this is calculated by using predictive values.

Positive predictive value: is the proportion of patients with positive test results who actually have the disease.

Negative predictive value: is the proportion of patients with negative test results who do not have the disease.

The predictive values of a test are dependent on the prevalence of the relevant disease in the population screened. The yield which is the measure of previously unrecognised disease found through screening is also related to the prevalence.

3.1.4.4 The likelihood ratio

The likelihood ratio (Radack et al, 1986) can be used to assess the clinical utility of test results. It compares the probability of obtaining a certain result if the patient was affected, with the corresponding probability if the patient was unaffected. It is calculated as sensitivity/false positive rate. The likelihood ratio indicates the value of the test for increased certainty about a positive diagnosis (Altman, 1991).
3.1.5 Aims

The aims of this component of the study were:

1. To measure the sensitivity and specificity of an oral examination for the detection of lesions which may be associated with oral cancer or precancer.

2. To measure the compliance rate in a defined population and to consider the acceptability and feasibility of invitational screening for oral cancer.

3. To determine the social structure of the defined population (patients of a medical practice) and of non attenders and attenders in this population.
3.2 Materials and Methods

3.2.1 The target group

The screening programme took place at two separate sites; a dental hospital and a neighbouring inner city medical practice. All men and women were considered eligible for screening if they were aged 40 years or over. The hospital group comprised patients and eligible relatives and friends attending on that day. For the medical practice, a list of registered patients was obtained from the local Family Health Services Authority (FHSA). There were 4348 patients aged 40 years or older on the medical practice list. The list contained details of the name, address, and date of birth of each patient.

3.2.2 Recruitment of subjects from the medical practice

All eligible patients (those aged 40 years and over) who were registered were invited to attend for mouth screening by postal invitation which included a fixed appointment at the medical practice. This was part of a large health centre with a community dental clinic on site. Patients were also offered an alternative open screening appointment during the day at a nearby dental hospital, an open evening at the medical practice or the opportunity to change the time by telephone, if their appointment was not convenient. To minimise anxiety (Marteau, 1990) the letter was sent from the medical practice and explained that the subject’s name had been obtained from their general practitioner as part of a mouth screening study for all
patients aged 40 years or over. The invitation also included an information leaflet.

After the first round of invitations, a second invitation was sent out in a slightly different format to the 3167 subjects who had failed to respond to the initial invitation. These remaining subjects were randomly divided into two approximately equal groups. One group received only a reminder and an appointment card, whereas the other received an appointment and an additional information leaflet. This was published by the British Dental Health Foundation (1991), and contained more explicit information about mouth cancer, including risk factors and the importance of early diagnosis. The decision to have two rounds of invitations was to allow for holidays and to follow the customary format of other screening programmes. The second invitation was sent six weeks after the first.

3.2.3 Recruitment of subjects from the hospital

At the dental hospital there were specific screening sessions where subjects were recruited from the various out-patient departments of the hospital. All adult out-patient departments and accompanying parents of children attending the orthodontic department were approached and asked to volunteer for the programme. They were given the same information leaflet as the medical practice group.

3.2.4 Information given to subjects

The subjects at both sites received the same information leaflet explaining the nature
of oral cancer, its associated risk habits, the screening method and the advantages of
being screened (Appendix 2). Advice on the format of the information leaflet was
obtained by personal communication with the Health Education Authority
(T Pemberton; London) and a dental psychologist (T Newton; UMDS) and was based
on the format of existing breast and cervical cancer screening leaflets. At both sites,
posters were displayed and information leaflets advertising screening sessions and
their times were available at all patient reception areas (Appendix 3; poster). The
information leaflet explained the screening process, and outlined the benefits of a
healthy mouth and the importance of early diagnosis of oral cancer.

3.2.5 The screening test

The screening test comprised a thorough visual examination of the surface of the oral
mucosa (British Postgraduate Medical Federation, 1991, Mock, 1985). The actual
procedure has been described in detail in Chapter 1. The examination took place in
a dental chair, using two mouth mirrors and a good light.

A subject was defined as positive when a white patch, a red patch or an ulcer which
had been present for more than two weeks was detected. A number of well defined
clinical entities which might have this appearance were designated as positive (Table
3.1)(Speight et al, 1992):
Table 3.1  Lesions classified as positive

<table>
<thead>
<tr>
<th>Positive lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>Erythroplakia</td>
</tr>
<tr>
<td>Leukoplakia</td>
</tr>
<tr>
<td>Lichen Planus</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
</tr>
<tr>
<td>Submucous fibrosis</td>
</tr>
<tr>
<td>Actinic keratosis</td>
</tr>
</tbody>
</table>

3.2.6 Selection of screeners

There were 24 voluntary screeners in total. Of these 10 were junior hospital staff, 3 were community dental officers, 4 were general dental practitioners and 7 were second year orthodontic students. The screeners were advised of the diagnostic criteria which should result in a positive or negative screen but apart from this no formal training or standardisation was undertaken. The screeners were not given any feedback on their performance until the completion of the study.

3.2.7 The specialist

Each subject was examined independently by a second more experienced dentist (the 'specialist'), who was able to refer subjects for further tests or review as appropriate, in order to establish a definitive diagnosis. The results were recorded on a standard form (Appendix 4) which was collated with the screeners’ form only after completion.
The specialist was unaware of the screeners' reported findings and provided the definitive diagnosis or gold standard for each subject. This was used to assess the sensitivity and specificity of the screeners.

3.2.8 The screening procedure

The actual screening procedure is outlined in figure 3.1. All participants were invited to take part in the screening programme either by direct approach (opportunistic) or letter (invitational). All subjects were provided with the same information. Informed consent was obtained from all participants. Prior to screening, all subjects completed a questionnaire (Appendix 5) concerning their age, gender, smoking and drinking habits, and dental attendance. This information was subject to further analysis (Chapter 3). After completing the relevant paperwork each subject was examined by one of the screeners. The results were recorded on a standard pre-numbered form (Appendix 6). When the screener had finished, the subject was examined independently by the specialist who notified them of their screening result and whether referral was necessary. At the end of each screening session, the questionnaire, screener and specialist forms (Appendix 4, 5, 6) for each individual were collected by the specialist.
Figure 3.1  

Screening procedure

Invitation

Information  
oral
leaflet

Consent

Questionnaire

Examination by screener

Examination by specialist

Referral if necessary

3.2.9  Referral procedure

If a subject was diagnosed as negative by the specialist (no precancer or cancerous lesions were detected) they were told immediately. All smokers and heavy drinkers were advised of the risk of oral cancer from their habits. Patients requiring treatment or further follow-up were advised of this and were given an appointment to attend at the dental hospital where they were reviewed by the specialist and a consultant oral physician and underwent biopsy and treatment as appropriate. The group requiring
referral contained both positive subjects and subjects classified as negative for oral cancer and precancer but who required treatment for benign pathology. No follow-up was arranged for subjects screened negative but all participants were advised to attend for a routine dental examination on a yearly basis.

3.2.10 Deriving the sensitivity and specificity of the test

Since there was a large variation in the number of subjects screened by each screener the results from all the screeners were pooled to calculate the overall sensitivity and specificity of the screening test. This analysis was repeated after excluding eight screeners who had not seen any positive subjects and the results were unchanged. However, since one third (eight) of the screeners were not exposed to any positive subjects it was not possible to calculate their sensitivity values individually.

3.2.11 Compliance and attendance (medical practice study)

Compliance was measured after the first and second rounds of postal invitations. Notified non-attenders were those who gave reasons for non-attendance. Non-responders were those subjects who failed to respond to two letters of invitation and did not attend for screening (McEwen et al, 1989). For the second round of invitations, (section 3.2.2), the proportion of attenders and non-attenders in each group were compared to see if the information leaflet had any effect on compliance. A null hypothesis was proposed that the proportions of attenders in the group receiving the invitation letter would be equal to that of the group receiving the letter
and information leaflet. By calculating the difference in the observed proportions and the standard error of the observed difference, a standard normal deviate (z value) was obtained. Confidence intervals were calculated using these values.

3.2.12 Classification of social class

The postcodes of all patients were analysed by ‘ACORN’, a commercially available service which provides A Classification Of Residential Neighbourhoods (ACORN Analysis, 1983). This information was used to obtain a socio-economic profile of the invited practice population. The frequency distribution in each ACORN group for non-attenders and attenders was compared statistically. The same statistical technique as described in section 3.2.11 was used. In this analysis, the null hypothesis proposed was that the proportions of attenders in each social group would not differ. A standard normal deviate was calculated enabling confidence intervals for the observed difference in proportions to be calculated.

A list of the electoral wards covered by the medical practice was obtained from the Family Health Services Authority. The social class distribution of each of these wards was derived from the Office of Population Censuses and Surveys (OPCS). Since OPCS data included all age groups it was not possible to analyse compliance on this basis since too many incorrect assumptions would have had to be made. These data were only used to compare the distribution of social class within the medical practice according to the ACORN and the Registrar General’s classification systems.
3.3 Results

3.3.1 Population profile

The population profile is shown in Table 3.2. All subjects were aged 40 years or over. The arithmetic mean was 57.21 but since the data were skewed (figure 3.2) it was not considered advisable to calculate confidence intervals around this mean. The geometric mean was therefore calculated by log transformation of the data, resulting in a value of 56.01 years (95 per cent CI, 55.47-56.48). Forty four per cent of the population were male and 56 per cent female. Seventy one per cent of subjects claimed to have attended a dentist during the previous twelve months.

Table 3.2 Profile of screened population

<table>
<thead>
<tr>
<th></th>
<th>Medical practice</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>(985)</td>
<td>(1042)</td>
<td>(2027)</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>59.85</td>
<td>54.8</td>
<td>57.21</td>
</tr>
<tr>
<td>Gender</td>
<td>47% M, 53% F</td>
<td>42% M, 58% F</td>
<td>44% M, 56% F</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>&lt; 1 yr: 57%</td>
<td>&lt; 1 yr: 85%</td>
<td>&lt; 1 yr: 71%</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 yr: 43%</td>
<td>&gt; 1 yr: 15%</td>
<td>&gt; 1 yr: 29%</td>
</tr>
</tbody>
</table>
Distribution of the invited practice population by age.

(Figure 3.2)
The results of the screening programme are summarised in Table 3.3. A total of 2027 individuals received a screening examination of which 1967 were screened negative and 60 screened positive. All subjects were examined by a specialist who provided an independent definitive diagnosis (gold standard). The true prevalence of positive lesions in the subjects screened was 2.7 per cent (54 lesions). The sensitivity was 0.74 (95 per cent CI, 0.62-0.86), specificity, 0.99 (95 per cent CI, 0.985-0.994) and positive and negative predictive values, 0.67 and 0.99 respectively.

The results from the two sites were similar and are given in Tables 3.4 and 3.5 Nine hundred and eighty five subjects were screened in the medical practice and 1042 in the hospital, the prevalence of positive lesions was 2.2 per cent (22 lesions) and 3.0 per cent (32 lesions) respectively.

The definitive diagnosis provided by the specialist resulted in 54 positive findings: two cases of squamous cell carcinoma and one basal cell carcinoma, 18 leukoplakias, 31 cases of lichen planus and two of lupus erythematosus. All the carcinomas were detected by the screeners but fourteen subjects with potentially malignant lesions were missed. These were five with leukoplakia, and nine with lichen planus. There were 20 false-positives, which the screeners recorded as lichen planus (15), ulceration (two), leukoplakia (two) and one pigmented lesion. The distribution of positive lesions between the two screening sites is shown in table 3.6.
Table 3.3  Agreement between screeners and specialist - all subjects.

<table>
<thead>
<tr>
<th></th>
<th>Specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screener</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>40</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
</tr>
</tbody>
</table>

Sensitivity = (40/54) = 0.74 (95 per cent CI, 0.62-0.86)

Specificity = (1953/1973) = 0.99 (95 per cent CI, 0.985 - 0.994)

Positive predictive value  = (40/60) = 0.67

Negative predictive value = (1953/1967) = 0.99
Table 3.4  
Agreement between screeners and specialist - medical practice subjects.

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Positve</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screeners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>955</td>
<td>963</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>963</td>
<td>985</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{14}{22} = 0.64 \) (95 per cent CI, 0.44-0.84)

Specificity = \( \frac{955}{963} = 0.99 \) (95 per cent CI, 0.984 - 0.996)

Positive predictive value = \( \frac{14}{22} = 0.64 \)

Negative predictive value = \( \frac{955}{963} = 0.99 \)
Table 3.5  Agreement between screeners and specialist - hospital subjects.

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screeners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>998</td>
<td>1004</td>
</tr>
</tbody>
</table>

Total 32 1010 1042

Sensitivity = (26/32) = 0.81 (95 per cent CI, 0.67-0.95)

Specificity = (998/1010) = 0.99 (95 per cent CI, 0.984 - 0.996)

Positive predictive value = (26/38) = 0.68

Negative predictive value = (998/1004) = 0.99
Table 3.6    Distribution of lesions between screening sites

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Medical practice</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Lichen Planus</td>
<td>13</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Lupus erythematosis</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Of the 4348 invitations sent out, there were 522 notified non-attenders and 2841 subjects who did not respond at all. Of the 3826 eligible attenders 985 (25.7%) accepted the invitation for mouth screening. There was no significant difference between the numbers or proportions of males (479; 21%) and females (506; 24%) who attended. The breakdown of attendance by age group is shown in Table 3.7. The 522 notified non-attenders are detailed in Table 3.8, these included those who could not be contacted and those who refused for reasons of ill-health, immobility or other, unspecified, reasons.

ACORN classification of the patients at the medical practice resulted in 4 (A, C, E, F) of the 6 (A to F) possible classifications (Table 3.9), with over 98% of the population being in either group C or F. Groups A and E were excluded from any analysis since the numbers of patients in each group were small. The numbers of patients in groups C and F, and the number of attenders in each group is shown in Figure 3.3. The true proportion of attenders in each ACORN group after correction of notified non-attenders was 20.3% (411/2022) in C and 24.8% (566/2274) in F. The observed difference was thus 4.5% (24.8% - 20.3%); 95% confidence intervals of 2.1% - 7.1%. Although this was found to be statistically significant (SND = 3.56, p < 0.001), the actual numerical difference between the groups was only 155 patients.
Distribution of subjects by social class (ACORN)

(Figure 3.3)

- Attenders: Total number of patients in each group

SND = 3.56, 95 per cent CI, 2.1% - 7.1%

P < 0.001
Table 3.7. Distribution by age of subjects obtained from the FHSA register and acceptance of invitations to screening (first and second rounds combined)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total</th>
<th>Acceptance</th>
<th>Response rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>609</td>
<td>139</td>
<td>22.8</td>
</tr>
<tr>
<td>45-54</td>
<td>1069</td>
<td>246</td>
<td>23.0</td>
</tr>
<tr>
<td>55-64</td>
<td>939</td>
<td>260</td>
<td>27.7</td>
</tr>
<tr>
<td>65-74</td>
<td>873</td>
<td>211</td>
<td>24.2</td>
</tr>
<tr>
<td>75-84</td>
<td>562</td>
<td>109</td>
<td>19.4</td>
</tr>
<tr>
<td>85-94</td>
<td>241</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>95-104</td>
<td>50</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>105-114</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>115-124</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All groups</td>
<td>4348</td>
<td>985</td>
<td>25.7 (*)</td>
</tr>
</tbody>
</table>

First mailing = 659
Second mailing = 326
Total = 985

* corrected for 522 notified non-attenders (985/3826)
Table 3.8 Details of the notified non-attenders

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to sender</td>
<td>329</td>
</tr>
<tr>
<td>Dead</td>
<td>36</td>
</tr>
<tr>
<td>Other reasons*</td>
<td>65</td>
</tr>
<tr>
<td>Not interested</td>
<td>65</td>
</tr>
<tr>
<td>Visits Dentist</td>
<td>27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>522</strong></td>
</tr>
</tbody>
</table>

*Other reasons includes patients who could not attend due to ill health or immobility.
Table 3.9. ACORN classification of the invited subjects compared to that of the United Kingdom.

<table>
<thead>
<tr>
<th>ACORN</th>
<th>Defining factors</th>
<th>Study%</th>
<th>UK%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Thriving, wealthy achievers prosperous pensioners</td>
<td>0.2</td>
<td>19</td>
</tr>
<tr>
<td>B</td>
<td>Expanding, affluent families</td>
<td>0</td>
<td>10.4</td>
</tr>
<tr>
<td>C</td>
<td>Rising, prosperous urbanites</td>
<td>46.5</td>
<td>9</td>
</tr>
<tr>
<td>D</td>
<td>Settling, Skilled workers mature home-owners</td>
<td>0</td>
<td>24.5</td>
</tr>
<tr>
<td>E</td>
<td>Aspiring, white collar better off ethnic areas</td>
<td>0.7</td>
<td>13.9</td>
</tr>
<tr>
<td>F</td>
<td>Striving, low income high unemployment</td>
<td>52.3</td>
<td>23.1</td>
</tr>
</tbody>
</table>
According to the Family Health Services Authority computer records there were 10,395 patients registered with the medical practice of whom 9491 reside in a particular electoral ward in the Camden and Islington area. This included all patients of the practice and not just those aged 40 years or greater. Although the patients were distributed throughout 34 wards, 89.8% lived in one of six wards. For this reason only the social classes of these wards were analysed. These tables do not include those classified as economically inactive (people who have retired, students, the permanently sick or persons looking after the family). All the figures are taken from table 90 of the 1991 census, based on a 10% sample of each ward. Table 3.10, defines the social class according to the OPCS. Table 3.11 contains the breakdown of the medical practice by electoral ward. The predominant social class appeared to be social class II. This table can only be taken as a general description of the patients of the medical practice as a whole since as noted above, it also contains all patients aged under 40 years. At the same time, the actual proportion of the population from each ward who were registered with the practice was not known. Table 3.12 contains all the data from all the wards covered by the medical practice, and social class II appeared to predominate.
Table 3.10  Registrar General Classification of social class

<table>
<thead>
<tr>
<th>Social Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Professional occupations</td>
</tr>
<tr>
<td>II</td>
<td>Managerial and technical</td>
</tr>
<tr>
<td>IIIN</td>
<td>Skilled occupations - non-manual</td>
</tr>
<tr>
<td>IIIM</td>
<td>Skilled occupations - manual</td>
</tr>
<tr>
<td>IV</td>
<td>Partly skilled occupations</td>
</tr>
<tr>
<td>V</td>
<td>Unskilled occupations</td>
</tr>
<tr>
<td>Armed</td>
<td>Armed forces</td>
</tr>
<tr>
<td>Govt</td>
<td>On a government scheme</td>
</tr>
<tr>
<td>Inadequate described</td>
<td>Occupation inadequately described or not stated</td>
</tr>
<tr>
<td>Not worked &gt; 10 years</td>
<td>Head of household has not worked for over 10 years</td>
</tr>
</tbody>
</table>
Table 3.11  The main six wards covering 89.8% of the medical practice
(Barnsbury, Bunhill, Clerkenwell, St Mary, St Peter and Thornhill)

<table>
<thead>
<tr>
<th>Social class</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>125</td>
<td>9.8</td>
</tr>
<tr>
<td>II</td>
<td>376</td>
<td>29.5</td>
</tr>
<tr>
<td>III N</td>
<td>184</td>
<td>14.4</td>
</tr>
<tr>
<td>IIIM</td>
<td>232</td>
<td>18.2</td>
</tr>
<tr>
<td>IV</td>
<td>162</td>
<td>12.7</td>
</tr>
<tr>
<td>V</td>
<td>89</td>
<td>7.0</td>
</tr>
<tr>
<td>Armed</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Govt</td>
<td>13</td>
<td>1.0</td>
</tr>
<tr>
<td>Inadequate</td>
<td>23</td>
<td>1.8</td>
</tr>
<tr>
<td>Not worked</td>
<td>74</td>
<td>5.8</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (10% sample)</strong></td>
<td>1276</td>
<td>100</td>
</tr>
</tbody>
</table>

103
Table 3.12  Breakdown of medical practice by electoral ward

<table>
<thead>
<tr>
<th>Ward</th>
<th>Number</th>
<th>Percentage of practice population</th>
<th>Social class (predominant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnsbury</td>
<td>3268</td>
<td>34.4</td>
<td>II</td>
</tr>
<tr>
<td>Bunhill</td>
<td>420</td>
<td>4.4</td>
<td>IIIM</td>
</tr>
<tr>
<td>Clerkenwell</td>
<td>1810</td>
<td>19.1</td>
<td>II</td>
</tr>
<tr>
<td>St Mary</td>
<td>1470</td>
<td>15.5</td>
<td>II</td>
</tr>
<tr>
<td>St Peter</td>
<td>358</td>
<td>3.8</td>
<td>II</td>
</tr>
<tr>
<td>Thornhill</td>
<td>1194</td>
<td>12.6</td>
<td>II</td>
</tr>
<tr>
<td>Other</td>
<td>971</td>
<td>10.2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>9491</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

904 patients did not live in the Camden and Islington area and could not be classified by the FHSA computer records.
The inclusion of an information leaflet about oral cancer with the second mailing appeared to be of no benefit, 136 (9%) patients attended from the group who received both a card and a leaflet, and 190 (12%) from the group sent only an appointment card (Table 3.13). When these groups were compared it was found that the group receiving both the card and the leaflet had a significantly poorer attendance than the card alone group (SND = 3.19, p < 0.001; observed difference in proportion was 3%; 95 per cent CI, 1.3% - 5.6%; ).

Table 3.13 Comparison of the effects on attendance of sending an information leaflet with the second mailing.

<table>
<thead>
<tr>
<th></th>
<th>Attend</th>
<th>No reply</th>
<th>Total sent</th>
</tr>
</thead>
<tbody>
<tr>
<td>With leaflet</td>
<td>136</td>
<td>1450</td>
<td>1586</td>
</tr>
<tr>
<td>No leaflet</td>
<td>190</td>
<td>1391</td>
<td>1581</td>
</tr>
<tr>
<td>Total</td>
<td>326</td>
<td>2841</td>
<td>3167</td>
</tr>
</tbody>
</table>

SND = 3.19, 95 per cent CI 1.3% - 5.6%; p < 0.001.
3.3.3.1 Referral for further assessment from the medical practice

All subjects were screened as positive or negative. The criteria for a positive screen have been defined previously (Table 3.1) (Speight et al, 1992) as the presence of a white or red patch, or an ulcer of more than two weeks duration. Negative subjects were those whose mouths were normal or who might have benign pathology with no recognised malignant potential. All subjects who were considered by the specialist to require further follow-up or treatment were referred to an oral medicine clinic to be seen as soon as possible. Of the 22 positive subjects (Table 2.6), 12 were referred. Of the twelve who were referred, four subjects failed to attend; 2 with leukoplakia and 2 with erosive lichen planus.

Twelve subjects required referral for benign pathology including 1 lipoma, 1 sebaceous cyst, 1 trigeminal neuralgia, 2 polyps and 7 denture related conditions. Of these 12 subjects, only one (referred for a denture related condition) failed to attend.

3.3.3.2 Referral for further assessment from the dental hospital

Of the 1042 patients screened at the dental hospital there were 32 positive subjects identified of whom 15 required referral. Some patients were already patients in the hospital and were therefore under regular review. Of the 15 subjects referred for treatment 3 failed to attend; 2 with leukoplakia and 1 with lichen planus.

Fourteen subjects required referral for benign lesions of whom all attended except
one. Five negative patients required biopsies or removal of their lesion. One subject refused biopsy and a provisional diagnosis of frictional keratosis was made. Of the four subjects biopsied, histological examination revealed, two lichenoid lesions, one of normal tissue and one fibro-epithelial polyp. One subject was found to have uraemic white patches. Seven subjects had trauma related lesions, either attributed to dental restorations or dentures, which all eventually resolved. The subject who failed to attend had been referred for a trauma related lesion.
3.4 Discussion

3.4.1 Evaluation of a screening test for oral cancer

The purpose of a screening test is to distinguish individuals who probably have a disease from those who probably do not (Wilson and Jungner, 1968). The test is not intended to be diagnostic but positive findings must be confirmed by a specialist diagnostic procedure. The detection rate (sensitivity) of the test may be determined by the criteria for a positive result. For some tests, for example screening for cholesterol or iron deficiency, the result may be an objective value which can be altered to determine the proportion of individuals to be referred for further investigation. Increasing use of technology may also influence screening, for example, with the arrival of more sophisticated blood analysis machines the ranges of normality are now being redefined. For oral cancer, however, there is no single appropriate test for the detection of malignant or premalignant disease (Zakrzewska et al 1993) and a simple but thorough examination of the oral mucosa is regarded as the most effective method (Pindborg, 1984; Mock, 1985). However the criteria for a positive result must depend to some extent on the subjective decision of the examiners and on their ability to recognise aberrations from normal. To make the test as objective as possible, it is necessary to define simple and unequivocal criteria for a positive result (Kleinmann et al, 1991). Warnakulasuriya and Pindborg (1990) evaluated a screening programme in Sri Lanka and defined a positive test as the presence of a white or red lesion or an area of ulceration. This criteria can be modified by defining a number of identifiable lesions to be included or excluded as positive (Speight et al, 1992). For
an oral cancer screening test to be most effective it is important to have a high sensitivity to minimise the number of false-negative results. However, in practice, to achieve a high sensitivity usually means a lower specificity and an increase in false positives (Prorok et al, 1990; Chamberlain, 1993). Sensitivity and specificity are inversely related to each other (Cochrane and Holland, 1971). Attempts to increase the sensitivity by changing the criteria for a positive result may lead to more individuals being unnecessarily referred for further diagnostic procedures. A screening test which included all mucosal abnormalities, would result in the referral of a large number of benign lesions, such as fibro-epithelial polyps, which are not associated with cancer. The resulting false positives would be unacceptable because of the cost to the secondary care services as well as the possible psychological trauma for those individuals unnecessarily referred (Marteau, 1990).

The sensitivity and specificity of the screening test in this study were 0.74 and 0.99 respectively which compare favourably with other cancer screening programmes. Ikeda et al (1991) reported that the positive predictive value of an oral examination to detect leukoplakia was 0.73 and the specificity 0.73 with a disease prevalence of 2.5 per cent. In Sri Lanka, Warnakulasuriya and Pindborg (1990), using primary health care workers, reported positive and negative predictive values for oral screening of 0.58 and 0.98 respectively. A recent study in a work-place environment achieved a sensitivity and specificity of 0.71 and 0.99 respectively with 5.5 per cent prevalence of lesions associated with oral cancer and precancer (Downer et al, 1995).
In a study of breast cancer screening which compared the diagnostic ability in reading radiographic films for a radiographer, non-radiologist doctor and a radiologist, the sensitivity and specificity achieved were both in the region of 0.80 (Haiart and Henderson, 1991). Hakama et al (1991) quote a specificity of 0.96 for mammographic screening with a detection rate 1.6 times greater in those screened compared to those unscreened. This is comparable to a similar study by Sienko et al (1993) who found a sensitivity of 0.71 and specificity of 0.98. A study of cervical cytology screening achieved an overall sensitivity of 0.80 and specificity of 0.99 (Soost et al, 1991). Screening for malignant melanoma by visual examination alone has an estimated sensitivity of 0.75 and specificity of 0.98 (Koh et al, 1991b).

Screening for prostate cancer can be performed by several methods, the most commonly used are prostate specific antigen levels (PSA), digital rectal examination (DRE) and trans-rectal ultrasound (TRUS). These tests have the following sensitivity and specificity values: 0.67 and 0.97 (PSA), 0.50 and 0.94 (DRE) and 0.81 and 0.84 (TRUS) as measured by Mettlin et al (1991) and Babaian et al (1992). Favennac et al (1992) compared three screening tests for colo-rectal cancer which depend on the detection of occult blood in the stools. They found that the sensitivity ranged from 0.70 to 0.94 and the specificity from 0.73 to 0.99 depending on which guaiac test was used. They concluded that since the poor positive predictive values obtained were dependant on certain dietary factors, to increase accuracy of screening it would be prudent to use a combination of all three tests.

Although the sensitivity achieved by the screeners in the present study was comparable with other screening programmes it was still low and this may be due to
a low index of suspicion on the part of the screeners. General dental practitioners and community dental officers constituted over a third of the screeners employed in this study, and this may provide some indication of the present screening potential of the general dental service. With training in the detection of oral precancer and cancer it could be presumed that the sensitivity may be improved. This assumption is suggested by the differences in sensitivity between the screeners in the hospital (junior hospital staff, 0.81) and the screeners in the medical practice (0.64) who were mainly general dental practitioners.

A major problem in screening for any type of cancer is the lack of absolute knowledge of progression and regression rates for precancerous lesions (Speight and Morgan, 1993). These lesions must be treated, since a 'wait and see' policy would defeat the objective of early detection if a lesion were allowed to progress. Further studies of disease progression are therefore essential in order to truly assess the value of detecting and treating precancerous lesions.

3.4.2 Compliance

During the six month period of screening at the medical practice almost 1000 individuals accepted the invitation for screening giving an overall compliance rate of 25.7%. It is vital to measure compliance since a low compliance rate, particularly when associated with a disease of relatively low prevalence, will result in a markedly reduced detection rate in a screening programme. Ikeda et al (1995b) also found low compliance following postal invitations for oral cancer screening in Japan. In their
study a compliance of 15.5% was measured for postal invitations to all subjects over 60 years old in Tokoname city, but compliance was in the range of 60% to 76% for opportunistic screening among company workers in two industrial organisations. There are no published studies in the United Kingdom for invitational screening of the mouth, although opportunistic screening is offered to employees in some companies (Feaver, 1990; Downer et al, 1995). These programmes, where screening is offered on site and encouraged by the company, achieve compliance rates of about 50%, far in excess of the present figure. A similar oral cancer screening study in the United States, (Eckert et al, 1982) used an opportunistic method to obtain high risk subjects but this study is not comparable with the present invitational study since these workers did not measure compliance.

A problem of screening for oral cancer appears to be a lack of public knowledge of the disease and this may have contributed to overall low compliance. In a recent investigation in the same medical practice it was found that only 65.8% of subjects questioned were aware that cancer can affect the mouth (Bhatti et al, 1995).

Although invitational screening generally results in low attendance rates it may achieve a wider coverage among those people who do not attend a health care professional on a regular basis. Garton et al (1992) found that response rates from invitational screening rarely exceed 80%. The NHS Breast screening programme (NHSBSP, 1991) which was established in 1988 following the Forrest report (Forrest, 1986) used an invitational screening method with targets of 70% uptake. In fact, Blamey (1994) stated that over 70% of the population must accept an invitation to
participate if a screening programme is to decrease mortality. Initial trials for breast screening in Edinburgh and Guildford had an uptake of 64% (Austoker and Humphreys, 1988). Cervical screening in the United Kingdom is also by invitation and doctors are encouraged by government financial incentives to persuade their patients to be screened. Other comparable invitational screening programmes have compliance rates in the region of 70% for breast (Chamberlain et al, 1993), 50-55% for colorectal (Farrands et al, 1984), and 30% for cervical cancer (Doyle, 1991). Majeed et al (1993) have shown that the uptake rates for cervical smears can vary from 16.5% to 94.1% depending upon a number of patient and practice variables, including the socio-economic profile of the population and the type of medical practice.

An alternative to invitational screening is an opportunistic method where subjects are screened when they attend a health care professional for some other unrelated purpose. This method was used in the present study in the hospital population but it was not possible to measure compliance because of the open invitation and widespread advertising. In a computer simulation model of opportunistic screening in a general practice, it was calculated that it could take up to 12 years to screen 90% of the population (Norman and Fitter, 1991). However systematic approaches to screening either by invitation or tagging patient notes has been reported as more successful than unsystematic opportunistic programmes (Pierce et al, 1989). Ross (1989) invited patients to be screened for cervical cancer whilst they were attending the doctor for other reasons and found that the patients preferred this system since it provided anonymity for the purpose of their visit to surgery. However Ward et al
(1991) found that opportunistic screening with persuasion by the doctor could increase compliance by 12%.

Another problem with spontaneous or opportunistic screening is that it attracts a relatively limited and selected proportion of the population with repeated examinations at short intervals, but fails to cover the population who would benefit from regular screening (Hakama, 1985). In cervical cancer screening, it has been found in Nordic countries that a population based screening programme with a wide target range was more successful (Hakama, 1990).

The type of invitation offered may also be important. Screening participants are usually invited to attend either with an appointment time or to an open session on a 'first come, first served' basis. There is also the option of having to confirm the appointment by post or telephone. In a recent osteoporosis study (Garton et al, 1992) a fixed appointment time produced 75% attendance compared to 69% for confirmable and 54% for open appointments. Similar studies of breast cancer screening programmes have shown a 10% higher level of compliance by sending invitations with fixed appointments (Williams and Vessey, 1989). However, fixed appointments can result in a wastage of resources due to lost appointment slots (Torgerson and Donaldson, 1994). The efficiency of the method of invitation is considered to depend on the target group. For example, screening for cervical cancer is less likely to be successful with an open method of invitation than that for breast cancer since social classes I and II are more likely to participate in screening and breast cancer is more common in this group (Donaldson, 1994). In the present study, wastage was reduced
by sending large numbers of invitations for each appointment time. All letters were personally signed by the screener to encourage attendance, as recommended by Turnbull et al (1991), and the address of the medical centre and a contact number were given. Turnbull et al (1991) and Scofield et al (1994) found that attendance was increased if the screening invitation was personally signed. Other studies have found the inclusion of a doctor's letter to be important (French et al, 1982; Fallowfield et al; 1990) and in one study the inclusion of a doctor's letter to non-attenders seemed to be an effective and feasible method of increasing uptake (Turner et al, 1994). In a study comparing the effect of television media alone, television media with a letter of invitation and television media with general practice recruitment, Byles et al (1994) found that the latter method was most effective since it succeeded in recruiting previously unscreened women. In fact they concluded that television media alone would have little effect in screening previously unscreened women and it was the combination with a general practice based campaign which was the more important.

In the present study, posters and information sheets were displayed in the waiting rooms throughout the screening period to help increase awareness of oral cancer and the mouth screening programme. In the second round, invitations were mailed to arrive at least two days in advance of the fixed appointment time (Haynes, 1979). Hurley et al (1992) concluded from their breast screening study, that the most cost-effective method was an invitation without a specified time followed by a second letter to non-attenders.
It is of interest to note that there was a significant difference in attendance, in the second mailing, between those subjects who were, or were not given the BDHF information leaflet. Those who did not receive the leaflet showed a better attendance. One reason may be that people who had decided not to attend for screening would not be influenced by any additional information and that many people would be prompted by the reminder card alone. The actual numerical difference was small and it may be due to other factors, such as sampling error. It is possible, however, that the leaflet actually dissuaded some individuals from wanting to be screened. Further research is needed to identify the reasons for non-attendance and in particular, to further evaluate the effectiveness of different types of educational material.

One of the main causes for non-attendance of subjects for screening is fear and anxiety (Calnan, 1984) and several studies have sought to investigate these influences (Fallowfield et al., 1990; Calnan, 1984; Vaile et al., 1993). Ciatto et al. (1992) found that the fear of cancer being detected and laziness were the most common reasons for non-attendance for breast screening. Having a cancer affected blood relation appeared to promote attendance for breast screening (Chaitchik and Kreitler, 1991). Sutton et al. (1994) found that the best predictions for attendance were perceived importance of regular screening, its effectiveness and the subjects' chances of getting breast cancer. They recommended that attendance rates could be improved by targeting relevant attitudes and beliefs. The effect of pre-education, for example in melanoma screening has been found to decrease resistance to being examined (Leffel et al., 1993).
There was an obvious problem regarding the accuracy of the FHSA list of registered patients' names and addresses. This problem was also highlighted by Muir Gray in the NHSBSP (1991). The computerised system is however currently being modernised according to recommendations in the Health of the Nation (Department of Health, 1992), and this should avoid problems such as a patient who would have been 121 years old remaining on the register. This is a particular problem in London compared to most other parts of the country and arises from high population mobility (McEwen et al, 1989). In other invitational screening studies for breast and cervical cancer it was found that up to 69% (McEwen et al, 1989) and 35% (Beardow et al, 1989) of the letters sent were inaccurate. Bickler and Sutton (1993) demonstrated that accuracy could be increased by almost 20% by checking the FHSA list against the electoral role and only inviting those people whose names appeared on both. However, unlike some countries such as Australia, registration on an electoral role is not mandatory in the United Kingdom so people will still be missed. Muir Gray (1991) estimated the accuracy of an FHSA register as the proportion of people on the register who are actually living at the address on the register. Obviously there are many disadvantages and inaccuracies in using age/sex registers from family practitioner lists for screening programmes but they will continue to be used until a more efficient system can be developed.

The socio-economic status of the population selected for screening must also be taken into account and it would be of interest to conduct a similar study in an area with a differing socio-economic profile in order to obtain typical response rates in other ACORN groups. ACORN, or other similar techniques, may be of use in targeting
individuals by encouraging uptake in areas where the disease is likely to be more prevalent. Cervical cancer screening for example shows low response rates in inner city areas (Williams, 1992) where the incidence of the disease is greatest. Examination of the social structure of the medical practice differed when analysed by ACORN and the Registrar General classification. It is possible that this disparity (Table 3.9 and 3.12) may be explained by an influx of younger affluent people into a previously deprived area, thus the social class distribution would change accordingly. These 'new' people were not included in the ACORN data since they only relate to those aged over 40. However this is only an assumption and without knowledge of social class of the whole medical practice, it cannot be substantiated.

The low compliance rate found in this study suggests that an invitational screening programme for oral cancer may not be cost-effective. Low compliance, particularly when associated with a disease of relatively low prevalence, would result in a markedly reduced detection rate in a screening programme (Hakama, 1985). This introduces the concept of programme sensitivity and specificity. Hakama defines the sensitivity of the programme as 'the proportion of persons diagnosed as having the disease as a result of screening, among all of the persons with the disease in the target population'. Programme specificity is the proportion of persons who are disease free in the disease free part of the target population.

Programme sensitivity: Diseased people detected by screening
Diseased people in the target population
Programme specificity: Disease free people detected by screening

Disease free people in the target population

Compliance may effect the validity of the programme since failure to attend for screening or for diagnostic confirmation of a screening result will effect the potential yield of both positive and negative subjects. A valid test is a pre-requisite for a successful programme.

It would seem more appropriate for screening for oral cancer to be done opportunistically during routine dental or health check-ups. However the population coverage would depend on the age of the patients and the frequency of visits to health professionals. For example, it is known that in the over 55 year age group, the frequency of visiting the doctor is over twice that to the dentist (Fedele et al, 1991). Since only 50% of the adult population are currently registered with a dentist (Dental Practice Board, 1994), a large proportion will not be screened and it is arguable that the non-attenders are likely to be those at higher risk of oral cancer. In a recent review, Smart (1993) recommended that oral screening should be part of both routine dental and general health check-ups.

Such an opportunistic method would seem to be a more cost-effective approach, but first it is essential to increase public awareness of oral cancer, particularly the benefits of a regular oral examination and the need to seek treatment as early as possible.
3.4.3 *Referral for assessment*

There was an overall compliance rate of 80% for patients referred for positive lesions compared to 92% for benign lesions. Lack of knowledge about oral cancer may account for the lower attendance among those individuals referred with positive lesions compared to those with benign lesions. Although the numbers are small, anxiety and fear about the nature and treatment of the disease may also have been the cause.

The compliance rate for positive lesions compares favourably with other similar studies. Warnakulasuriya *et al* (1988) found a 54.1% compliance rate for referral for treatment following screening. They found that the degree of compliance depended on a number of factors such as the referring screener and the distance from the referral centre. In the present study the referral centre was very close to the medical practice and this may have contributed to the higher compliance rates. Warnakulasuriya *et al* also found that they could achieve a 10.9% increase in compliance with postal reminders. Barra *et al* (1990) measured the compliance rate of individuals at high risk of oral cancer in attending an ear, nose and throat clinic. They found a 65% rate of attendance. Talamini *et al* (1994), in a similar study found only 34% of referred high risk individuals attended for examination and concluded that despite advising on the high risks, the programme was expensive and the compliance for referral too low.
3.5 Conclusions

- This study has shown that a screening test which comprises a simple oral examination with clear criteria for a positive and negative result, produces a sensitivity and specificity comparable to other screening programmes.

- The compliance rates achieved by an invitational method for screening for oral cancer were disappointingly low compared to other successful screening programmes.

- The proportion of attenders for screening was higher in the lower socioeconomic group. However, in view of low overall compliance in this study, no final conclusion as to the relationship between socioeconomic group and attendance for invitational screening for oral cancer can accurately be made.
Chapter 4

Evaluation of a slide test to determine the screening ability of dental personnel and its potential use as an adjunct in screening programmes
4.1 Introduction

The ability of a screening programme to distinguish between individuals in a population who probably have a given disease or condition from those who probably do not is assessed by its detection rate (sensitivity) and false positive rate (1-specificity) (Wald, 1994). These factors may depend on the screening ability and knowledge of the examiners. One of the problems of screening for oral cancer is that there is no single objective test and therefore the criteria for a positive result will depend to some degree on the subjective views of the screener. There is also a general misconception about the clinical appearance of an early lesion of oral cancer (Mashberg, 1984) and this may determine the number of lesions detected.

4.1.1 Training in oral cancer screening trials

Although there have been few oral cancer screening trials, there have been several epidemiological surveys which have involved the training or calibration of examiners. Bouquot and Gorlin (1986), Eckert et al (1982) and Moore et al (1987) held seminars on oral cancer and precancer, whilst Warnakulasuriya and Pindborg (1990) provided clinical demonstrations. Suggs et al (1990) used colour photographic slides of oral cancer as part of their training programme for screeners. Ikeda et al (1988) trained and calibrated examiners according to a technique described by the World Health Organisation (1980) and found this to be an effective method. In a review of epidemiological studies of oral mucosal conditions, Kleinmann et al (1991) stated that although the oral examination is routine to dentists there is a need for a routine
approach to be encouraged in addition to training and calibration of examiners. Use of a calibration process which requires replicate examinations is difficult and has not been used widely since most oral mucosal pathologies are rare. However there have been some instances where inter-examiner reliability has been measured, for example in smokers palate (Saietz, 1975) and denture associated lesions (Mikkonen et al, 1984). Zakzrewska et al (1993) recommended that for any professional group intending to undertake oral screening, training and education should be mandatory. In the pilot screening study described in Chapter 3, no preliminary training was provided other than in the screening procedure and the criteria for positive lesions which may be oral precancer or cancer. This was in order to test the ability of general dental practitioners to detect target lesions without specific training.

4.1.2 Training techniques in oral cancer detection

Cade et al (1994) developed a dental undergraduate course in the early diagnosis of oral cancer. This was integrated into a community based oral cancer screening programme. Walton et al (1992) prepared a series of quizzes followed by a final examination to assess student knowledge of diagnosis, treatment and rehabilitation of oral cancer after they had completed a 24 hour lecture course. Brody et al (1993) have developed a computer based educational package for evaluating oral lesions associated with cancer and HIV infection. An advisory committee on the training of dentists (1988) in conjunction with the 'Europe against cancer' group recommended that undergraduate students should be 'aware of their role in the early detection of oral precancer and cancer and the part they can play in it's prevention'. In a recent
editorial Hutchison (1994) called for a short course of teaching by oral surgeons to be incorporated into medical school curricula since doctors do not receive adequate training in this area yet are the source for up to 40% of all referrals (Scully et al., 1986). Moore et al (1987) highlighted the problems of screening the upper aerodigestive tract, in that dentists are well trained to examine the mouth and doctors, the oropharynx, unfortunately neither are trained to examine both.

Prout et al (1992) developed an educational programme to promote screening for oral cancer through primary health care. This resulted in a large increase in the number of people being screened compared to baseline rates. However despite training there were variations in both the quality and quantity of screening. The aim of the United States public health service is that 40% of Americans should receive an annual examination for oral cancer, yet recent findings have demonstrated that only 1 in 7 adults are being screened (Anonymous, Morbidity, Mortality Weekly report, 1994). In a study of 1000 Texan dentists (Chen, 1990), it was found that the majority did screen for oral cancer. This correlated positively with attendance at professional meetings and negatively with patient load.

A recent survey within the Community Dental Service in England and Wales found that over 50% of those interviewed believed that training in the identification of oral cancer and precancer was required (Iceton, 1994). Most of the current training had been obtained through attendance at post-graduate meetings or use of the British Postgraduate Medical Federation (1991) video. Surveys within general dental practice found that failure to participate in post graduate education was due to lack of
commitment or a preference to make alternative use of spare time (Vlitos, 1994). Several groups have attempted to improve the ability of dentists to detect oral cancer and precancer. These training packages have used slide presentations, teaching clinics and lectures (Hall et al, 1980; Sadowsky et al, 1988). One of these studies found that there was no significant association between attained knowledge and increased action by the dentist (Sadowsky et al, 1988). A pilot study by Yellowitz and Goodman (1995) compared knowledge of oral cancer and number of oral examinations performed by physicians and dentists. They found that almost half the physicians considered they were not trained to examine for oral cancer and, as expected, the dentists performed more oral examinations. However, since the physicians saw more high risk patients, the authors concluded that they should assume a greater responsibility in the detection of oral cancer.

Vlitos (1994) concluded that 'it is a great mistake to assume that all dentists go to continuing education courses to learn something that will help them to change the way they practise dentistry'. There is obviously a need to widen post graduate knowledge since this will help to encourage early detection of oral cancer.

4.1.3 Other screening programmes

'Specific training and programmes for continuing education related to screening should be mandatory for all professionals involved in the programme. Regular audit and review of individual and programme results are essential'. (Blamey et al, 1994)
Robertson and Woodend (1993) concluded, through audit, that quality assurance in cervical cytology may be improved by the identification of poor smears and liaison with the screeners (ie those carrying out the smears). Chou et al (1990) set up an intensive training programme following identification of technical errors which had resulted in high false negative rates for cervical screening. Palli et al (1993) recommended peer review in cervical cytology with measurement of inter-examiner variability in order to improve performance. Gifford and Coleman (1994) developed a method to assess the competence of pathologists and cytotechnologists in screening cervical smears. They found that their method was able to identify unacceptable levels of performance which could then be rectified to improve screening techniques. Gaw et al (1991) developed a programme to improve mammography skills since they concluded that wide variability may compromise quality and any benefits from screening. Certainly when the NHS breast screening programme (1991) was introduced strict guidelines were implemented for all clinicians involved.

The Europe against cancer group has initiated pilot programmes for quality assurance both in breast and cervical screening which involves training of all screeners (Tubiana, 1993).

4.1.4  Statistical evaluation of measuring variability between examiners

Measurement is 'the procedure of applying a standard scale to a set of values' (Last, 1983). There are five types of measurement scales, these being:
**Dichotomous**: two mutually exclusive categories, for example, yes/ no; positive/ negative

**Nominal**: non-ordered qualitative categories, for example, race; religion

**Ordinal**: ordered qualitative categories, for example, social class; stages of cancer.

**Interval**: categories with a particular distance between them, for example, date of birth; temperature.

**Ratio**: interval scale with absolute zero, for example, weight; height.

Problems are often encountered when describing the properties of measurement in that a measurement is expected to be accurate, precise, valid, reliable, repeatable and reproducible. A test is considered valid when it measures what it is presumed to measure (Guilford, 1965). The validity of a test is dependent on whether a result is right or wrong (or an error). There are two types of error; random and systematic. Random or sampling error is due to chance and is detected by lack of consistency or repeatability of equivalent measurements. Systematic error is due to a constant inability to interpret a value or characteristic correctly. The validity of a test is dependent on both types of error.

The repeatability of a diagnostic test may be defined as 'the extent to which it provides the same results on the same subject on two or more occasions, either in the hands of the same or of more than one observer, the subject of the test being in the same state of health or disease’ (Fletcher and Oldham, 1964). Guilford (1965) defines the reliability of a set of measurements as the proportion of its variance that is true variance, where total variance is made up of two sources; true and error variance.
Variance is defined by Last (1983) as the measure of variation shown by a set of observations (statistically the sum of squares divided by the degrees of freedom). Reliability and repeatability are therefore two separate concepts the former being a statistical concept, which, in the case of ordinal scale measurements can be calculated for a single or multiple group of examiners by apportioning the components of variance.

Examiner variability is the variation noted between and within examiners in observing a set of data. Since this is an important source of measurement error it is usual to conduct repeatability tests to assess examiner variability. It is important to assess the degree of variation to allow true interpretation of the data (Brennan and Silman, 1992). In order to assess agreement between examiners, the simplest method is to calculate how many exact agreements in a set of data were observed.

**Kappa**

Kappa (Cohen, 1960; Altman, 1991) is the actual measure of agreement between examiners and ranges between 0 where there is no agreement between examiners to 1 where there is perfect agreement. Values less than zero are worse than chance agreement. If agreement is unsatisfactory it is usually due to bias (Silcocks, 1983). Kappa is calculated as the difference in the observed \( (P_o) \) and expected probability \( (P_e) \) of agreement divided by unity minus the probability of expected agreement:

\[
\frac{P_o - P_e}{1 - P_e}
\]
Landis and Koch (1977) defined the interpretation of values for kappa. Although these values are only arbitrary, they provide some index for agreement. Less than 0.60 is considered as moderate agreement whereas 0.81 or above is almost perfect.

Dice's index

Dice's coincidence index provides a measure of whether a subject diagnosed as positive by one examiner will be diagnosed as positive by another, or similarly negative. Thus the likelihood of agreement can be compared.

Spearman Rank Correlation Coefficient

Correlation is a method of analysis to study the possible linear association between two continuous variables (Altman, 1991). The degree of association is measured by calculating the correlation coefficient. The Spearman rank correlation coefficient is obtained by ranking the subjects for each variable and comparing the rank orders.

Wilcoxon matched signed ranks test

This procedure is used for paired data (and takes the pairing into account unlike the sign test). The method involves subtracting one member of the pair from the other and ranking the differences. The plus or minus signs are ignored. After ranking is completed, the plus and minus signs are restored. Z is calculated and compared to the Normal distribution.
**Kruskal Wallis one way analysis of variance**

The Mann-Whitney test is derived from the hypothesis that two independent samples come from populations having the same distribution. It is a non-parametric test. In the same way that analysis of variance is an extension of the t-test, the Kruskal Wallis test is an extension of the Mann Whitney test. The procedure involves combining all the cases from each set and ranking them. Average ranks are given for ties. For each group the ranks are summed and the Kruskal Wallis $H$ statistic obtained. The $H$ statistic has a chi squared distribution assuming that all the groups have the same distribution.
4.2 Aims

Although there are several lesions and conditions of the oral mucosa which are generally accepted to be precursors to oral cancer, there is no absolute agreement. A slide test was designed, based on those lesions and conditions considered to be positive (Pindborg, 1980), with the objective of being able to discriminate between different levels of dental personnel and provide some assessment of their screening ability.

A second aim of this study was to evaluate the range of ability of the screeners who took part in the main screening study (Chapter 3) and to determine the need to train practitioners prior to screening. The effect of participation in a screening programme was also evaluated to determine if it led to an improvement in performance in the slide test.
4.3 Materials and Methods

4.3.1 Selection of subjects

Group study

A set of colour photographic slides was developed to estimate clinicians' ability to identify oral precancer and cancer. It was piloted on a range of dental personnel comprising all levels of hospital staff, post-graduate dental students and general dental practitioners. There were two hundred and ten subjects in total. The subjects were divided into 4 groups depending on their level of training and experience in clinical dentistry. The groups were classified as (1) consultant in oral surgery and oral medicine, (2) junior staff of a dental hospital (including post-graduate students), (3) general dental practitioners and community dental officers, and (4) dental auxiliaries (dental surgery assistants and student dental hygienists).

Screeners

There were a total of 24 dentists who participated as screeners in the main study (Chapter 3). They were junior members of the dental hospital staff, general dental practitioners and community dental officers. Although no training or standardisation was undertaken other than an outline of the screening technique, it was decided to expose the screeners to the set of colour photographic slides. The screeners were exposed to the slide set before and after participation in the screening project.
4.3.2 The slide set

A set of 80 colour photographic slides was used to evaluate each subject's screening ability. Each slide had a predetermined diagnosis which had been provided by a consultant oral physician and pathologist. There were 40 slides of normal mucosa or benign pathology which were designated as negative since by definition no malignant potential was associated with these conditions. The participants were informed that a positive slide depicted a cancer or precancer and it was defined as one in which a white or red patch or ulcer was present. Aphthous ulcers and ulcers of traumatic origin were classified as negative. It was explained to all participants that although some of the benign conditions might require treatment the decision was between being a positive or negative slide as defined by the given criteria for oral cancer and precancer. The slide test was shown to each group individually under standardised conditions.

Since no clinical information was provided for any of the slides, the decision of whether a slide was positive or negative was purely visual. The aims of the slide presentation were explained to all candidates. Each colour photographic slide was projected for 15 seconds on a display of 0.9 m by 1.5 m. All slides were numbered to avoid confusion. A non-answer was considered to be an error. All the slides were coded and randomised according to a random numbering technique (Altman, 1991). The subjects were unaware of the total numbers of negatives and positives.
4.3.3 Statistical Analysis

The performance of the various groups of personnel and screeners was evaluated in terms:

1. Mean sensitivity, specificity and total score.

2. Likelihood ratio.

3. Dice’s and Kappa values were obtained for each screener; post screening result was compared with the pre-screening result.

4. Wilcoxon matched pair signed ranks test was used to compare the results of the screeners performance in the slide test before and after screening.

5. Spearmans rank correlation coefficient for both sensitivity and specificity was obtained for the screeners who had been exposed to both positives and negatives in the screening programme.

6. A Kruskal-Wallis test was used compare the means of the group study and two sample Mann-Whitney tests were used to assess where the differences lay.
4.4 Results

4.4.1 Group study

Table 4.1 contains a summary of the mean sensitivity (the proportion of positive slides scored correctly), mean specificity (the proportion of negative slides scored correctly) and the mean total score. As can be seen the sensitivity ranged from 0.72 in the auxiliary group through to 0.90 in the consultant group with the junior hospital staff and general dental practitioner groups having values lying in between. Likewise the mean specificity ranged from 0.65 in the group with the least training (auxiliary) in oral surgery and medicine to 0.92 in those with the most training (consultant). A one-way non-parametric analysis of variance (Kruskal-Wallis test) demonstrated a highly significant difference in all measurements between the groups. Two sample Mann-Whitney tests were used to assess where the differences lay and comparisons between the auxiliaries and consultants, auxiliaries and junior staff and auxiliaries and dentists were all significant for sensitivity, specificity and total score.

There were no significant differences in sensitivity, specificity and total score between the dentists, junior staff or consultants. The likelihood ratio was calculated for each group and it can be seen that the consultants were almost 5.5 times more likely to make a correct positive diagnosis than the auxiliaries.
Table 4.1  Group study: sensitivity, specificity and total score

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Total Score</th>
<th>False positive rate</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auxiliary</td>
<td>38</td>
<td>0.73</td>
<td>0.65</td>
<td>55</td>
<td>0.35</td>
<td>2.08</td>
</tr>
<tr>
<td>Dentist</td>
<td>83</td>
<td>0.83</td>
<td>0.79</td>
<td>65</td>
<td>0.21</td>
<td>3.95</td>
</tr>
<tr>
<td>Junior</td>
<td>63</td>
<td>0.84</td>
<td>0.80</td>
<td>66</td>
<td>0.20</td>
<td>4.20</td>
</tr>
<tr>
<td>Consultant</td>
<td>26</td>
<td>0.91</td>
<td>0.92</td>
<td>73</td>
<td>0.08</td>
<td>11.38</td>
</tr>
</tbody>
</table>

\( H (\text{corrected for ties}) \)

\[
\begin{align*}
\text{H} & \quad 36.33 \quad 74.12 \quad 90.80 \\
\text{p} & \quad <0.05 \quad <0.05 \quad <0.05 \\
\end{align*}
\]
4.4.2 Screeners

4.4.2.1 Performance in the slide test

The sensitivity of the screeners in the slide test ranged from 0.68 to 0.98 with a mean of 0.87, whereas the specificity ranged from 0.33 to 0.95 with a mean of 0.81 (Table 4.2). Some of the screeners had likelihood ratios equivalent to the performance of the consultant group but two had lower likelihood ratios than the auxiliary group. However the majority of the screener group had similar likelihood ratios in the middle range.

Table 4.3 contains the Kappa and Dice’s index for the screeners calculated from the slide test. Of the sixteen screeners who completed screening tests before and after screening, 13 demonstrated good or very good levels of agreement according to Landis and Koch (1977) guidelines (Table 4.4). The remaining three exhibited a moderate level of agreement. The mean level for inter-examiner agreement (kappa) was 74.5. Dice’s coincidence index for the probability that the screeners would consistently determine a slide as positive ranged from 72% to 94% (mean 86.9%) and as negative as 77% to 95% (mean 87.8%). Since total consistency would be equivalent to 100% these values are within an acceptable range.
Table 4.2  Results of the slide test for the screeners

<table>
<thead>
<tr>
<th>Screeners</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False positive</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>0.90</td>
<td>0.90</td>
<td>0.10</td>
<td>9.0</td>
</tr>
<tr>
<td>DC</td>
<td>0.98</td>
<td>0.65</td>
<td>0.35</td>
<td>2.8</td>
</tr>
<tr>
<td>DP</td>
<td>0.95</td>
<td>0.90</td>
<td>0.10</td>
<td>9.5</td>
</tr>
<tr>
<td>FH</td>
<td>0.90</td>
<td>0.83</td>
<td>0.17</td>
<td>5.3</td>
</tr>
<tr>
<td>HM</td>
<td>0.88</td>
<td>0.88</td>
<td>0.12</td>
<td>7.3</td>
</tr>
<tr>
<td>IG</td>
<td>0.88</td>
<td>0.80</td>
<td>0.20</td>
<td>4.4</td>
</tr>
<tr>
<td>IH</td>
<td>0.75</td>
<td>0.93</td>
<td>0.07</td>
<td>10.7</td>
</tr>
<tr>
<td>JG</td>
<td>0.78</td>
<td>0.93</td>
<td>0.07</td>
<td>11.1</td>
</tr>
<tr>
<td>JI</td>
<td>0.98</td>
<td>0.78</td>
<td>0.22</td>
<td>4.5</td>
</tr>
<tr>
<td>JK</td>
<td>0.93</td>
<td>0.75</td>
<td>0.25</td>
<td>3.7</td>
</tr>
<tr>
<td>JT</td>
<td>0.88</td>
<td>0.90</td>
<td>0.10</td>
<td>8.8</td>
</tr>
<tr>
<td>KH</td>
<td>0.95</td>
<td>0.88</td>
<td>0.12</td>
<td>7.9</td>
</tr>
<tr>
<td>LL</td>
<td>0.75</td>
<td>0.83</td>
<td>0.17</td>
<td>4.4</td>
</tr>
<tr>
<td>MB</td>
<td>0.88</td>
<td>0.75</td>
<td>0.25</td>
<td>3.5</td>
</tr>
<tr>
<td>MG</td>
<td>0.83</td>
<td>0.80</td>
<td>0.20</td>
<td>4.1</td>
</tr>
<tr>
<td>NB</td>
<td>0.78</td>
<td>0.80</td>
<td>0.20</td>
<td>3.9</td>
</tr>
<tr>
<td>NJ</td>
<td>0.90</td>
<td>0.90</td>
<td>0.10</td>
<td>9.0</td>
</tr>
<tr>
<td>SA</td>
<td>0.68</td>
<td>0.33</td>
<td>0.67</td>
<td>1.0</td>
</tr>
<tr>
<td>SC</td>
<td>0.80</td>
<td>0.95</td>
<td>0.05</td>
<td>16</td>
</tr>
<tr>
<td>SD</td>
<td>0.93</td>
<td>0.73</td>
<td>0.27</td>
<td>3.4</td>
</tr>
<tr>
<td>SN</td>
<td>0.90</td>
<td>0.90</td>
<td>0.10</td>
<td>9.0</td>
</tr>
<tr>
<td>SP</td>
<td>0.93</td>
<td>0.48</td>
<td>0.52</td>
<td>1.8</td>
</tr>
<tr>
<td>TR</td>
<td>0.90</td>
<td>0.93</td>
<td>0.07</td>
<td>12.9</td>
</tr>
<tr>
<td>ZA</td>
<td>0.88</td>
<td>0.88</td>
<td>0.12</td>
<td>7.3</td>
</tr>
<tr>
<td>MEAN</td>
<td>0.87</td>
<td>0.80</td>
<td>0.19</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Likelihood ratio is calculated as Sensitivity / false positive rate.

False positive rate: 100 - specificity.
<table>
<thead>
<tr>
<th>Screeners</th>
<th>Kappa</th>
<th>Dices +</th>
<th>Dices -</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>88</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>DC</td>
<td>73</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>DP</td>
<td>65</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>FH</td>
<td>87</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>HM</td>
<td>73</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>IG</td>
<td>85</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>IH</td>
<td>77</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>JG</td>
<td>53</td>
<td>71</td>
<td>82</td>
</tr>
<tr>
<td>JI</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>JK</td>
<td>73</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>JT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KH</td>
<td>90</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>LL</td>
<td>59</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>MB</td>
<td>80</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>MG</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NB</td>
<td>50</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>NJ</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SA</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SC</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>72</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>SN</td>
<td>90</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>SP</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TR</td>
<td>77</td>
<td>89</td>
<td>88</td>
</tr>
<tr>
<td>ZA</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEAN</td>
<td>74.5</td>
<td>86.9</td>
<td>87.8</td>
</tr>
</tbody>
</table>
Table 4.4  Interpreting values of Kappa  
(adapted from Landis and Koch, 1977)

<table>
<thead>
<tr>
<th>Value of Kappa</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.20</td>
<td>Poor</td>
</tr>
<tr>
<td>0.21-0.40</td>
<td>Fair</td>
</tr>
<tr>
<td>0.41-0.60</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.61-0.80</td>
<td>Good</td>
</tr>
<tr>
<td>0.81-1.00</td>
<td>Very good</td>
</tr>
</tbody>
</table>
In the screening project (Chapter 3) only a small number of screeners were exposed to positive patients or had a false positive rate of zero and it was only possible to calculate likelihood ratios for 7 screeners from their results in the field (Chapter 3), (Table 4.5). For the screeners who had screened both positive and negative subjects a Spearman rank correlation coefficient was calculated comparing the results obtained in the slide test with those obtained in the field (Table 4.6 and 4.7). This analysis gave a non-significant result for the sensitivity (Spearman rank coefficient -0.25, p>0.05) and a significant result for specificity (Spearman rank coefficient 0.60, p<0.05). The difference in performance was analysed by comparing the results obtained in the slide test before and after participating in the screening project. The slides were shown in a different order on the post-screening viewing. A Wilcoxon matched pair sign ranks test was used to compare both sets of results (Table 4.8). This was calculated for 23 screeners since one failed to complete the final test. A significant difference was found in the specificity values for the slide test (z:-3.70, p<0.05). The mean of specificity increased to 0.92 after participation in the screening project from a mean pre screening specificity of 0.83. The mean sensitivity decreased from 0.87 (pre-screening) to 0.85 (post-screening). However the differences in sensitivity values pre and post screening were not significant, (z:-1.33, p>0.05).
<table>
<thead>
<tr>
<th>Screeners</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False positive</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DC</td>
<td>-</td>
<td>0.88</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DP</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>FH</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HM</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>IG</td>
<td>-</td>
<td>0.98</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IH</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>JG</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>JI</td>
<td>0.50</td>
<td>0.92</td>
<td>0.08</td>
<td>6.3</td>
</tr>
<tr>
<td>JK</td>
<td>1</td>
<td>0.99</td>
<td>0.01</td>
<td>100</td>
</tr>
<tr>
<td>JT</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KH</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LL</td>
<td>1</td>
<td>0.96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MB</td>
<td>0.91</td>
<td>0.99</td>
<td>0.01</td>
<td>91</td>
</tr>
<tr>
<td>MG</td>
<td>0.75</td>
<td>0.96</td>
<td>0.04</td>
<td>18.8</td>
</tr>
<tr>
<td>NB</td>
<td>0.66</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>NJ</td>
<td>0.50</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>SA</td>
<td>1</td>
<td>0.94</td>
<td>0.06</td>
<td>16.7</td>
</tr>
<tr>
<td>SC</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>0.73</td>
<td>0.99</td>
<td>0.01</td>
<td>73</td>
</tr>
<tr>
<td>SN</td>
<td>0.50</td>
<td>0.96</td>
<td>0.04</td>
<td>6.3</td>
</tr>
<tr>
<td>SP</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TR</td>
<td>0.50</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>ZA</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Likelihood ratio is calculated as Sensitivity / false positive rate.

False positive rate : 100- specificity.
Table 4.6: Calculating Spearman's rank correlation coefficient for sensitivity of screeners in the slide show and in the field

<table>
<thead>
<tr>
<th>Screeners</th>
<th>Sensitivity field</th>
<th>Rank field</th>
<th>Sensitivity slide</th>
<th>Rank slide</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>1</td>
<td>13</td>
<td>0.95</td>
<td>15</td>
</tr>
<tr>
<td>HM</td>
<td>1</td>
<td>13</td>
<td>0.88</td>
<td>8</td>
</tr>
<tr>
<td>JG</td>
<td>1</td>
<td>13</td>
<td>0.78</td>
<td>3.5</td>
</tr>
<tr>
<td>JI</td>
<td>0.50</td>
<td>3.5</td>
<td>0.98</td>
<td>16</td>
</tr>
<tr>
<td>JK</td>
<td>1</td>
<td>13</td>
<td>0.93</td>
<td>13.5</td>
</tr>
<tr>
<td>LL</td>
<td>1</td>
<td>13</td>
<td>0.75</td>
<td>2</td>
</tr>
<tr>
<td>MB</td>
<td>0.91</td>
<td>9</td>
<td>0.88</td>
<td>8</td>
</tr>
<tr>
<td>MG</td>
<td>0.75</td>
<td>8</td>
<td>0.83</td>
<td>6</td>
</tr>
<tr>
<td>NB</td>
<td>0.66</td>
<td>6</td>
<td>0.78</td>
<td>3.5</td>
</tr>
<tr>
<td>NJ</td>
<td>0.50</td>
<td>3.5</td>
<td>0.90</td>
<td>11</td>
</tr>
<tr>
<td>SA</td>
<td>1</td>
<td>13</td>
<td>0.68</td>
<td>1</td>
</tr>
<tr>
<td>SC</td>
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<td>0.80</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>0.73</td>
<td>7</td>
<td>0.93</td>
<td>13.5</td>
</tr>
<tr>
<td>SN</td>
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<td>3.5</td>
<td>0.90</td>
<td>11</td>
</tr>
<tr>
<td>TR</td>
<td>0.50</td>
<td>3.5</td>
<td>0.90</td>
<td>11</td>
</tr>
<tr>
<td>ZA</td>
<td>1</td>
<td>13</td>
<td>0.88</td>
<td>8</td>
</tr>
</tbody>
</table>

Spearman rank correlation coefficient: -0.25, p > 0.05.
Table 4.7: Calculating Spearman's rank correlation coefficient for specificity of screeners in the slide show and in the field

<table>
<thead>
<tr>
<th>Screeners</th>
<th>Specificity field</th>
<th>Rank field</th>
<th>Specificity slide</th>
<th>Rank slide</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>1</td>
<td>3</td>
<td>0.90</td>
<td>12</td>
</tr>
<tr>
<td>HM</td>
<td>1</td>
<td>13</td>
<td>0.88</td>
<td>9.5</td>
</tr>
<tr>
<td>JG</td>
<td>1</td>
<td>13</td>
<td>0.93</td>
<td>14.5</td>
</tr>
<tr>
<td>JI</td>
<td>0.92</td>
<td>1</td>
<td>0.78</td>
<td>5</td>
</tr>
<tr>
<td>JK</td>
<td>0.99</td>
<td>7.5</td>
<td>0.75</td>
<td>3.5</td>
</tr>
<tr>
<td>LL</td>
<td>0.96</td>
<td>4</td>
<td>0.83</td>
<td>6.5</td>
</tr>
<tr>
<td>MB</td>
<td>0.99</td>
<td>13</td>
<td>0.75</td>
<td>6.5</td>
</tr>
<tr>
<td>MG</td>
<td>0.96</td>
<td>7.5</td>
<td>0.80</td>
<td>12</td>
</tr>
<tr>
<td>NB</td>
<td>1</td>
<td>2</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>NJ</td>
<td>0.99</td>
<td>13</td>
<td>0.90</td>
<td>16</td>
</tr>
<tr>
<td>SA</td>
<td>0.94</td>
<td>7.5</td>
<td>0.33</td>
<td>2</td>
</tr>
<tr>
<td>SC</td>
<td>1</td>
<td>4</td>
<td>0.95</td>
<td>16</td>
</tr>
<tr>
<td>SD</td>
<td>0.99</td>
<td>7.5</td>
<td>0.73</td>
<td>2</td>
</tr>
<tr>
<td>SN</td>
<td>0.96</td>
<td>4</td>
<td>0.90</td>
<td>12</td>
</tr>
<tr>
<td>TR</td>
<td>1</td>
<td>13</td>
<td>0.93</td>
<td>14.5</td>
</tr>
<tr>
<td>ZA</td>
<td>1</td>
<td>13</td>
<td>0.88</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Spearman rank correlation coefficient: 0.60, p<0.05.
Table 4.8: Comparing the results of the screeners pre and post screening (Wilcoxon matched pairs signed ranks test).

<table>
<thead>
<tr>
<th>Screeners</th>
<th>Sensitivity 1</th>
<th>Sensitivity 2</th>
<th>Specificity 1</th>
<th>Specificity 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>0.90</td>
<td>0.93</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>DC</td>
<td>0.98</td>
<td>0.90</td>
<td>0.65</td>
<td>0.80</td>
</tr>
<tr>
<td>DP</td>
<td>0.95</td>
<td>0.88</td>
<td>0.90</td>
<td>1</td>
</tr>
<tr>
<td>FH</td>
<td>0.90</td>
<td>0.90</td>
<td>0.83</td>
<td>0.93</td>
</tr>
<tr>
<td>HM</td>
<td>0.88</td>
<td>0.85</td>
<td>0.88</td>
<td>0.95</td>
</tr>
<tr>
<td>IG</td>
<td>0.88</td>
<td>0.78</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>IH</td>
<td>0.75</td>
<td>0.75</td>
<td>0.93</td>
<td>0.98</td>
</tr>
<tr>
<td>JG</td>
<td>0.78</td>
<td>0.65</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>JI</td>
<td>0.98</td>
<td>0.93</td>
<td>0.78</td>
<td>0.93</td>
</tr>
<tr>
<td>JK</td>
<td>0.93</td>
<td>0.98</td>
<td>0.75</td>
<td>0.78</td>
</tr>
<tr>
<td>JT</td>
<td>0.88</td>
<td>0.80</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>KH</td>
<td>0.95</td>
<td>0.93</td>
<td>0.88</td>
<td>0.90</td>
</tr>
<tr>
<td>LL</td>
<td>0.75</td>
<td>0.73</td>
<td>0.83</td>
<td>0.93</td>
</tr>
<tr>
<td>MB</td>
<td>0.88</td>
<td>0.88</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>MG</td>
<td>0.83</td>
<td>0.90</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>NB</td>
<td>0.78</td>
<td>0.70</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>NJ</td>
<td>0.90</td>
<td>0.95</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>SA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SC</td>
<td>0.80</td>
<td>0.85</td>
<td>0.95</td>
<td>0.98</td>
</tr>
<tr>
<td>SD</td>
<td>0.93</td>
<td>0.93</td>
<td>0.73</td>
<td>0.94</td>
</tr>
<tr>
<td>SN</td>
<td>0.90</td>
<td>0.88</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>SP</td>
<td>0.93</td>
<td>0.95</td>
<td>0.48</td>
<td>0.63</td>
</tr>
<tr>
<td>TR</td>
<td>0.90</td>
<td>0.75</td>
<td>0.93</td>
<td>0.90</td>
</tr>
<tr>
<td>ZA</td>
<td>0.78</td>
<td>0.88</td>
<td>0.90</td>
<td>0.88</td>
</tr>
<tr>
<td>MEAN</td>
<td>0.87</td>
<td>0.85</td>
<td>0.83</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Specificity: \( z = -3.70 \quad p < 0.05 \)

Sensitivity: \( z = -1.32 \quad p > 0.05 \)
4.5 Discussion

4.5.1 The pilot study

In this part of the study it was apparent that the scores achieved in the slide test were related to the degree of experience in oral surgery and oral medicine with the results of the consultants being the highest and those of the auxiliaries the lowest. There were no significant differences between the dentists, junior and consultant staff in either the sensitivity or the specificity.

Although one would naturally assume a consultant to be better at screening than a general dental practitioner, the scores in the slide test may provide some indication of the aptitude of a potential screener. It is of interest that a consultant is 5.5 times more likely to recognise oral cancer or precancer than an auxiliary, however the cost in terms of money and in time required to use consultants for screening would be immense. Wannakulasuriya and Pindborg (1990) used primary health care workers for the early detection of oral cancer in Sri Lanka and achieved favourable results. This slide test was therefore able to discriminate between the diagnostic ability of various groups of dental personnel.

4.5.2 The screeners

The success of a screening programme is dependent on its effectiveness in detecting disease early and treating it effectively. It is important that the screeners are adept at
recognising disease early in its development. In the slide test the screeners achieved a mean sensitivity of 0.87 and a mean specificity of 0.81. Both these values would be acceptable for screening. The range of sensitivity values was 0.75 - 0.98 which is still within acceptable levels but the specificity range of 0.33 - 0.95 shows great disparity in the diagnostic skills of the screeners. A high sensitivity is desired in cancer screening programmes in order to minimise the number of false negatives, even if this is at the expense of generating a number of unwanted false-positives. It was difficult to compare the values obtained in the slide test to the performance in the field since not all of the screeners were exposed to subjects with disease. This is an obvious problem with oral cancer programmes as pointed out by Kleinmann et al (1991). They stated that since most oral mucosal pathology is rare it was difficult to become skilled at recognising it compared to other pathology, for example, dental caries. This probably explains why there was no association between sensitivity values in the field and in the slide test. There is no obvious reason however why there should be a significant association between pre and post screening specificity values and not for sensitivity values, although it is generally assumed that sensitivity is not affected by prevalence, the very low prevalence of positive lesions in the field must have had a confounding influence.

Eddy (1980) developed a mathematical model of breast cancer screening which can be adapted for oral cancer screening. As can be seen from the graph (Figure 4.1) it is expected that the screener with the most ability (or highest sensitivity) would be able to detect a lesion when the tumour is small. When the tumour gets bigger it is easier to detect so the general practitioner may notice it before the patient does.
Eventually the tumour may enlarge to a size at which the patients seeks treatment and the level of detection required to identify the tumour is small (low sensitivity). Theoretically by increasing the level of knowledge of the general practitioner by training programmes the sensitivity of that individual should increase. It could also be assumed that by making the patient aware of the disease, they should seek treatment earlier.

No studies which have sought to train either undergraduates or post graduates have measured their performance in terms of sensitivity and specificity and it is therefore not possible to compare them to the present study. However this study compares well with other screening studies for example in the detection of gastric cancer where Stebbe and Vetner (1977) found a 74.5% inter-examiner agreement. Higgins et al (1990) found a very low inter-observer variation in screening for ovarian cancer with a correlation coefficient of 0.96. Lambourne and Lederer (1973) found only moderate consistency between cytology centres in the United Kingdom and concluded that the differences in criteria used in interpreting slides was partly responsible for the variations in sensitivity of the smear test. Axell (1976) found the inter-examiner tests and comparisons in clinical diagnosis were acceptable in his prevalence study of oral mucosal lesions. Smith and Catalona (1995) found only fair agreement (0.22 kappa) for urologists in screening for prostate cancer by digital rectal examination. They concluded that there was a need to evaluate inter-examiner agreement between primary care physicians and urologists. Although Pindborg et al (1985) did not actually measure inter-examiner agreement in evaluating oral dysplasia (from histological slides) they found a wide spectrum of diagnoses and called for an
international consensus of criteria for dysplasias.

The slide test may be useful as an adjunct to teaching and training screeners to recognise early signs of oral cancer and in auditing future performance in screening programmes assuming the diagnostic criteria are established and widely accepted. It is interesting to note that there was a large divergence between the screeners, especially in specificity; some having performances equivalent to consultants and two with performances comparable to auxiliaries. There is obviously a need to standardise the screeners for future screening programmes prior to screening. Screening experience did not apparently change the level of diagnostic ability, as measured in the slide test, this could be due to the lack of positive subjects in the field or lack of training.

In conclusion it was found that the slide test had the ability to discriminate between different levels of oral surgery and medicine experience in diagnosing oral cancer and precancer. It has also shown the need to train screeners prior to screening in order to reject those with poor screening ability and since participation in a screening programme does not seem to improve diagnostic ability.

In the United Kingdom the most obvious method of instituting screening for oral cancer would be by use of general dental practitioners, further research into the most effective method of training practitioners in the detection of the early oral cancer is thus required. This could be included in undergraduate and postgraduate dental training programmes.
Simulated relationship between development of oral cancer and detection

Figure 4.1 (Adapted from Eddy, 1980)
Chapter 5

Estimating the relative risk of lifestyle factors on oral cancer and their use in identifying high risk individuals
5.1 Introduction

5.1.1 Strategies for prevention

Preventive medicine involves the promotion, preservation and restoration of health in an individual or population (Last, 1983). The purpose of prevention in medicine is to reduce the risk of a person contracting a disease or to reduce the risk of subsequent disability once a disease has happened (Butler, 1993). There are three types of prevention:

Primary prevention is aimed at preventing a disease from starting, for example vaccinations.

Secondary prevention involves the early detection of a disease and prevention of further progression, for example screening.

Tertiary prevention is aimed at reducing any disabilities which arise from a disease and instituting appropriate rehabilitation, for example restoring a tooth rather than extraction.

There are two main strategies for any preventive programme, these being high risk or population based (Downer, 1994).
5.1.2 High risk strategy

This involves the identification of those individuals at high risk of contracting a disease. The disease is prevented by either provision of health education which encourages a behaviour change, for example anti-smoking advice to prevent lung cancer or fluoride tablets to prevent tooth decay. The advantage of this method is that there is motivation of the subject and the doctor on a one to one basis. The advice will thus be appropriate for that individual. The disadvantages are that it may be difficult to reach the most vulnerable groups for targeting, the cost of identifying them may be high and compliance may be low.

5.1.3 The population based approach

This involves altering the general factors in a population which contribute to the overall causes of a disease. The population based approach has a greater potential than the high risk approach since it targets the underlying causes of a disease, as well as being behaviorally appropriate for the population. The main disadvantage is that although it may provide large benefits to the community only small benefits may be obtained on an individual basis. This is known as the prevention paradox.

Obviously the approach taken will depend on the prevalence and severity of the disease. Austoker (1994b) discussed the benefits of intervention at a primary care level and at a community based level and suggested both methods could be used where appropriate. For example to prevent coronary heart disease, which is
widespread in the United Kingdom, using a high risk strategy would have a limited impact and be very expensive. However using a population approach (that is targeting everybody), the overall distribution of the disease should change. If this was measured in terms of blood pressure, for example, the ideal would be to shift the mean blood pressure of the population to the left of the normal distribution so that there are less people with high blood pressure (Figure 5.1).

Oral cancer although severe (in terms of mortality and morbidity) is not as prevalent as coronary heart disease so the numbers are much reduced and this means that a population based strategy just targeting oral cancer would not be cost-effective. However it is possible that incorporation of oral cancer prevention into a wider population based strategy such as Health of the Nation (Anderson, 1991; Chambers et al, 1991) which aims to reduce the prevalence of diseases such as lung and upper aero-digestive cancers which have similar aetiological factors (Doll et al, 1994 a & b) may be more successful. Prevention of oral cancer thus benefits through a 'common risk factor approach'.

Since oral cancer is closely associated with personal habits such as smoking and drinking alcohol it is open to a high risk strategy for prevention since those needing advice can be identified easily. The criteria for selective screening (a secondary prevention strategy) is based on the likelihood of that patient contracting a disease. It assumes that few cancer cases will arise in the low risk groups not screened (Hakama, 1985) Since the yield of patients from a group with high risk habits would be higher this strategy may be more cost-effective. Binnie and Rankin (1984)
discussed the possibility of a prospective study 'to yield probability data for individuals at risk of oral cancer'. He surmised that it would be possible to determine relative risk factors from individual profiles for tobacco and alcohol. However prospective studies would be very expensive requiring large samples and long follow-up. Since oral cancer is rare the sample would have to be immense to obtain sufficient numbers of oral cancer cases.
Figure 5.1  High risk and population based strategies

Population based strategy shifts the mean of population B to the mean of population A.

High risk strategy targets only those in this area.
5.1.4 Multiple linear logistic regression

Logistic regression is used to predict the probability of a dichotomous outcome variable from a set of independent variables (Norusis; SPSS Inc, 1990). It is possible to estimate the odds ratio for each variable from its regression coefficient. It is a method which is used widely in epidemiological studies to relate disease to exposure. In the screening study (Chapter 3) each subject provided a set of lifestyle variables (from their habits questionnaire) and had been designated as positive or negative for oral cancer or precancer by the specialist. This information was used to create a logistic regression model, the dichotomous outcomes being positive or negative.

5.1.5 Artificial intelligence

Sophisticated computer programmes are currently being developed which perform functions similar to logistic regression analysis. Neural networks are one type of development and are commonly used in medicine to analyse data in order to provide a weighted risk for each individual of having a certain outcome or disease.

Neural computing is a new concept which is derived from the structure and functioning of the brain. Central to this technology is a device known as a neural network, which is a large number of simple processing units connected together in a complex net-like structure which resemble in very simplified form, the interconnections of the neurons in the brain.
Use of artificial intelligence and neural networks has increased considerably over recent years. They have been extensively used in all aspects of cancer research (Burke, 1994), for example as an aid in the diagnosis of cancer through interpreting mammographs (Wu et al, 1993), cervical smears by image recognition (Boon and Kok, 1993; Mango, 1994), ultrasound measurements of hepatic masses (Maclin and Dempsey, 1992; Maclin et al, 1991), early detection of colo-rectal cancer using nuclear resonance spectroscopy (Dwarakanath et al, 1994) and of malignant melanoma by colour images (Ercal et al, 1994) and analysis of laboratory data (Aston and Wilding, 1992; Wilding et al, 1994). Neural computing has also been used in cancer outcome predictions (Ravdin and Clark, 1992; Kappen and Neijt, 1993, Floyd et al, 1994) and treatment decisions (McGuire et al, 1992). There are many other diverse uses of neural network systems such as estimating fetal weight in the macrosomic fetus from ultrasound measurements (Farmer et al, 1992) and in the differential diagnosis of various lung diseases (Asada et al, 1990) where the decision performances of NN were found to be similar to those of standard methods.
5.2 Aims

There are several studies in the literature which have found relationships between an individual’s lifestyle and risk of cancer, (Chapter 1). Each participant in the main screening project (Chapter 3) provided information about their age, gender, attendance at the dentist and tobacco and alcohol habits, and this information was used in an analysis of risk factors.

The aims of this part of the study were:

1. To create a logistic regression model to assess the relative risk of the various factors on a subject having a positive lesion.

2. To evaluate the use of artificial intelligence for identifying a subject at high risk of oral cancer or precancer based on lifestyle factors.
5.3 Material and Methods

5.3.1 Selection of subjects

The methods of recruitment and selection of the subjects for screening have been described in Chapter 3. A total of 2027 adults were screened by twenty four screeners (dentists from hospital, general practice and the community service) in conjunction with one specialist who examined all subjects independently and provided the definitive diagnosis or 'gold standard'. All subjects completed a pre-screening questionnaire (appendix 5) with regard to their age, gender, smoking and drinking habits, and dental attendance and provided informed consent. A total of ten items of personal information were collected for each subject.

This information was collected since age (Hindle and Nally, 1991), gender (Office of Population Censuses and Surveys, 1994), tobacco and alcohol (McCoy and Wynder, 1979; Mashberg et al, 1993; Gupta et al, 1992) may influence oral cancer risk status. Dental attendance was used as an indication of oral health awareness.

5.3.2 Creating a logistic regression model

A calculation of relative risk for oral cancer and precancer, was obtained by logistic multiple regression (SPSS) using personal characteristics and lifestyle factors as independent variables. These values were obtained from the pre-screening
questionnaire (appendix 5). Among these, age was considered as a continuous independent variable with all subjects being aged 40 years or over, since 98% of all oral cancer cases occur in those aged over 40 (Hindle and Nally, 1991). Gender (male or female) was included as a dichotomous variable; according to recent OPCS data (1994) oral cancer is twice as common in males as females. Dental attenders were those subjects who claimed to have attended within the past year. This variable was used since it gave some indication of mouth awareness and participation in prevention. Alcohol and tobacco consumption are considered to be risk factors for oral cancer and precancer and subjects were divided into three groups according to claimed levels of use. Several studies have demonstrated a rising risk of oral cancer with increased use of tobacco or alcohol (Brugere et al, 1986; Blot et al, 1988; Rothman and Keller, 1972). The levels were set according to the recommendations for smoking and drinking levels for males and females in the United Kingdom (Department of Health 1992). A current smoker was defined as one who smokes now or had done so within the past ten years. The heavy and moderate groups for both smoking and drinking were compared to the light drinking and non-smoking groups by creating dummy variables for the heavy and moderate groups (Altman, 1991). Light drinking and non-smoking groups were therefore entered into the analysis as zero for each of the dummy variables. Variables labelled, z1, z2, z3 and z4 were created for the heavy and moderate groups. All the variables are contained in table 5.1.
Table 5.1: Input variables from personal information of the screened population

<table>
<thead>
<tr>
<th>Risk</th>
<th>Definition</th>
<th>Specification in logistic multiple regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$\geq 40$ years</td>
<td>Continuous variable</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/ Female</td>
<td>Male: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: 0</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>$&gt; 1$ or $&lt; 1$ year</td>
<td>$&gt; 1$ year: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&lt; 1$ year: 0</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>$\geq 20$ cigarettes/ day</td>
<td>dummy variable, $z_1 = 1$ ($z_1 = 0$ for moderate and non-smokers)</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>$&lt; 20$ cigarettes/ day</td>
<td>dummy variable, $z_2 = 1$ ($z_2 = 0$ for heavy and non-smokers)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>no cigarettes/ $&gt; 10$ years</td>
<td>compared to heavy and moderate smokers</td>
</tr>
<tr>
<td>Alcohol (units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>$&gt; 21$ M / $&gt; 14$ F</td>
<td>dummy variable, $z_3 = 1$ ($z_3 = 0$ for moderate and light drinkers)</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>$&gt; 5$ units $&lt; $ Heavy</td>
<td>dummy variable, $z_4 = 1$ ($z_4 = 0$ for heavy and light drinkers)</td>
</tr>
<tr>
<td>Light drinker</td>
<td>$&lt; 5$ units/week</td>
<td>compared to heavy and moderate drinkers</td>
</tr>
</tbody>
</table>
5.3.3 Training the neural network

The neural network was prepared by a co-researcher (Mr Alan Elliot, personal communication) using Turbo Pascal programming language (Borland International Inc. California). All the data from the pre-screening questionnaire had been entered into Paradox database (Borland International Inc. California) and it was therefore possible to import all the data directly into the neural network, after conversion to binary variables. The prevalence of positive lesions in the 2027 subjects screened for oral cancer and precancer was found to be 2.7% and the neural network was programmed to produce two groups of subjects each with 2.7% prevalence of positive lesions. The two groups were a training set of 1662 individuals and a test set of 365 individuals.

The neural network was trained by providing ten items of personal information pertaining to age, gender and habits (from the pre-screening questionnaire) and the specialist's diagnosis, which was positive (oral cancer or precancer present) or negative (disease-free). In effect the neural network was therefore provided with an input and an output, this enabled it to set up a recognition pattern. Once a recognition pattern has been set up it is possible to input the personal information of an individual which can be processed to provide an output or a 'screen' diagnosis for that individual.
5.3.4 Testing the neural network

The neural network was tested by presenting it with the same ten variables of personal information for each of the 365 individuals in the test set. Since the neural network had set up a recognition pattern it was able to provide an output value for each individual. An individual is determined as positive or negative depending on their output value and whether this is greater or less than a pre-determined threshold value which was 0.4 in this study. The sensitivity and specificity of the neural network's ability to predict the presence or absence of oral precancer or cancer was calculated as described previously (Altman, 1991; Downer, 1994) and compared to the sensitivity and specificity obtained by the screeners who screened the same subjects in the main screening programme (Chapter 3). For ease of analysis the results of the 24 screeners were pooled into one group and the overall sensitivity and specificity calculated.

The network's ability to differentiate between positive and negative cases (decision threshold) could be altered by adjusting the weight given to each of the ten variables. The state of optimum performance was evaluated by plotting receiver operating characteristic (ROC) curves (Altman and Bland, 1994c). These plot the true positive (sensitivity) against the false positive (1-specificity) rates at different decision making thresholds and determine a test's ability to differentiate between normal and abnormal. The diagnostic accuracy of the neural network is represented by the area under the curve where a perfect test gives an area of 1.0 and a random classification produces a value of 0.50 (McClish, 1987; Kay and Knill Jones, 1992). The likelihood
ratio (Radack et al., 1986) which is calculated from the sensitivity/ false positive rate was also calculated for the neural network and this was compared with that for the screeners.

5.4 Results

5.4.1 Profile of all the input variables

The overall population profile is shown in Table 5.2. All subjects were aged 40 years or over, the mean being 57.21 years. Forty four per cent of the population were male and 56 per cent female. Seventy one per cent of subjects claimed to have attended a dentist during the previous twelve months. Heavy smokers comprised eight per cent of the screened population and heavy drinkers, three per cent. The light drinking group contained 71 per cent of the screened population and the remaining 26 per cent were classified as moderate drinkers. Claimed non smokers comprised 62 per cent of the screened population and moderate smokers 30 per cent.

There was a slightly greater number of smokers and drinkers in the medical practice population. As expected the number of regular dental attenders in the dental hospital group (85%) was much higher than that of the medical practice (57%) which had an attendance level comparable to that reported by the Dental Practice Board (1994); 60% of all adults registered with a dentist.
Table 5.2  Breakdown of screened population (2027 subjects)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Medical practice</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.85</td>
<td>54.8</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>47% M, 53% F</td>
<td>42% M, 58% F</td>
<td>44% M, 56% F</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>&lt; 1 yr: 57%</td>
<td>&lt; 1 yr: 85%</td>
<td>&lt; 1 yr: 71%</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 yr: 43%</td>
<td>&gt; 1 yr: 15%</td>
<td>&gt; 1 yr: 29%</td>
</tr>
</tbody>
</table>

**Smoking**

<table>
<thead>
<tr>
<th></th>
<th>Medical practice</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy smoker</td>
<td>9%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>33%</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Non smoker</td>
<td>58%</td>
<td>66%</td>
<td>62%</td>
</tr>
</tbody>
</table>

**Drinking**

<table>
<thead>
<tr>
<th></th>
<th>Medical practice</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy drinker</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>29%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td>Light drinker</td>
<td>67%</td>
<td>74%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Medical practice: 985  
Hospital: 1042  
Total: 2027
5.4.2 Calculating the relative risks

Age, gender, smoking, drinking and dental attendance were analysed in a logistic regression model to assess the relative risk for oral cancer and precancer for each variable. Logistic regression was used to determine which of the prognostic variables, (age, gender, smoking, drinking and dental attendance) could predict the outcome (Table 5.3). Only those in the heavy smoking group had a significant risk of 2.36 (95 per cent CI, 1.13-4.93, p<0.05) of being diagnosed positive compared to non-smokers. Interactions between smoking and drinking were found to be non-significant.
Table 5.3 Logistic multiple regression with specialist diagnosis as dependent variable and individual characteristics as independent variables.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>b coefficient (SE)</th>
<th>Odds ratio</th>
<th>Confidence Intervals (95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01 (0.12)</td>
<td>1.01</td>
<td>0.99 - 1.00</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>0.33 (0.29)</td>
<td>1.38</td>
<td>0.79 - 2.44</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>-0.21 (0.32)</td>
<td>0.81</td>
<td>0.43 - 1.51</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>0.86 (0.38)</td>
<td>2.36</td>
<td>1.13 - 4.93</td>
<td>p&lt;0.05*</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>0.54 (0.31)</td>
<td>1.72</td>
<td>0.93 - 3.19</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>0.78 (0.48)</td>
<td>2.19</td>
<td>0.86 - 5.60</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>0.46 (0.31)</td>
<td>1.59</td>
<td>0.87 - 2.91</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>
5.4.3 The neural network

The neural network achieved a sensitivity of 0.80 and a specificity of 0.77, in that it correctly identified 8 of the 10 positive cases in the test set of 365 subjects (prevalence 2.7%) (Table 5.4). The detection rate is the same as the sensitivity and is the proportion of affected individuals with a positive test result (Wald, 1994). The sensitivity and specificity of the dental screeners were 0.74 and 0.99 respectively (Table 5.5). The likelihood ratio was calculated and compared to that of the screeners. It was found to be 3.48 compared to 74.00 for the screeners. The optimal performance of the network achieved a receiver operator characteristic curve with an area under the curve of 0.84 (figure 5.2).
Neural Network Test Set ROC Curve

(area = 0.84)

True positive ratio

False positive ratio

area = 0.84
### Table 5.4  Specialist result compared with neural network’s screening result

<table>
<thead>
<tr>
<th></th>
<th>Specialist</th>
<th>Neural Network</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>273</td>
<td>275</td>
</tr>
<tr>
<td>Total</td>
<td><strong>10</strong></td>
<td><strong>355</strong></td>
<td><strong>365</strong></td>
</tr>
</tbody>
</table>

Sensitivity: \( \frac{8}{10} \) = 0.80  
Specificity: \( \frac{273}{355} \) = 0.77  
Positive predictive value: \( \frac{8}{90} \) = 0.09  
Negative predictive value: \( \frac{273}{275} \) = 0.99  
Positive prevalence: \( \frac{10}{365} \) = 2.7%  
Likelihood ratio (0.8/0.23) = 3.48
Table 5.5 Specialist result compared with dentists’ screening result.

<table>
<thead>
<tr>
<th>Screener</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>40</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Negative</td>
<td>16</td>
<td>1951</td>
<td>1967</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>1971</td>
<td>2027</td>
</tr>
</tbody>
</table>

Sensitivity: \( \frac{40}{56} \) = 0.71
Specificity: \( \frac{1951}{1971} \) = 0.99
Positive predictive value: \( \frac{40}{60} \) = 0.67
Negative predictive value: \( \frac{1951}{1967} \) = 0.99
Positive prevalence: \( \frac{56}{2027} \) = 2.8%
Likelihood ratio (0.74/0.01) = 74.00
5.5 Discussion

Logistic regression analysis is widely used throughout epidemiology to calculate odds ratios. The odds ratio is used to relate disease risk to exposure. Brugere et al, (1986), by use of this method, demonstrated a relationship between the site of oral cancer and level of daily alcohol consumption whilst Mashberg et al (1993) were able to demonstrate an increasing odds ratio of oral cancer with tobacco (35 cigarettes a day) and alcohol (21 whisky equivalents a day). By evaluating the relative risk of different lifestyle habits it is possible to use this information for developing more sophisticated means of identifying individuals who could be targeted for screening or health education. Wilkinson et al (1994) evaluated a risk scoring system for cervical cancer to be used in primary care. The system enabled identification of 75% of those women with cervical neoplasia, they concluded that further research was required to assess the effectiveness of risk targeting.

Although logistic regression is a useful tool for assessing risks it would not be practical in the primary care setting, where time and ease of use is of the essence. The use of neural networks, which has become more accepted in recent years, may be more feasible. There are few references to neural networks in the literature prior to 1988 but their use is increasing in the field of cancer control, prevention and treatment.

In the screening programme reported in Chapter 3 the overall performance of the dentists was superior to that of the neural network. However the sensitivity of the
neural network was similar to that of the junior hospital dentists. This is not surprising since the network will have determined that most of the subjects with lesions were smokers and/ or drinkers. The specificity achieved by the neural network was, however quite low with a false positive rate of 23%, and the odds of having a lesion if classified as positive by the network were only 3.5 compared to over 60 if screened positive by a dentist. This was probably due to the network selecting all those individuals who, from their risk habits could be considered to have a high likelihood of being diagnosed positive but had not developed lesions. In a preliminary screening procedure such as this, a high false positive rate is not a cause for concern, and indeed may be beneficial since these individuals will be subjected to a further test (oral examination) and can be selected for preventive education. In a similar study in which a neural network was used to predict breast cancer malignancy Floyd et al (1994) found that the network achieved sensitivity of 1.0 and a specificity of 0.59. Ercal et al (1994) found that their neural network designed to detect malignant melanomas from colour images was able to classify correctly over 80% of the malignant and benign tumours on real skin images. Snow et al (1994) used a neural network to assess the diagnosis and prognosis of prostate cancer. The network was able to predict a biopsy result with 87% overall accuracy from serum prostate specific antigen levels. It was also able to predict tumour recurrence with 90% overall accuracy.

The role of neural networks in screening programmes may be as an adjunct in identifying high risk individuals. If the cost of setting up a screening programme and the cost of a dentist’s time is taken into account, then a neural network may prove to
be more economical since it could make an *a priori* selection of high risk individuals that ought to be screened by a clinician. In dental practice, the system could be used to assign a risk status to a patient in order to help decide who should receive a detailed oral mucosal examination.

Although artificial intelligence is relatively new to the field of medicine and dentistry, its usefulness in clinical decision making is becoming more apparent. This part of the study has shown that this system, or a more user friendly version, could have a place in the dental surgery. A simulation of how a neural network (NN) would be able to predict the likelihood of an individual having a precancerous or cancerous lesion of the oral mucosa, given the age, gender, smoking, drinking and dental habits of each screened individual, is shown in Figure 5.3. In the economic climate which exists today it is important to get the best output from the minimum input in terms of cost and patient satisfaction. If the neural network is used as a filtering mechanism it avoids the unnecessary cost, time and potential distress of screening low risk asymptomatic patients.

Despite the projected use of advanced computer technology in the early detection of oral cancer, it is still of utmost importance to increase awareness of oral cancer and its risk factors within the dental and medical profession and general public. From the findings in this study it is tentatively proposed that neural networks will have an increasing place in the early detection of oral cancer following further studies.
Neural network (NN) for oral cancer screening
(Figure 5.3)
Chapter 6

Health outcomes and utilities
The rationale behind the National Health Service was to create a system in which health care could be fairly distributed (Williams, 1988). Obviously in a climate of economic restraints most government policies are concerned with setting priorities since even the richest nation cannot afford to do everything that is possible to improve the health of its citizens. Every health intervention - that is an action which is intended to improve someone’s health (or reduce the rate at which it deteriorates) is judged by the health economist in terms of patient health benefits and use of resources. Over the years attempts have been made to quantify the health status of individuals and the population to enable comparisons of various health interventions. The objective is to obtain a measure which is sensitive to any changes in health status over time. Health status measurements are used widely in resource allocations and in economic appraisal of health care programmes.

6.1.1 Assessing a health care programme

In analysing the economic benefits of a health care programme, the input resources must be compared to the output resources. The 'output' is generally termed as health improvement (Figure 6.1; Torrance, 1986). The input resources can be broken down into direct costs of personnel and drugs used and indirect costs, in terms of lost production from patients participating in the program. The output from the programme is measured in such terms as morbidity and mortality avoided, economic benefits from keeping people healthy, in that they continue to work, and value of
health improvement. This last aspect is referred to as the 'value' or health status measurement and can be measured in three ways, these being willingness to pay, utilities and quality of life years.

6.1.1.1 Willingness to pay

In order to quantify this, individuals are told to imagine that they have to pay for health care and they are asked the maximum amount that they would be willing to pay for the intervention described. Miedzybrodzka et al (1994) described this method to evaluate the difference between 2 types of cystic fibrosis screening tests.

6.1.1.2 Utilities

Utilities are cardinal values assigned to each health state on a scale that is established by assigning 1.0 to health and 0 to death (Walker and Rosser, 1988). The values obtained reflect the quality of health states and allow morbidity and mortality to be combined into quality of life years (QALYs).
Figure 6.1  Health programmes (adapted from Torrance, 1986)

Health programme

Input

Costs of personnel, drugs lost production

Output

Better health

Economic gain

Value of health gain (Qualys)
The theory of QALYs was developed in the 1970's by Fanshel and Bush (1970) who termed it 'function years gained'. It is derived from the idea of life being divided into two main components; those being quantity and quality of life. A model combining these two components is shown in Figure 6.2 (Torrance, 1987) from which it is possible to calculate the QALY. The QALY is based on the idea of a year of healthy life expectancy being worth unity whereas a year of unhealthy life expectancy would be worth less than one (Torrance and Feeny, 1989). Death is considered to be equivalent to zero and therefore other health states lie between these two fixed points. If the health state is considered to be worse than death then the QALY becomes a negative value. Quality of life is a concept encompassing a broad range of physical and psychological characteristics and limitations, which describe an individual’s ability to function and to derive satisfaction from doing so (Walker and Rosser, 1988).

There are many outside influences other than health which will influence one’s quality of life such as economic, political, cultural, environmental, aesthetic and spiritual factors (Torrance, 1987) and it is therefore not unusual for researchers to refer to health related quality of life. Since there is little consensus on the concept of quality of life it is important that any measurement should at least incorporate four core areas of function:

1. Physical
The concept of a measure for quality of life is that it can be used in the comparisons between different types of interventions in research, clinical trials and in predicting long-term outcomes in terms of morbidity and mortality. It can also be related to the costs of respective interventions. Beneficial health care will therefore generate positive QALYs and efficient health care will have a low cost per QALY. Therefore a health care programme with a low cost QALY is considered as a high priority intervention (Lockwood, 1988).

As with the introduction of any new methodology, the concept of QALYs has been criticised most notably by Harris (1988) who claims it violates the equality principle which is that peoples' lives and fundamental interests are of equal value and therefore must be of equal weight. He claims that QALYs are inherently ageist preferring to treat a younger person for life saving treatment over an older person. However the 'good innings' argument (Lockwood, 1988) discounts this in terms of fairness in that the older person has had their 3 score years and ten. Another argument put forward by Harris (1988) is that QALYs tend to favour patients who can be treated at less cost when faced with limited resources. This is probably a valid point but in terms of health economy it is arguably fairer to successfully treat 10 patients at £100 than only one at £1000.
Figure 6.2  Calculating quality adjusted life years gained from a health intervention (adapted Torrance, 1987)
Obviously any system which involves choices having to be made will result in some individuals losing out and this lends support to developing an efficient system to calculate maximal benefits in a climate of limited resources. At present the Department of Health is in the process of developing QALY league tables (Robinson, 1993).

6.1.2 Other methods of quantifying the impact of disease on life and its quality

6.1.2.1 Premature mortality rates

The number of deaths associated with specific diseases before 65 or sometime 75 years of age is measured. A higher value is placed on life before this cut-off age. Obtaining this life span for as many people as possible is important.

6.1.2.2 Life years saved

This assumes a life span of 75 years thus saving a young person’s life, for example at 25 years of age would save 50 years of life.

6.1.2.3 SAVE (Save young life equivalent)

This a method in which the SAVE unit of measurement (Nord, 1992) is based on consideration of medical benefit (quality of well life produced) by valuing outcomes.
These are measured by movements from various levels of dysfunction to normality. It has been criticised as being ageist (Glicher, 1992; Sayers, 1992) and disadvantageous to disabled people who cannot move between levels. However it is generally accepted that most people would consider the saving of a young person's life more important than prolonging an old person's (Lewis and Charny, 1989). Certainly from an economic and societal point of view this is advantageous in terms of years of potential benefit a young person's life can provide to the state. However Nord (1992) suggests that the SAVE procedure is only to be used as an aid to priority setting and not in assessing benefits to the economy.

6.1.2.4 *Healthy Years equivalent*

This is used as a measure of outcome of health combining two outcomes of interest—quality and quantity of life. Mehraz and Gafni (1991) who developed this technique claim that it fully represents patients' preferences since it is based on a standard gamble method (Von Neumann and Morganstern, 1953).

An extreme example of using a QALY type of analysis was the Oregon trial (Kitzhaber, 1989) where health states and their treatments were ranked and funding of these conditions would depend on their rank. This project has been openly criticised in that it produced anomalies such as cosmetic breast surgery being rated higher than treatment for an open thigh fracture and, although the public was consulted, those who actually presented themselves at open meetings for discussion tended to be involved in the medical profession (Klein, 1991).
6.1.3 Choosing an appropriate instrument to measure quality of life

It is important to choose an instrument which is appropriate to the conditions it is to measure. The choice of the instrument will be determined by the aim of the study, what is defined by the quality of life, resources and patient characteristics. The questionnaire used, needs to be reliable and valid in that it needs to be able to discriminate between different groups of respondents. The following parameters are used to judge the suitability of an instrument to measure quality of life. (Selby, 1988; Clark and Fallowfield, 1986).

6.1.3.1 Acceptability

This can be measured in terms of speed to complete a questionnaire and the number of participants who are unable to complete or find it unacceptable.

6.1.3.2 Reliability

This is an indication of how reproducible the questionnaire is and therefore the amount of random error associated with its use. Reliability estimates are expressed as correlation coefficients and are measured as test-retest reliability and internal consistency.
6.1.3.3 Validity

This is a measurement of how well the instrument measures what it is supposed to be measuring. This is done by comparing it to a gold standard such as expert judgement. The instrument also needs to be able to document changes in quality of life over time. Validity and reliability are discussed further in Chapter 4.

6.1.3.4 Ease of administration and analysis

It is important that the questions and response categories are simple and easy to understand. Pre-coded boxes tend to be simpler to complete than visual analogue scales.

6.1.3.5 Patient versus operator

Self assessment avoids the introduction of bias by the interviewer but interviews may uncover otherwise unvolunteered information.

6.1.4 Who should measure quality of life

Several studies have attempted to correlate the perception of quality of life by the patient and the professional treating them. In one study of a group of cancer patients it was found that the doctors were unable to measure the quality of life of the patients. However the patients had a variety of malignant diseases and it is possible
that this may have had an effect on the performance of the questionnaire (Slevin et al, 1988). Another study which compared the views of cancer patients, the general public and doctors and nurses on chemotherapy, found that patients with cancer were more likely to opt for radical treatment, with a small chance of benefit, compared to those with no cancer. (Slevin et al, 1990). This demonstrates that it is difficult for those without disease to make decisions for those with the disease and how a slight increase in quantity of life will be traded for a drastic reduction in quality of life. In a study of rectal cancer (Boyd et al, 1990) it was found that patients with a colostomy attached a higher value on their quality of life than those with no experience of a colostomy (general public and doctors). This paper demonstrated that assessment of quality of life may change when a person enters that state of health and becomes accustomed to it. An evaluation of possible change in a patient's perception of quality of life was measured in a study of laryngeal cancer patients prior to and after a course of radiotherapy. The study found that the patients' assessment of their quality of life was consistent throughout treatment (Llewellyn-Thomas et al, 1993).

Over the past decade there has been an increasing emphasis on the patient or the general public as a health care consumer who has a right to information and participation in decision making. It is possible that participation in these decisions may help patients adapt to their disease and increase public awareness.

6.1.5 Quality of life in cancer trials

The number of cancer trials incorporating quality of life measurements has risen
dramatically since a review of 200 trials by Bardelli and Saracci (1978). They found that quality of life was rarely measured and proposed that this may be due to the complexity of the dimensions which comprise quality of life and the difference between different treatment regimes. Another factor was that survival was regarded as a greater priority than quality of life. However this situation has now changed and improving quality of life is an important goal of cancer treatment and prevention. (Kaplan, 1993).

6.1.6 Instruments for measuring quality of life in cancer patients

Although there are many instruments used to measure quality of life, those described below are generally accepted as effective measures of non-disease specific questionnaires.

6.1.6.1 Karnofsky performance scale

This was developed by Karnofsky and Burcehnal (1949) to assess the physical well being of cancer patients in response to chemotherapy. It is measured by the clinician. Ratings are between 100 (normality) and 0 (death). Clark and Fallowfield (1986) suggested that although it provided a useful scale for measuring health it was not useful in measuring quality of life.
6.1.6.2 Linear analogue self assessment

These tests have lines, the length of which is related to the experience under question, for example pain (Priestman and Baum, 1976; Selby et al 1984). The subject would then have to mark on the line their perceived amount of pain. This test is simple and representative but the problem lies in whether the measurement may not actually be related to the experience. Contraction bias is another problem where the subjects may underestimate the effects and therefore cluster their points in the middle of the line.

6.1.6.3 Spitzer QL Index

This test is designed for use by clinicians and has 5 items with a range of scores 0-10 (Spitzer et al, 1981). The items can be summarised as covering activity, living, health support and outlook on life. The system has been validated and correlates well with other tests. However a problem that arises is that it gives equal weighting to all questions. It can be completed in a minute.

6.1.6.4 Cancer Inventory of problem situations

This is now known as the CARES (cancer rehabilitation evaluation system), (Heinrich et al, 1984). The test is self-administered and divided into four categories these being personal care, medical, interpersonal interactions and miscellaneous. All the parameters have been obtained from the literature and it is of use in assessing the psychosocial and physical impact of treatment (Clark and Fallowfield, 1986).
6.1.6.5 European Organization for Research and Treatment of Cancer

This was developed by the quality of life study group of the European Organization for Research and Treatment of Cancer (EORTC), (Aaronson et al, 1988). It is a multi-dimensional method investigating symptoms, psychological distress and functional status. It is being evaluated in lung cancer patients and has been used by one group in cancer of the head and neck (Jones et al, 1992).

6.1.6.6 Euroqol

This questionnaire is being developed to measure several health states across a variety of people to allow comparisons between countries. SF36 is a modification of the Euroqol. It is a 36 item questionnaire covering 8 dimensions of quality of life and although developed in North America it is now in general use in Britain. It has been shown to be reliable and comparison between various socioeconomic groups and patients with long-term chronic illnesses give the correct expected results. The patients assess their medical state in this questionnaire and the results appear to correlate well with the professional assessment of that patient’s state. It is intended that this type of questionnaire can be used for comparison between studies and countries and as a potential measure of patient outcome within the NHS (Ware, 1993; Garrett et al, 1993).
6.1.6.7 Other questionnaires for quality of life.

Included in the psychosocial and social group of questionnaires is the HAD (hospital anxiety and depression) scale (Zigmond and Snaith, 1983), which measures non-somatic symptoms of depression and anxiety; the PAIS, psychological adjustment to illness scale (Derogatis and Lopez, 1983). The PAIS includes 45 items covering a wide range of areas such as social, family and sexual relationships and psychological distress. The Rotterdam Symptom checklist-90 which was developed by de Haes et al (1990) measures physical, social and psychological adjustment as well as daily activities and is widely used. A broader questionnaire is the Sickness Impact profile (SIP). This method measures the impact of health on behaviour, function, social interactions and emotional behaviour (Bergner et al, 1981).

It is probably still true that 'the perfect test to measure quality of life has yet to be developed' (Clark and Fallowfield, 1986). Although little work has been done in determining which type of questionnaire is best for head and neck cancer, one study (Hassan and Weymuller, 1993) compared a disease specific instrument for measuring quality of life with the Karnofsky scale and SIP and found that the disease specific was best at detecting change in quality of life in patients with head and neck cancer. However a general consensus is required so that comparisons between centres can be undertaken.
6.1.7 **Measuring quality of life in head and neck cancer**

'Without appropriate measurement of quality of life of patients with head and neck cancer, policy makers and clinicians making judgements about patient selection and treatment type will be doing so on the basis of beliefs and guesses' (Morris, 1990).

Quality of life is being considered increasingly as an important indicator of treatment outcome and is regularly used in cancer trials. Quality of life measurements are of particular relevance in head and neck cancers since some patients present with advanced disease which may be treated palliatively. Another reason that quality of life measurements are so important to cancers of the head and neck region are that some treatments result in gross physical dysfunction preventing normal life (Morris, 1994) and it is not possible to hide this disfigurement.

In comparison with breast cancer there is little research into the psychosocial effects of treatment for head and neck cancer. The effect of surgery to the face was compared to that of bereavement by Christine Piff (Let's face it) in that there is the need to accept the spoilt image that a patient may have of themselves following surgery (Harrison and Lund, 1993). As well as the anxiety and uncertainty faced by head and neck cancer patients, there is the difficulty of being able to communicate this since there may be loss of speech. There are several studies which evaluate the effect of various treatment on patients treated for oral cancer which are discussed later in this chapter.
6.1.7.1 Problems with measuring quality of life in head and neck cancer patients.

Morris (1990) in her review of studies into the quality of life in head and neck patients criticised them for being retrospective and having too small samples although she conceded that this was due to the low incidence of oral cancer. Since most studies are retrospective it is difficult to assess the influences of other factors present prior to the onset of oral cancer. The studies tended to be descriptive and little reference has been made to the site of the disease (again this is probably a reflection of the numbers of oral cancer patients). There has been very little information gathered on the influence that oral cancer may have on the carers of these patients.

However with the development of further questionnaires which can be used between different diseases it is hoped that some of these problems will be overcome and the limited insight into the problems experienced by oral cancer patients increased (Pruyn et al, 1986)

6.1.8 Utilities

Utility measurements are widely used within health economics to assess the benefits of health care programmes. A utility is a numerical value assigned to a state of health and lies between 0 (death) and 1 (health). There are three sources of obtaining utility values; expert opinion, from published literature, or from direct measurement. Judgement involves simply establishing plausible values for a health state from the
opinion of experts. Since there are a growing number of studies which have measured utilities for various health states (Sackett and Torrance, 1978; McNeil et al, 1982), these values can be used for other similar studies. However in head and neck cancer there are few examples (Velanovich, 1990) with most concerning laryngeal cancer (Llellwyn-Thomas et al, 1993; Maas and Stalpers, 1992). Direct measurement will provide the most accurate method of calculating utilities. Each state will need to be described in terms of emotional, physical and social function. Several methods to describe the health states can be used such as verbal description to video tapes. The decision on what to use greatly depends on the subjects questioned. There is much discussion as to whose utilities should be measured, but it can basically be divided into patients, health care professionals or the general public.

6.1.9 Utility measurement

Utilities can be measured by ordinal scales by ranking the health states or outcomes in order of preference. Cardinal scales are sets of numbers assigned to health states where the number represents the strength of preference. The cardinal scale method is more often used. As mentioned previously the scale lies between 0 and 1.

6.1.9.1 Rating scale

A typical rating scale is a line which represents several health states (Figure 6.3). The preferred health state is at one end of the line with the least preferred health state being the other endpoint. The subject is then requested to choose which point best
refers to their present health state. Visual aids have been used to help subjects make their preference (Torrance et al, 1982). It is important to make it obvious to the subject that the distances between the health states should correspond to the subject’s feeling about the various health states.
Imagine yourself living the rest of your normal life expectancy with a colostomy. Please make an overall judgement about this health state in relation to perfect health and death by making a mark on the line.

Death Perfect health
6.1.9.2 Standard gamble technique

This is a classic method generally used in the field of decision analysis which was proposed by Von Neumann and Morganstern (1953). The subject is required to make a choice between two alternatives (Figure 6.4). Choice A is the health state with certainty whereas choice B takes the risk of death (worst outcome; 1 - p) or a healthy life (best outcome; p=1). The probability of health is varied until the subject is indifferent to choices A or B. When the probability of a healthy life is equal to 1.0 the subject will prefer choice B since there is no risk of immediate death. Whereas if the probability of healthy life is 0 the subject will prefer choice A since choice B is certain immediate death. Somewhere in between these extremes the subject will be indifferent to choice A and B. This is the utility that is assigned therefore to choice A. For example if the subject assigns a low utility to state A they are willing to take a large risk of immediate death. Variations on the above can be used since health and death need not be used as alternatives. It would be possible to substitute differing health states as long as one outcome is preferred to another. It would therefore be possible to compare 3 health states.
Figure 6.4  Standard gamble technique (Von Neumann and Morganstern, 1953)

Choice A

Health state for the rest of life

Choice B

Healthy for the rest of life

Immediate death

p: probability
This technique was developed by Torrance et al (1972). In this method the subject is required to choose between a chronic health state for a certain time followed by death or health for less time followed by death (Figure 6.5). It is considered possibly simpler to use than the standard gamble technique although both techniques obtain preference values for the subject’s response to decision situations as compared to the rating scale which obtains values from explicit responses.
Figure 6.5 Time trade-off (Torrance, 1986)

The subject has to choose between health for time (x) or illness for time (t), both of which are followed by immediate death.

<table>
<thead>
<tr>
<th>Health state</th>
<th>Alternative 1</th>
<th>Alternative 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

x | t
6.1.10 **Aims**

This part of the study had two objectives detailed below:

**6.1.10.1 Assessing utility values for oral cancer from the general public**

The aim of this study was to obtain utility values for a sample of the general public for various stages of oral cancer to enable comparison between utility values of treatment outcomes for small and large cancers as perceived by a sample of the general public.

**6.1.10.2 Assessment of quality of life in patients treated for oral cancer**

The aim of this study was to obtain a quantitative measurement of the quality of life in patients who have been treated for oral cancer. As part of the overall assessment of an oral cancer screening programme it is important to evaluate the present outcomes for oral cancer not only in terms of survival but also in terms of quality of life.
6.2 Materials and methods

6.2.1 Recruitment of subjects

Members of the general public aged 40 years or over were approached whilst purchasing goods from a tuck shop situated within Unilever Colworth House, Bedford. All subjects were aged 40 years or over since over 98% of oral cancer cases occur in this age group and age may influence the outcome chosen. For example the response of a 90 year old compared to a 19 year old in having only 5 years to live will be vastly different. They were invited to complete a questionnaire. People who had relatives or friends with oral cancer or medical knowledge of the disease were excluded. It was not possible to measure compliance since there was a rapid flow of customers and not all eligible subjects could be approached. 100 eligible subjects participated and were personally interviewed. Consent was verbal and the subjects remained anonymous.

6.2.2 Standard Gamble questionnaire

A standard gamble technique (Von Neumann and Morganstern, 1953) was used. Each subject was asked to imagine that they had to choose between the situations of two people, person A having a type of mouth cancer (a description of each stage was provided,) and person B being perfectly healthy, with no mouth cancer but with the risk of immediate death, such as being run over by a bus. The first question related to a state of oral precancer, the second to having a small oral cancer and the third
question to having a large oral cancer. All the subjects participating were told that it was a measure of 'what they would choose' if they were in the situation described. The full questionnaire and description of each stage (precancer, small and large cancer) is given in Appendix 7.

6.2.3 Analysis of data for utilities

The value at which the subject will not take any further risk of immediate death (the point at which the oral cancer state is equivalent to the probability) is accepted to be the preference value or utility. For example if a subject will not take a 20% risk of death compared to having oral precancer, the value for oral cancer will be 80% since this is equivalent to the probability of health (0.80). The mean for each stage of oral cancer was calculated. A Wilcoxon matched-pairs signed-ranks test was used to analyse the responses to each question to evaluate if there was any difference in the publics' perception of each stage.

6.2.4 Recruitment of oral cancer patients

72 patients attending for follow-up of intra-oral cancer at University College Hospital, The Middlesex Hospital or the Royal Ear, Nose and Throat hospital were invited to complete a questionnaire relating to their quality of life. The project aims were explained to each individual and informed consent received. All subjects had completed treatment a minimum of 6 months previously and had no obvious evidence of recurrence of oral cancer. The subjects were assigned to one of two groups
depending on the clinico-pathological stage of their primary lesion. Group A included those subjects with Stage 1 oral cancer and comprised 22 subjects. Group B included those subjects with Stage 2, 3 or 4 oral cancer and comprised 50 subjects. The staging of oral cancer is described in Chapter 1.

6.2.5 Quality of life questionnaire

All the subjects were personally interviewed as this method produces greater reliability and may also uncover important information which would otherwise have been overlooked (Selby, 1988). The questionnaire took approximately 30 minutes to complete and was based on a questionnaire previously used by Rathmull et al (1991). It comprised 18 questions which related to the physical, psychosocial and disease specific aspects of quality of life following oral cancer treatment. The full questionnaire is contained in Appendix 8.

6.2.6 Analysis of quality of life data

The data were analysed by comparing the response of group A (stage 1 cancers) and group B (those greater than stage 1) for each question. There were 18 questions and the responses were dichotomised into having symptoms or not, due to the small number of subjects. The presence of symptoms was assigned unity and the absence as zero. A chi squared test was used for each question.
6.3 Results

6.3.1 Assessing utility values for oral cancer from the general public

One hundred subjects participated in the study. There were 62 males and 38 females in the sample questioned. The mean age was 49.81 years. A utility for oral precancer, stage 1 cancer and stage 2 or greater was obtained using the technique described by Von Neumann and Morganstern (1953).

The mean utility for each state was calculated by pooling all the subjects’ responses. The following mean utilities were obtained: oral precancer: 0.92, stage 1 cancer: 0.88 and stage 2 cancer or greater 0.68.

A Wilcoxon matched-pairs signed-rank test was used to compare the response for each subject between precancer and stage 1 cancer; stage 1 cancer and stage 2+ cancer and precancer and stage 2+ cancer. There was a significant difference between all three comparisons. The results are summarised below.
### Utility

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Precancer</td>
<td>0.92</td>
</tr>
<tr>
<td>Stage 1 cancer</td>
<td>0.88</td>
</tr>
<tr>
<td>Stage 2+ cancer</td>
<td>0.68</td>
</tr>
</tbody>
</table>

#### Wilcoxon Matched pairs analysis

- Precancer by Stage 1: $Z = -3.51$, $p < 0.05$
- Precancer by Stage 2+: $Z = -7.29$, $p < 0.05$
- Stage 1 by Stage 2+: $Z = -7.50$, $p < 0.05$

### 6.3.2 Assessing quality of life in oral cancer patients

A total of 72 subjects were eligible to participate in this study. The low number is partly due to the nature of oral cancer. In patients with stage 1 cancer there were a large number with areas of field change, and thus not free of disease and therefore not eligible for entry into the study. Control of the primary lesion is also difficult and a number of subjects attending clinics often had areas of recurrence or occasional metastases. However the numbers were considered to be sufficient as a pilot study. The breakdown of oral cancer patients is contained in table 6.1. Of the 72 subjects,
62% were male. The average age of the group was 58.51. Cancer of the tongue comprised 36.6% of all the cancers. The distribution of gender and sites in the pilot study was similar to the oral cancer registrations found in the general population (OPCS, 1994) of which 65% are male and cancer of the tongue accounts for 29%.

The subjects were subdivided by stage into the types of treatment they had received (table 6.2 a-d). As expected those with large cancers received more aggressive surgery and radiotherapy usually with chemotherapy. However there is a large divergence of types of treatment provided and this is often listed as a problem when trying to evaluate difference in survival rates for oral cancer between different establishments or indeed which type of treatment provides the best result in terms of survival and quality of life. Laser therapy is still relatively new compared to more established modes of treatment hence the small numbers of treated cases.

The proportion of subjects with symptoms were compared with a chi squared test using a statistical package (SPSS/PC+). Fisher’s exact test was used for those questions containing low frequencies. These results are contained in the table 6.3. There were 18 questions and the numbers of subjects in group A (small cancers) and group B (large cancers) were compared. The null hypothesis was that there should be no difference in the frequency of patients with symptoms in each group. The following responses were found to be significantly different between the two groups in that group B had a larger number of patients with this symptom than group A. These symptoms were dry mouth, loss of weight, difficulty in eating or drinking, eat alone or with family and impaired social time. Eating and drinking difficulties could
possibly account for the difference between the two groups in eating alone or just with close family. It probably accounts also for the loss of weight and lack of appetite found in the large cancer group. There was also a significantly higher number with a dry mouth in the large cancer group. This is to be expected since this group would have a higher proportion of people treated with radiotherapy. Large oral cancer patients had a significantly different social time post-treatment compared to those in the small cancer groups. A small proportion of both groups had difficulty in being understood or were concerned about their appearance but the differences between the groups was not significant.
Table 6.1 Breakdown of oral cancer patients

<table>
<thead>
<tr>
<th></th>
<th>Stage 1 cancer</th>
<th>Stage 2+ cancers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13 (59%)</td>
<td>32 (64%)</td>
<td>44 (62%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (41%)</td>
<td>18 (32%)</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>Average age</td>
<td></td>
<td></td>
<td>58.51</td>
</tr>
<tr>
<td>(years)</td>
<td>57.71</td>
<td>58.84</td>
<td></td>
</tr>
<tr>
<td>Sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>11 (50%)</td>
<td>15 (30%)</td>
<td>26 (36.6%)</td>
</tr>
<tr>
<td>(ICD 141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gum</td>
<td>5 (23%)</td>
<td>11 (22%)</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>(ICD 143)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor mouth</td>
<td>2 (9.0%)</td>
<td>13 (26%)</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>(ICD 144)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>2 (9.0%)</td>
<td>1 (2%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>(ICD 140)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>2 (9.0%)</td>
<td>10 (20%)</td>
<td>12 (16.9%)</td>
</tr>
<tr>
<td>(ICD 146)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stage 1 cancer n=22
Stage 2+ cancer n=50
Table 6.2a Stage 1 cancer (n:22)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Laser</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>11</td>
</tr>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>1</td>
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<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 6.2b Stage 2 cancer (n:21)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Laser</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>7</td>
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<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>7</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>2</td>
</tr>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 6.2c  
Stage 3 cancer (n:10)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Laser</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>✓</td>
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<td>x</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 6.2d  
Stage 4 cancer (n:19)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Laser</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>2</td>
</tr>
<tr>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>1</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>13</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>2</td>
</tr>
</tbody>
</table>

213
Table 6.3: Frequency of small and large oral cancer subjects with symptoms.

<table>
<thead>
<tr>
<th>Question</th>
<th>Symptom</th>
<th>Small</th>
<th>Large</th>
<th>$X^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you in pain</td>
<td>Yes (1); No (0)</td>
<td>0.27</td>
<td>0.36</td>
<td>0.52</td>
<td>NS</td>
</tr>
<tr>
<td>How often are you in pain</td>
<td>At all (1); Never (0)</td>
<td>0.27</td>
<td>0.36</td>
<td>0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Do you have a dry mouth</td>
<td>Yes (1); No (0)</td>
<td>0.45</td>
<td>0.72</td>
<td>4.66</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Do your clothes fit the same</td>
<td>Yes (0); No (1)</td>
<td>0.27</td>
<td>0.68</td>
<td>10.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Are you aware of bad breath</td>
<td>Yes (1); No (0)</td>
<td>0.09</td>
<td>0.16</td>
<td>0.61</td>
<td>NS</td>
</tr>
<tr>
<td>Difficulty in eating &amp; drinking</td>
<td>Yes (1); No (0)</td>
<td>0.23</td>
<td>0.76</td>
<td>18.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eat alone or only with family</td>
<td>Yes (1); No (0)</td>
<td>0.00</td>
<td>0.18</td>
<td>4.52</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Do you have a bad taste</td>
<td>Yes (1); No (0)</td>
<td>0.14</td>
<td>0.36</td>
<td>3.69</td>
<td>NS</td>
</tr>
<tr>
<td>How would you describe your appetite</td>
<td>Normal (0); Not (1)</td>
<td>0.00</td>
<td>0.42</td>
<td>13.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Do you feel tired</td>
<td>Yes (1); No (0)</td>
<td>0.36</td>
<td>0.58</td>
<td>2.86</td>
<td>NS</td>
</tr>
<tr>
<td>How would you describe your social time</td>
<td>Same (0); Changed (1)</td>
<td>0.05</td>
<td>0.44</td>
<td>10.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Question</td>
<td>Symptom</td>
<td>Small</td>
<td>Large</td>
<td>$X^2$</td>
<td>p</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>How do you spend your day</td>
<td>Same (0); Changed (1)</td>
<td>0</td>
<td>0.12</td>
<td>2.88</td>
<td>NS</td>
</tr>
<tr>
<td>How would you describe your mood</td>
<td>Same (0); Changed (1)</td>
<td>0.18</td>
<td>0.36</td>
<td>2.29</td>
<td>NS</td>
</tr>
<tr>
<td>Do you work</td>
<td>Same(0); Changed (1)</td>
<td>0</td>
<td>0.12</td>
<td>2.88</td>
<td>NS</td>
</tr>
<tr>
<td>Can people understand you</td>
<td>Yes (0); No (1)</td>
<td>0.14</td>
<td>0.28</td>
<td>1.75</td>
<td>NS</td>
</tr>
<tr>
<td>Are you more concerned about appearance</td>
<td>Yes (1); No (0)</td>
<td>0.14</td>
<td>0.26</td>
<td>1.35</td>
<td>NS</td>
</tr>
<tr>
<td>Problems with personal relationships</td>
<td>Yes (1); No (0)</td>
<td>0.09</td>
<td>0.14</td>
<td>1.38</td>
<td>NS</td>
</tr>
<tr>
<td>More concerned about health</td>
<td>Yes (1); No (0)</td>
<td>0.50</td>
<td>0.60</td>
<td>0.62</td>
<td>NS</td>
</tr>
</tbody>
</table>
6.4 Discussion

6.4.1 General Public

In this part of the study it was demonstrated that it was possible to evaluate the public's perception of oral cancer since there was a significant difference in the utilities assigned to each of the stages of oral cancer described. There was also a trend as expected in that precancer had a greater utility than the small cancer which was greater than the large cancer.

The general public have been used by several investigators (Boyd et al., 1990; Fyffe and Kay, 1992; Sackett and Torrance, 1978) on the grounds that since it is society's resources that are used for various health care programmes it should be society which decides where these are allocated (Sackett and Torrance, 1978). Difficulty arises in informing the subject and knowing that the information provided to the subject is unbiased and complete. A short description of each stage of cancer was given to each subject since it was decided that photographs would not be appropriate and might upset some people. Kay (1991) claims that if the health state for which the utility is to be measured is unlikely to have been experienced by the individual then the description must be made in functional terms.

Health care professionals have also been used to evaluate various health states. Using this group minimises the descriptions required to envisage a health care state but studies have shown that health care professionals are notoriously inaccurate in
assessing patient utilities. (Slevin et al, 1990). A third group which could be used to evaluate utilities for oral cancer are the patients, although there is the possibility that they may exaggerate or underestimate the severity of their condition.

It was decided to use the standard gamble technique since it is a simple method and requires the subject to make an active choice based on the information provided. Fyffe and Kay (1992) used this technique for evaluating the utility of a decayed tooth and found not unexpectedly that the health care professionals placed a higher utility on a diseased tooth than the general public. Boyd et al (1990) found that the general public placed a lower utility on the treatment of colorectal cancer compared to health care professionals and patients. This is an area for further research and would have provided a useful comparison to the study described.

6.4.2 Comparing the quality of life in patients treated for large and small cancers

This study demonstrated that in terms of everyday living there is a difference in being treated for a small or large cancer. This is probably due to the type of treatment received. In terms of function and eating those treated for small cancers were significantly better off. The large cancer groups reported that their social life had changed since before treatment and was now mainly confined to close friends and family, if there was any. However it was encouraging that only a small percentage of patients had difficulty in being understood or were concerned with their appearance. In terms of the difference between being treated for a small or large cancer this study shows that there are considerable benefits to the individual in terms
of everyday living. The numbers in this study are small for reasons given previously.

Pruyn et al (1986) reviewed the literature on psychosocial aspects of head and neck cancer and concluded that there was limited insight into the problems faced by patients with oral cancer. He pointed out that head and neck cancer patients face not only anxiety related to their disease but also have problems with communicating, physical appearance and intake of food. Gamba et al (1992) found that of 66 patients treated for head and neck cancer and now free of disease, 18% stated that the disadvantages of therapy outweighed the advantages and recommended setting up rehabilitation programmes to offer support following surgery. He compared two groups and found that those with major facial disfigurement had a significantly poorer outcome with regard to appearance, self-image, partner relationships, sexuality and social isolation. In a study of 28 patients with treated head and neck cancer it was recommended that although psychological preparation for surgery may be difficult to achieve, some benefit may be gained in that it may help to decrease post-operative anger and depression (Strauss, 1989). In this sample of 28, over 50% had found themselves stigmatised because of their appearance. This stigma was not found in this study. Espie et al (1989) found that the level of psychological distress was higher in females and younger patients treated for intra-oral cancer. There was no significant difference in psychological outcome between the different sites where surgery was performed. However despite the small sample size, initial results suggested greater social dysfunction in surgery to the tongue and greater anxiety levels in patient treated for surgery to the buccal mucosa. In the present study the groups were too small to evaluate any difference between sites. Telfer and Shepherd (1993) found that 47% of
their patients exhibited symptoms of psychiatric disturbances, preoccupation with their physical symptoms following treatment was a frequent problem. They found that explanation for surgery related physical symptoms was important since they were often interpreted by the patient as disease recurrence. Again this study emphasised the need for counselling and support for oral cancer patients. Rapoport et al (1993) found that, although medical problems associated with treatment of head and neck cancer decreased with time, the psychosocial problems increased especially health fears, communication with partners and social relations. They concluded that this could be due to 'patient burnout' which could be decreased by acquisition of adequate coping skills.

Slevin (1992) pointed out that although counselling was an integral part of managing patients with HIV it seemed incredible that it was not incorporated into the treatment of cancer patients especially those receiving palliative care.

Although there is no consensus on methods of treatment for patients with advanced head and neck cancer, any treatment will initially result in adverse effects on the patient’s quality of life (Maher and Jefferis, 1990). A number of studies have investigated the effects of different types of treatment on quality of life. Morton et al (1984) compared the effects of surgery versus radiotherapy on a group of patients treated for bucco-pharyngeal cancer and found higher life satisfaction in patients treated by radiotherapy. He also found that there was greater dissatisfaction among patients treated with surgery. In a study of oral function following treatment of oral cancer, Teichgraber et al, (1986) found the best results in oral function were in those
patients treated by radiotherapy alone and the worst in those patients treated with both radiotherapy and surgery. Communication was also a problem and interference with swallowing was most severe in those patients treated for tumours of the buccal mucosa. All patients had increased eating times. Jones et al (1992) used the European Organisation for Research into Treatment for Cancer (EORTC) with a specific head and neck module to question 48 patients surgically treated for head and neck cancer. There was a low health index and poor quality of life, however the group included patients with recurrent disease. Patients treated with a hemi-glossectomy found difficulties in eating and swallowing. Rathmull et al (1991) interviewed 96 patients treated for head and neck cancer by surgery, radiotherapy or a combination of the two. All the patients were disease free at the time of questioning. They found that quality of life was greater in those patients treated by surgery alone but concluded that although quality of life was diminished in those treated by surgery and radiotherapy this would be outweighed if long-term survival was increased. This demonstrates the inevitable trade-off between quality of life and survival. Assessment of function, using food intake, was measured by Haribhatti et al (1993) who found that it depended closely on the type of reconstructive surgery performed. The majority of patients with small cancers questioned in the present study had been treated using laser therapy and further work is required in this area to assess the effects of this treatment compared to more conventional invasive treatments. The tables (6.2 a-d) listing the types of treatment provided for these oral cancer patients shows a wide divergence in such a small sample. For example for those patients with stage II cancer there were seven possible combinations of treatment modalities. Choice of treatment is obviously dependent on the establishment and surgeon but without
consistency it is not possible to evaluate which is the most successful type of treatment. This is a major problem in most forms of cancer and has been highlighted in particular by the Department of Health and the media for the treatment of breast cancer. It is an essential area which needs further research especially since five year survival rates are not improving.

In conclusion it has been demonstrated that it is possible to evaluate a utility for precancer and small and large cancers. This information is essential when attempting to assess the possible impact of a screening programme. The general public have an increasing role to play in determining health care needs and in a climate of economic restraints it is important that an intervention is deemed to be of benefit to many by reducing both mortality and morbidity. A reduction in morbidity from improved staging distribution has been shown since those patients with small cancers have a better post treatment quality of life in terms of functional eating and social life than those with large cancers.
Chapter 7

A possible decision model for oral cancer screening
7.1 Introduction

A model is an object or concept which is used to represent something else. It is reality scaled down and converted to a form we can understand. It enhances our understanding of systems and enables predictions to be made about their behaviour. (Bedford, 1993).

Prior to recommending the implementation of a screening programme it is important to assess the costs, benefits and risks to all participants. Unfortunately there are no simple methods to evaluate every aspect of a screening programme. In an ideal world randomised controlled clinical trials would be undertaken to observe the impact of screening different populations with different tests at different frequencies and assess various outcomes. However such an exercise would neither be practicable nor economically viable since it would involve many thousands of participants over many years. However, models of screening only provide general insight and understanding and not definitive answers. Although they cannot replace randomised controlled trials they have a place in aiding clinical judgement.

7.1.1 Types of model

The literature refers to two types of model, these being deep and surface. Deep models consider all aspects of a disease and how the course of the disease is affected by screening. They can therefore be used to estimate the value of screening
programmes which have never been studied in clinical trials. Deep models will be
dependent on several factors, such as the progression of disease since detection of
disease at a particular time in its development may effect the outcome. Surface
models however, are only used to repeat directly observed clinical events and can
therefore serve only to observe and estimate the consequences of existing
programmes.

7.1.2 Limitations of modelling

If models are used incorrectly they can perpetuate poor understanding, create errors
in clinical reasoning and produce incorrect results. Other difficulties may lie in the
construction of the model and the viability of quantifying the quality of life aspects
of cancer.

7.1.3 The Eddy model

The Eddy model (Eddy, 1986) for cancer control programmes was designed at the
request of the World Health Organization for use in developing counties. The
programme assesses the long-term effects of various interventions in the control
of cancer including prevention, screening, detection, treatment and rehabilitation, and
their effect on outcome in terms of quality of life, mortality and morbidity. Each
intervention provides varying degrees of health gain in terms of costs and increased
life expectancy. It is the overall health gains which are compared in assessing the
advantages and disadvantages of each intervention.
The initial step of the Eddy method is to construct a profile of the cancer in question in terms of incidence, detection, treatment and mortality. The profile will include five points:

A: initiation
B. detection
C. stages at which cancers are detected
D. mortality at each stage
E. numbers of deaths.

A specific time period is selected and the number of new cases is denoted by $N_c$ and the number of deaths from the cancer is denoted by $N_d$. The number of stages will depend on the cancer. For oral cancer, there are four defined stages of the disease dependent on size and spread (see Chapter 1 for staging of oral cancer). The model is illustrated in figure 7.1. It demonstrates the expected progression of a cancer in the absence of any secondary care interventions, in other words the status quo.
Figure 7.1: Profile of a cancer (Eddy, 1986)

- $N_c$: total number of new cases
- $N_d$: total number of deaths
- $S_1$-$S_4$: the numbers in each stage of the cancer
- $m_1$-$m_4$: the numbers of deaths in each stage
7.1.4 Effect on the Eddy model of different approaches to cancer control

7.1.4.1 Primary prevention

This is aimed at preventing the disease process from starting. The effect of this type of intervention would therefore be to reduce the number of new cases arising, i.e. reduce the value of $N_e$. 

7.1.4.2 Secondary prevention

This aims to detect disease at the earliest possible stage and to institute measures to prevent its further progression. Screening is an example of secondary prevention. It will therefore influence the values of S1-4 since one would expect a higher number of cancers to be detected at earlier stages (Shapiro, 1992). However it must be remembered that not all precancers will progress to cancers and that some will regress. This is certainly the case for some cervical cancers. On the one hand there may be no preclinical phase leading to rapid progression to cancer from a normal cervix, and on the other hand spontaneous regression of a cancer in situ (Gordis, 1994). Similarly increasing patient awareness will serve a similar function to that of screening in that the proportions in the S1-4 stage will change, since people may self-present earlier for treatment.
7.1.4.3 Tertiary prevention

This aims at preventing progression of disease by modifying risk factors and incorporating rehabilitation programmes. These activities will influence the number of people in point $N_d$ since improving treatment will decrease the number who die. Support activities such as pain control will not influence the outcome of the disease in terms of mortality but may have some influence on the quality of life of an individual and thus have some worth (or utility).

Eddy also includes values which need to be incorporated into assessing a cancer control programme. Cancer points are used to compare various types of cancers. Quality points measure the difference that each intervention will have on that patient's quality of life. Age points take into account the increase in life expectancy that an intervention will have, for example saving an 18 year old will provide more age points than a 50 year old.

7.1.5 Decision analysis

Decision analysis is a method of breaking complex problems down into manageable component parts, analysing those parts in detail and then combining them, in a logical way to indicate the best course of action (Thornton et al, 1992). In performing decision analysis there are four basic steps to be taken, these are to identify the decision problem, structure the problem over time, measure the uncertainties (these being the probabilities and utilities) and combine the uncertainties to choose the
preferred option (Fukui, 1992). The preferred option will be that course of action with the greatest expected utility.

7.1.6 Sensitivity analysis

This allows assessment of the potential impact of changing specific criteria. It is done by varying the key probabilities and their values. It is the 'what if' (McCreery and Truelove, 1991) component of decision analysis. Sensitivity analysis is also used in health economics to assess the most cost-effective route to take (Brown, 1992). The simplest analysis is a one-way sensitivity analysis where only one variable is altered.

7.1.7 Aims

The aim of this study was to develop a simple decision model based on one described by Hisamichi et al (1991) to demonstrate any health gains from the implementation of a screening programme for oral cancer. The concept of cancer and quality points as described by Eddy (1986) have been incorporated into the decision model in terms of utilities. A basic decision tree was constructed for the screening model using values obtained from the screening programme described in Chapter 3.
7.2 Materials and methods

Any clinical problem, which involves diagnostic or treatment options is amenable to decision analysis (Velanovich, 1990). A decision pathway is constructed in which outcomes are determined either by choice or chance.

7.2.1 Building the decision model

A hypothetical population of one hundred thousand people was entered into each model. Each avenue of the model represented the events occurring during one run of the screening cycle (say one year). All the people entered were aged on average 55 years of age with a life expectancy (LE) of 20 years. Costing was not incorporated in this study. The prevalence of 2.66% (54/2027) for precancer and cancer was obtained from the screening programme. The prevalence of cancer was considered to be 0.098% (2/2027) as calculated from the screening programme (section 3.3.1). The values used in the decision model are contained within table 7.1.

The neural network (Chapter 5) appears to be able to identify high risk individuals from their lifestyle. From the 365 subjects it deemed 90 (25%) to be at high risk of oral cancer. Of this ninety, eight subjects were actually positive giving a prevalence of 8.89% (8/90) in the pre-selected group. The overall prevalence of positive lesions in the neural network study was 10/365 (2.74%). It would appear that the neural network could be used as a filtering mechanism to identify subjects requiring screening.
The neural network was therefore applied to the same hypothetical population of 100,000. All the following figures used were approximate and rounded for illustrative purposes. The hypothetical population contained the same 2660 (actual 2664) positive subjects (prevalence of 2.66%). Using the information gained from the neural network (NN) study, the decision model was adapted to a high risk situation in which the NN suggested that 25% (90/365; actual 24.66%) of the population (ie 25,000) were at high risk of oral cancer and thus should be screened. In this 'high risk' population, 8.89% would actually be positive giving a total of 2222 subjects. Since the actual overall number of positive subjects was 2660 and 2222 were present in the high risk population (25,000), it follows that the remaining 438 were contained in the low risk population (75,000). The difference in the observed number of positive subjects in the low risk group (438) varied from that expected (545) due to the small variation in prevalence of disease between the neural network (2.74%) and that in the screening programme population (2.66%). However in order to be consistent, a prevalence of 2.66% was used in both models.

The positive test rate is the number of subjects out of all subjects who are screened positive by the screeners. Since the positive and negative predictive values are dependent on prevalence they were recalculated and the positive test rate readjusted (table 7.2). Sensitivity and specificity values remained constant since they are said to be unaffected by prevalence, these were the values obtained from the screening programme (presented in Table 3.3). The calculated values for a high risk situation with an 8.89% positive prevalence are contained in the table below (7.1).
Table 7.1: Screening data used for decision models

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Rate positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>2.66</td>
<td>0.74</td>
<td>0.99</td>
<td>0.67</td>
<td>0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>High risk</td>
<td>8.89</td>
<td>0.74</td>
<td>0.99</td>
<td>0.88</td>
<td>0.98</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Sens: sensitivity; Spec: specificity.
NPV: negative predictive value; PPV: positive predictive value.
Table 7.2 Values used in the neural network decision model.

<table>
<thead>
<tr>
<th>Specialist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Screener</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1645</td>
</tr>
<tr>
<td>Negative</td>
<td>577</td>
</tr>
<tr>
<td>Total</td>
<td>2222</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{1645}{2222} \) 0.74

Specificity = \( \frac{22550}{22778} \) 0.99

Positive and negative predictive values are given in table 7.1

Prevalence: \( \frac{2222}{25000} \) 8.89%

True positives 1645

True negatives 22550

False negatives 577

False positives 228
The useful life years gained within the whole population, after applying the screening procedure were compared to those in the population not screened (status quo). There were three possible outcomes for the non screened population. These were health, precancer and cancer. Those with cancer were subdivided into 40% stage I cancers and 60% stage II, II or IV (Stage 2+), which is an estimate for a Western population (Speight and Morgan, 1993).

It was assumed that after screening there would be a stage shift between Stage I and Stage 2+. This model (Connor et al, 1989) assumes that screen detected cancers are shifted from their usual presentation to a stage lower. Therefore in the screened population a value of 40% was given to cancers found in stage 2+, whereas the remaining 60% would be stage 1.

The outcomes for each intervention were compared in terms of quality adjusted life years (QALYs). These QALYs were calculated by multiplying the number of people (N) by the utility (U) by the life expectancy (LE) of that end point. As mentioned above each person could be either healthy, or have precancer or stage 1 or 2+ cancer. The utilities for each of these positions were obtained from questioning a sample of the general public (Chapter 6). For health, the utility is generally accepted to be equivalent to 1. The values obtained from the questionnaires were 0.92 for precancer, 0.88 for stage 1 cancer and 0.68 for stage 2+ cancer. Each life expectancy was calculated from the 5 year survival rates for oral cancer assuming a healthy 55 year old individual to have a 20 year life expectancy. Thus stage 1 was given a life expectancy of 14.6 (calculated from 73% of cases surviving 5 years) and
stage 2+ an expectancy of 10.8 (54% of cases surviving 5 years). For precancer, the malignant transformation rate was assumed to be 4%, therefore 96% would survive 20 years giving an overall life expectancy of 19.2 years. These calculations were based on the assumption that the outcome of having any oral cancer was either immediate death or 20 year survival. This assumption was made for the practical purposes of arriving at an average life expectancy for cancer at each stage. These values are summarised in table 7.3.

Table 7.3: Utility and life expectancy values used in decision models

<table>
<thead>
<tr>
<th></th>
<th>Utility</th>
<th>Life expectancy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>1.00</td>
<td>20</td>
</tr>
<tr>
<td>Precancer</td>
<td>0.92</td>
<td>19.2</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0.88</td>
<td>14.6</td>
</tr>
<tr>
<td>Stage 2+</td>
<td>0.68</td>
<td>10.8</td>
</tr>
</tbody>
</table>

QALY: Utility x Life expectancy x Number of people at this end point

The outline for the basic model is shown in figure 7.2.
Summary of decision model for oral cancer screening versus no screening (status quo)

(Figure 7.2)

- **Status quo A**
  - no cancer
  - cancer

- **Screen B**
  - Test positive
    - True positive cancer/precancer
    - False positive healthy
  - Test negative
    - False negative precancer/cancer
    - True negative Healthy
7.4 Results

The decision model using the data from the screening programme is contained in figures 7.3 a-d.

Figure 7.3a: This is a summary of the possible outcomes of screening a hypothetical population of 100,000 using the data from the screening programme described in Chapter 3.

Figure 7.3b: This model was used to calculate the QALYs contained in a population not screened (status quo). The QALYs for the status quo were calculated from the prevalence of precancer and cancer. The cancers were divided into stage 1 (40%) and stage 2+cancers (60%).

Figure 7.3c: This part of the model presents the total QALYs for the screened population who were recorded as negative. There are two possible outcomes from being screened negative these being a true negative or a false negative. Since all the false negatives in the screening programme were precancers, it was assumed that all false negatives in this model would also be precancers. The utility and life expectancy values for precancer were used (Table 7.3).

Figure 7.3d: This avenue of the model contains the total QALYs in the population screened positive. There were two outcomes from this, these being a true positive or a false positive. A false positive was classified as healthy and was assigned a utility
of unity. No adjustments were made for possible adverse psychological effects from being screened positive, albeit incorrectly. As explained previously there is assumed to be a stage shift produced by screening in that the screened cancers are divided into stage 1 (60%) and stage 2+ (40%).

Table 7.4. This table demonstrates the effect of compliance on the number of QALYs achieved and the possible number of lives gained. For example 100% compliance in the screening programme would result in a gain of 5.6 lives of 20 years each. The number of lives gained are calculated for 90%, 75%, 50% and 25% compliance rates. If all dentists were to screen the mouth as part of the integral dental examination it might be possible to achieve a saving of 2.8 lives, assuming that 50% of the population are registered with a dentist (Dental Practice Board, 1994).
Figure 7.3 a: Data from the screening programme  
(prevalence: 2.66%)

Status quo is equivalent to 'not screening'
Figure 7.3b: Data from screening programme (no screening)

<table>
<thead>
<tr>
<th>Status quo</th>
<th>n:100000</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>p=0.97337</td>
</tr>
<tr>
<td>Precancer</td>
<td>p=0.02565</td>
</tr>
<tr>
<td>Cancer</td>
<td>p=0.00098 (n:98)</td>
</tr>
</tbody>
</table>

- Healthy:
  - n:97337
  - LE:20
  - U:1
  - Qualy:1946740

- Preca:
  - n:2565
  - LE:19.2
  - U:0.92
  - Qualy:45308

- S1:
  - p:0.40
  - n:39
  - LE:14.6
  - U:0.88
  - Qualy:501

- S2+:
  - p:0.60
  - n:59
  - LE:10.8
  - U:0.68
  - Qualy:433

Total Qualys in the population: 1946740 + 45308 + 501 + 433 = 1992982

LE: life expectancy; n: number; U: utility
Figure 7.3c: Data from screening programme

Test negative
p=0.9704

True negative
p=0.9929 (NPV)

No cancer
n:96351
LE:20
U:1
Qualy: 1927020

False negative
p=0.0071

preca
n:689
LE:19.2
U:0.92
Qualy: 12170

Total Qualy in the screened negative population: 1927020 + 12170 = 1939190
Figure 7.3d: Data from screening programme

Test positive  
\[ \text{p:0.0296} \]

No cancer (FP)  
\[ \text{p:0.3333} \]

Healthy  
\[ \text{n:987 } \]
\[ \text{LE:20} \]
\[ \text{U:1} \]
\[ \text{Qualy:19740} \]

Preca  
\[ \text{p:0.95} \]
\[ \text{n:1875} \]
\[ \text{LE:19.2} \]
\[ \text{U:0.92} \]
\[ \text{Qualy:33120} \]

Cancer (TP)  
\[ \text{p:0.6667 n:1973} \]

0.60S1  
\[ \text{p:0.03} \]
\[ \text{n:59} \]
\[ \text{LE:14.6} \]
\[ \text{U:0.88} \]
\[ \text{Qualy:758} \]

0.4S2+  
\[ \text{p:0.02} \]
\[ \text{n:39} \]
\[ \text{LE:10.8} \]
\[ \text{U:0.68} \]
\[ \text{Qualy:286} \]

Total Qualy in the screened positive population: \[ 19740 + 33120 + 758 + 286 = 53904 \]
Table 7.4: Data from screening programme (QALYs achieved and notional lives gained)

<table>
<thead>
<tr>
<th>Compliance</th>
<th>Screen(A)</th>
<th>Non compliers(B)</th>
<th>Total(A+B)</th>
<th>Status quo(D)</th>
<th>Gain (A+B)-D</th>
<th>Lives gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1993094</td>
<td>0</td>
<td>1993094</td>
<td>1992982</td>
<td>112</td>
<td>5.6</td>
</tr>
<tr>
<td>90</td>
<td>1793784</td>
<td>199298</td>
<td>1993082</td>
<td>1992982</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>75</td>
<td>1494820</td>
<td>498245</td>
<td>1993065</td>
<td>1992982</td>
<td>83</td>
<td>4.2</td>
</tr>
<tr>
<td>50</td>
<td>996547</td>
<td>996491</td>
<td>1993038</td>
<td>1992982</td>
<td>56</td>
<td>2.8</td>
</tr>
<tr>
<td>25</td>
<td>498273</td>
<td>1494736</td>
<td>1993009</td>
<td>1992982</td>
<td>27.5</td>
<td>1.4</td>
</tr>
</tbody>
</table>
**Figure 7.4a:** This is a summary of the possible incorporation of a neural network as an integral part of a screening programme. It is compared to the status quo. The neural network would again be applied to the hypothetical population of 100,000 and those which it deemed to be at high risk would be screened by dentists (with the assumption that the sensitivity and specificity values would be the same as in the screening population).

**Figure 7.4b:** This model summarises the possible outcomes from both the high and low risk groups in the population. The prevalence of cancer and precancer in the high risk group was 8.89%. That in the lower risk group was adjusted so as to give an overall prevalence of 2.66% in the population.

**Figure 7.4c:** This part of the model calculates the QALYs for the high risk population screening negative. All false negatives were again assumed to be precancers as explained above.

**Figure 7.4d:** This part of the model calculates the QALYs for the high risk population screening positive.

**Figure 7.4e:** This part of the model demonstrates the QALYs in the low risk population. The stage 1 and 2+ cancer breakdown is equivalent to that in the status quo.
Figure 7.4a: Using the neural network to identify high risk subjects to screen

Choose

Do not screen

Prevalence 2.66%
n=2660

Total qualys

Neural network

High risk (screened)
p=0.25 n=25000

Prevalence 8.89% (8/90)
n=2222

Total qualys

Low risk (not screened)
p=0.75 n=75000

n=438

Total qualys

Number of positive subjects in both populations = 2660
Figure 7.4b: Screening a high risk population

Neural network

- High risk
  - n: 25000
    - Test negative
      - True negative
        - npv p = 0.975
      - False negative
        - p = 0.025
    - Test positive
      - No cancer (FP)
        - p = 0.122
      - Pre/Cancer (TP)
        - ppv p = 0.878
- Low risk
  - n: 75000
    - No cancer
      - n: 74562
    - Cancer /Preca
      - n: 438
        - 0.4S1 / 0.6S2 + preca
Figure 7.4c: Screening a high risk population (n=25000)

Test negative
p:0.925

True negative
p=0.975 (NPV)

Healthy

n:22550
(TN)
LE:20
U:1
Qualy: 451000

False negative
p=0.025

preca

n:577
(FN)
LE:19.2
U:0.92
Qualy: 10192

Total Qualy in the high risk population screening negative: 451000 + 10192 = 461192
Figure 7.4d: Screening a high risk population

n = 25000

Test positive
p: 0.075

No cancer
p: 0.122

Healthy

Preca
p: 0.95

Cancer (TP)
p: 0.878 n: 1645

0.60S1
p: 0.03

0.4S2+
p: 0.02

n: 228
(FP)
LE: 20
U: 1
Qualy: 4560

n: 1563
LE: 19.2
U: 0.92
Qualy: 27608

n: 49
LE: 14.6
U: 0.88
Qualy: 629

n: 33
LE: 10.8
U: 0.68
Qualy: 242

Total Qualy in the high risk population screening positive: 4560 + 27608 + 629 + 242 = 33039
Figure 7.4e: Low risk group (not screened)

Total Qualys in the low risk population:
1491240 + 7472 + 64 + 73 = 1498849
Summary of figures 7.4a-e using the neural network (NN) to identify high risk individuals

Total NN QALYs  high risk and low risk

High risk QALYs  \[
461192 + 33039 = 494231
\]

(Table 7.4c and 7.4d)

Low risk QALYs  1498849

(Table 7.4e)

Therefore total QALYs (NN)  1993080

Compared to the status quo  1992982

(Table 7.3b)

Difference: (1993080 - 1992982)  98

Total QALY gain of 98 is equivalent to 5 (4.9) healthy lives.

Comparing high risk strategy with no screening would result in a total QALY gain of 5 lives (each with 20 years). This would also involve screening a smaller predetermined population which would obviously be at a much lower cost to the state. Given the increasing usage of computers within general medical and dental practices this would seem to be a potentially good outcome for a small outlay in terms of data
input and manpower required to screen those considered high risk.

The calculations and figures used are only approximate and tentative but would appear to show some gain even in the absence of costing.

7.5 Discussion

In this study it was demonstrated that, using the data obtained from the screening study a simple theoretical model of the possible gains from screening could be evaluated. In the climate of increased usage of computers and computer modelling it is hoped that these data may provide the basis for more complex work in this area.

It is unlikely that invitational oral cancer screening would obtain the high compliance rates required to demonstrate a reasonable life gain since a compliance rate of only 25.7% was obtained in the main study (Chapter 3) and only 15.5% in a similar study elsewhere (Ikeda et al, 1995). However opportunistic screening by dentists in general practice would presumably be at a low cost to the state since the equipment required is already in place within the dental surgery. This is, however, ignoring the possible costs in terms of the increased training of general dental practitioners that might be required. Roberts et al (1985) stated that the cost of avoiding one death by screening for breast and cervical cancer was £80,000 and £300,000 respectively.

Opportunistic oral cancer screening might be economically feasible using the
following approximate calculations: The cost of a NHS examination is £5 and screening 25,000 high risk individuals would therefore be equal to £125,000 but would avoid 5 deaths. The cost of the neural network has not been included in this calculation.

The use of the neural network would also serve to decrease costs since it would mean that only those at high risk are screened. Since computers are increasingly used within the field of medicine, the addition of a simple programme to identify high risk individuals may be minimal and easy to use. It would also provide a way of informing people of their calculated risk of oral cancer, thus increasing patient knowledge, and this might encourage earlier self presentation. High risk habits such as smoking and alcohol consumption together with dietary deficiencies are aetiological factors not only for oral cancer but also for other diseases such as lung cancer and heart disease.

One problem is that those at high risk of oral cancer are also those who do not regularly attend the dentist or doctor and therefore may not be amenable to high risk strategies. Nevertheless, in view of increasing interest in the holistic care of the patient it may be possible to incorporate oral cancer screening with other high risk interventions such as cholesterol screening.

Decision trees have been used to develop guidelines as to who should be tested for HIV. Yawn (1992) compared four scenarios involving no testing, mandatory testing of health care workers and patients less than 65 years of age, risk screening and
voluntary testing. From sensitivity analysis, Yawn was able to determine that mandatory testing of health care workers was not of sufficient benefit to warrant the costs. Decision analysis has been applied to evaluate the need for extracting asymptomatic wisdom teeth since controversy exists as to whether early removal minimises morbidity (Tulloch et al, 1987). It is also used in management decisions in cancer control, for example in cervical cancer (Johnson, 1993) and stage 1 cancer of the floor of the mouth (Velanovich, 1990). Weiss et al (1994) used decision analysis in planning the management of a patient with a primary cancer of the head and neck region with no evidence of nodal metastasis and obtained an optimal threshold for treatment using values from the literature. Milsum (1989) demonstrated the use of decision analysis for determining costs of screening. Within the field of dentistry, decision analysis has been applied to comparison of various bacteriological tests of periodontal diseases and evaluating health gains in restorative dentistry (Douglass and Fox, 1991; Downer and O’Brien, 1994).

Hisamichi et al (1991) showed, using a similarly designed decision model, that screening for stomach cancer could result in a gain of 76.5 lives in a population of 100,000 with a marginal cost effectiveness of approximately $55,000 each. They concluded that this could be considered as expensive or cheap, depending on the economic position of the country involved and the value that country placed on life. In Japan where the value of life was calculated as $200,000-$300,000, approximately 4-6 times as great as the marginal cost effectiveness, they concluded that gastric screening should be conducted.
Decision analysis has weaknesses in that it may oversimplify problems, and outcome estimates (probabilities and utilities) may be biased. However decision making by intuition probably introduces more biases (Thornton et al, 1992) and in constructing decision trees the decision makers are required to explain why they have made certain decisions and how they were derived.

Validity of the model is dependent on the data used in its construction and it may be that, due to the small number of subjects with oral cancer, errors in rounding may have a large influence on the final outcome. The data used were those from previous studies described within this thesis. For example, the utilities for the various stages may vary in another population but in the absence of any other data they can at least provide a best estimate.

Fletcher et al (1995) used decision analysis for determining antenatal screening policies and concluded that the final choices depend on the relative importance ascribed to each outcome. In this study if the stage 2+ cancer outcome had had a utility of 0.30, instead of the 0.68 derived in Chapter 6, then it would have influenced the final QALYs gained in both screening and the absence of screening. Thornton and Lilford (1995) concluded that decision analysis was a method of comparing good and bad outcomes and that the perception of the community as a whole determined the values, but the value to the individuals involved must also be taken into account.

Decision analysis has been widely used in the business world and, with increasing competition for health care resources, it may provide a powerful means for defending
health care decisions (Thornton and Lilford, 1995). It must be reiterated that the figures used in this model are only approximate and the conclusions presumptive, however they provide an indication, albeit naive, of the possible gains that screening may provide.

In conclusion, although the model described is very basic and possibly oversimplified, it has the potential to provide a rough estimate of the usefulness of oral cancer screening especially in a climate of economic restraint and the unlikelihood of a randomised controlled trial. However further work is required to refine the decision model, including introducing accurate estimations of costs to enable a full economic appraisal to be made, and making the neural network even more accurate in identifying high risk individuals.
Chapter 8

Conclusions
8.1 Concluding remarks

The overall aim of this study was to evaluate aspects of screening for oral cancer. The question to be asked of any screening programme is whether there is any benefit to be gained through early diagnosis in terms of reduction of mortality, morbidity and cost to the state.

There are several studies in the literature which suggest that patients with small cancers fair better in terms of survival than those with large cancers (Platz et al, 1986; Henk and Langdon, 1993; Jones, 1994). In Chapter 6 it was shown that those with small cancers did indeed have a better quality of life in terms of function, eating and social life, than those with large cancers. In terms of restoring people back to the work force or reducing the need for special care it would appear that detection of small lesions of oral cancer is important. Although costing was not incorporated into this study it was shown in the decision model that, assuming over 50% of the population to be registered with a dentist, the equivalent of a theoretical 2.8 lives (of 20 years) could be gained. The model is clearly a very simplified representation of reality and the outcomes presented should be regarded as no more than tentative approximations. Nevertheless, such an analysis does permit a crude quantification of the relative health gain achieved under varying conditions.

The corner stone of any screening programme is a valid screening test. In this study it was shown that a simple visual examination of the oral mucosa (Mock, 1985; Pindborg, 1984) gave sensitivity and specificity values comparable with prostate
(Mettlin et al, 1991; Babaian et al, 1992), cervical (Soost et al, 1991), breast (Haiart and Henderson, 1991; Hakama et al, 1991) and colorectal screening (Favennac et al, 1992). When the cost of these screening tests are compared to that of a simple dental examination (£5.00, NHS), the argument for oral cancer screening becomes stronger.

A problem which needs to be overcome is the lack of knowledge of oral cancer found in the general public. In a recent study it was found that approximately 30% had not heard about oral cancer (Bhatti et al, 1995), yet other cancers have much higher profiles in the press and television. This lack of interest or knowledge may have contributed to the low compliance rate (25.7%) in the invitational component of the screening programme. Low compliance is a problem in other screening programmes but this is often related to socioeconomic factors (cervical cancer; Williams, 1992) or invasiveness of the test (colorectal cancer; Farrands et al, 1984). There is a need to educate the general public in self awareness of their mouths. In measuring the general public’s perception of oral cancer it was of interest to note the numbers of people who were unaware of oral cancer or the effects of treatment.

If invitational screening is not viable in terms of low compliance other methods must be investigated. Hakama (1985) discussed the cost-effectiveness of selective screening and one aspect of this study demonstrated the possible incorporation of computers to identify those at high risk of oral cancer. With increasing use of computers in the field of medicine and dentistry this may be the way forward. Certainly, the theoretical decision model demonstrated the potential QALYs that could be gained by using the neural network as a filtering mechanism before involving human screeners.
The screeners performed well in terms of sensitivity and specificity. No training was provided and all were exposed to the same slide test before embarking on the screening programme. It would have been of interest to evaluate the performance of these screeners with some degree of training. Certainly if screening of the oral mucosa was to be paid for by the Government, some type of course on screening the oral mucosa should be mandatory to establish criteria for the identification of precancer and cancer (Mashberg, 1984) and therefore reduce false positive registrations which may overload the secondary care services.

Oral cancer crosses the boundaries of medicine and dentistry (Moore et al, 1987) and this may be a problem in making a screening programme viable, in that since the introduction of charges for dental examinations, many patients seek advice from their doctor (Bhatti et al, 1995) for conditions such as mouth ulcers. Some degree of training is therefore required for doctors in examining the mouth (Hutchison, 1994) since it is unlikely in this economic climate that dental examination charges will be abolished.
The major conclusions from this study are:

- A visual examination of the oral mucosa is a valid screening test in terms of sensitivity and specificity.

- Invitational screening appears to be non viable in terms of low compliance.

- Selective screening, possibly by use of artificial intelligence may be a more successful option.

- The use of decision models has a place in investigating the possibility of screening for oral cancer.
There is a need for further research into many aspects of oral cancer including analytical epidemiology and elucidation of the natural history of the disease. In terms of health services research the following areas have been highlighted in this thesis:

1. Although the invitational screening programme had low compliance in this study it should be repeated in a population with differing social profile.

2. The possibility of opportunistic screening within general dental practice should be formally evaluated in terms of cost both to the state and the dentist.

3. An evaluation of health education methods should be investigated to increase the profile of oral cancer, its associated risk factors and to develop the role of dentists as monitors of oral disease.

4. Further development and evaluation of the neural network should be undertaken in a general practice setting.

5. Further sensitivity analysis using the decision model needs to be undertaken and the robustness of the model requires testing by varying the input data such as age and the end-point utilities, possibility by expert judgement.
6. Ultimately a demonstration oral cancer screening programme should be mounted to assess surrogate and interim measures of economic and health care outcomes.
Appendices
Appendix 1: Glossary of terms

Criterion norm: is the disease state defined as positive.

Detection rate: see sensitivity

Diagnosis: The process of determining health status and the factors responsible for producing it. It can be applied to an individual, family or group or community. The term is applied both to the process of determination and to its findings (Last, 1983).

'is the procedure of reaching the most probable conclusion based on the facts at hand’ (Garland, 1949)

False positive: The labelling of a healthy person as diseased when screening (Last, 1983).

False negative: The labelling of a diseased person as healthy when screening. (Last, 1983)

Gold standard: see validating criterion

Incidence: The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. (WHO Bulletin, 35:783-784, 1966)
Likelihood ratio: The probability of getting that result if the patient truly had the condition of interest with the corresponding probability if they were healthy (Altman, 1991). It is calculated as sensitivity/100 - specificity.

Positive predictive value: is the proportion of patients with positive test results who are correctly diagnosed, (Altman, 1991).

Prevalence: The proportion of a population affected by a disease at a designated time (Downer et al., 1994)

Negative predictive value: is the proportion of patients with negative test results who are correctly diagnosed, (Altman, 1991).

Reference criterion: see validating criterion

Reliability: The degree of stability exhibited when a measurement is repeated under identical conditions. Reliability refers to the degree to which the results obtained by a measurement procedure can be replicated. Lack of reliability may arise for divergences between observers or instruments of measurement or instability of the attribute being measured, (Last, 1983).

Repeatability: a test or measurement is repeatable if the results are identical or closely similar each time it is conducted, (Last, 1983).
Screening: The presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease form those who do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physician for diagnosis and necessary treatment, (US Commission on Chronic Illness, 1951).

Sensitivity of a screening test: The proportion of positives in a screened population that are correctly identified by the test, (Altman, 1991) or the probability of an individual having the disease being correctly identified.

Specificity of a screening test: The proportion of negatives in a screened population that are correctly identified by the test, (Altman, 1991) or the probability of an individual without the disease being correctly identified.

<table>
<thead>
<tr>
<th>Screening test results</th>
<th>True status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td>Not disease</td>
</tr>
<tr>
<td>Positive</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>
a: Diseased individuals detected by the test (true positives)

b: Non-diseased individuals positive by the test (false positives)

c: Diseased individuals not detectable by the test (false negatives)

d: Non-diseased individuals negative by the test (true negatives)

Sensitivity = \frac{a}{a+c}

Specificity = \frac{d}{b+d}

Positive predictive value = \frac{a}{a+b}

Negative predictive value = \frac{d}{c+d}

**Validating criterion:** is an independent measure of the condition under study to which the test results are compared, (Downer et al, 1994).

**Validity:** An expression of the degree to which a measurement measures what it purports to measure (Last, 1983).
Appendix 2: Eastman Dental Hospital Mouth Screening Programme

Why have mouth screening?

Screening picks up all types of diseases, that can effect the mouth.

However, like screening for other parts of the body it can also pick up any small changes which may be early signs of mouth cancer.

This is important because like breast, cervical, testicular and most other cancers if mouth cancer is found early the chance of successful recovery is very good.

Who should be screened?

Anyone who is aged 40 or over should be screened, especially those who smoke, chew tobacco or drink heavily.

Why should I have my mouth screened?

We can check that your mouth is healthy and that there are no obvious dental problems.

It is also important to have your mouth looked at even if you wear dentures.

You can help us in our mouth screening programme to find the best way of detecting any small changes which may be early signs of mouth cancer.

What does it involve?

The mouth screening takes about 5 minutes.

You will be asked about your smoking and drinking habits.

What does the screening involve?

You will have to answer a short questionnaire before you are seen.

The screen is rather like a dental check-up.

However you will be screened by 2 dentists separately, as part of our research.

Each dentist will only take a few minutes to look around your mouth.

Since we only use mirrors to look, it is not uncomfortable or painful.
What happens if my mouth is found to be healthy?

If your mouth is found to be healthy you will be told straight away.

It is a good idea to tell your dentist at your next check-up, this means that they can continue to screen you regularly.

What happens if something needs a closer look?

Occasionally one of the people examining you may suggest that you need to be sent for another opinion at the Eastman Dental Hospital or be seen by your dentist.

Screening often finds things which are not dangerous but, may cause you discomfort if not treated.

This does not mean that you have cancer.

Sometimes we find things that you may already know about and have had for ages.

Why is the Eastman Dental Hospital screening?

Unlike the breast and cervical screening programmes there is no organised national mouth screening programme.

Our hope is that through our research we will prove the benefits of mouth screening.

What you do to keep your mouth healthy?

Stop smoking

Moderate your alcohol intake

If you have any mouth problems, let your dentist check them out

Lots of fresh fruit and vegetables

Everyone should have regular check-ups for a healthy mouth.

If you are unable to have your mouth screened today, please ask at the Oral Surgery reception desk or ring (071) 915 1195 for other screening times
When did YOU last have your mouth screened?
Anyone over 40 is welcome.

Reprinted with permission from the Health Education Authority.
<table>
<thead>
<tr>
<th>SITE</th>
<th>NEGATIVE</th>
<th>POSITIVE</th>
<th>DESCRIPTION OF LESIONS</th>
<th>BIOPSY</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
<td>neg ca</td>
<td>preca/ca lesion</td>
<td></td>
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<td>preca cond</td>
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<td>e.g. size, colour, appearance, texture</td>
<td>inc/exc</td>
<td>Path.no, SNOMED</td>
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<tr>
<td>Lip/ commissures</td>
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<tr>
<td>Buccal mucosa/ gingivae</td>
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<td>Hard palate/ upper alveolus</td>
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<tr>
<td>Dorsum/ventrum tongue</td>
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<td>Lateral border of tongue</td>
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<tr>
<td>Soft palate/ Fauces</td>
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<tr>
<td>Lower alveolus/ Retromolar</td>
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<tr>
<td>Floor of mouth</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

TREATMENT: EDH MED/SURG GDP.

REFERENCE DIAGNOSIS:

DEFINITIVE RESULT:
Factors such as smoking and drinking can increase the risk of developing mouth diseases. We would appreciate if you could help us in our research by answering the questions below.

Have you ever smoked or chewed tobacco?
- Never
- Not for over 10 years
- Within the last 10 years
- Current user

How long have or did you smoke?
- For between 1 and 19 years
- For between 20 and 39 years
- For over 40 years

What did/do you smoke/chew?
- Filter cigarettes
- Unfiltered cigarettes
- Cigars
- Roll-ups
- Pipe
- Chew tobacco/dip snuff
- Chew betel nut with tobacco

How many cigarettes/cigars do you smoke a day?
- Under 10
- 11 to 20
- 21 to 39
- Over 40

If you have stopped smoking or have cut down recently, did you used to smoke a day?
- Under 10
- 11 to 20
- 21 to 39
- Over 40
How many ounces of tobacco do you smoke/ chew a week?
   Under 1 oz. (25g)
   1 to 2 oz. (25g to 50g)
   Over 2 oz. (50g)

If you have stopped or cut down recently how many ounces of tobacco did you smoke/ chew a week?
   Under 1 oz. (25g)
   1 to 2 oz. (25g to 50g)
   Over 2 oz. (50g)

Have you ever drunk alcohol?
   Never
   Occasionally
   Regularly

What types of alcohol do you drink on a regular basis?
   Beer (including lager and cider)
   Wine
   Fortified wines (sherry, port, martini etc.)
   Spirits

In a typical week how many units of alcohol do you drink?
   (1 unit = 1/2 pint beer or lager = 1 glass of wine = 1 measure of spirit)
   Less than 5 units
   Between 5 and 14 units
   Between 15 and 29 units
   Over 30 units

When did you last visit your dentist?
   Less than 6 months ago
   Between 6 and 12 months
   Between 1 and 5 years
   More than 5 years
Appendix 6
Primary Screening Form

NAME:
DATE OF BIRTH:
SEX:

1. Please check if completed

2. Please examine the mouth

<table>
<thead>
<tr>
<th>SITE</th>
<th>NEGATIVE NORMAL</th>
<th>NEGATIVE LESION</th>
<th>POSITIVE CONDITION</th>
<th>POSITIVE LESION CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lips/ commisures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal mucosa/gingivae</td>
<td></td>
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<tr>
<td>Hard palate/ upper alveolus</td>
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<tr>
<td>Dorsum/ventrum of tongue</td>
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<td>Lateral border of tongue</td>
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</tr>
<tr>
<td>Floor of mouth</td>
<td></td>
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</table>

SCREEN:  **POSITIVE/NEGATIVE**

SCREENER NUMBER:
Appendix 7: Description of stages given to general public and questionnaire

Q1. Precancer
You would have a red or white patch in your mouth. It can be treated with a simple operation or by a laser. The patch may return but this can be easily treated. Recovery is complete but you will be seen regularly at the hospital to have your mouth checked.

Q2. Early cancer
You would have an ulcer in your mouth (less than the size of a 20 pence piece). It can be treated by an operation or with a laser. Some hospitals treat the cancer by radiotherapy. Seven out of ten people are cured. Some people find it difficult to talk, eat or drink for a couple of weeks after the operation but eventually most people go back to normal everyday life. You will be kept under regular review by the hospital.

Q3. Late cancer
You would have a large ulcer in your mouth (bigger than a 20 pence piece). It can be treated by surgery which is often followed by radiotherapy and sometimes chemotherapy. Only 4 out of ten people will be cured. This depends on the size of the original cancer. Often the operation will result in difficulty talking, eating and drinking and may alter your facial appearance. However with time most people are able to cope with everyday living. You will be kept under regular review by the hospital.
1. **You must choose between:**

   a. 100% chance of a small red or white patch in your mouth which shows early signs of cancer. This will be treated by a minor operation. You will be in hospital for a day and be back to normal in 2 to 3 days.

   b. Where you have the choice of having no mouth cancer but take the risk of immediate death

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>100% chance of having no mouth cancer for the rest of your life. 0% chance of immediate death</td>
</tr>
<tr>
<td>2. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>99% chance of having no mouth cancer for the rest of your life. 1% chance of immediate death</td>
</tr>
<tr>
<td>3. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>95% chance of having no mouth cancer for the rest of your life. 5% chance of immediate death</td>
</tr>
<tr>
<td>4. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>90% chance of having no mouth cancer for the rest of your life. 10% chance of immediate death</td>
</tr>
<tr>
<td>5. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>80% chance of having no mouth cancer for the rest of your life. 20% chance of immediate death</td>
</tr>
<tr>
<td>6. 100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation</td>
<td>70% chance of having no mouth cancer for the rest of your life. 30% chance of immediate death</td>
</tr>
</tbody>
</table>

276
100% chance of having a small red or white patch in your mouth which shows early signs of cancer which can be treated by a minor operation

60% chance of having no mouth cancer for the rest of your life.
40% chance of immediate death

4 in 10 chance of immediate death

50% chance of having no mouth cancer for the rest of your life.
50% chance of immediate death

1 in 2 chance of immediate death

40% chance of having no mouth cancer for the rest of your life.
60% chance of immediate death

3 in 5 chance of immediate death

30% chance of having no mouth cancer for the rest of your life.
70% chance of immediate death

7 in 10 chance of immediate death

20% chance of having no mouth cancer for the rest of your life.
80% chance of immediate death

4 in 5 chance of immediate death

10% chance of having no mouth cancer for the rest of your life.
90% chance of immediate death

9 in 10 chance of immediate death

0% chance of having no mouth cancer for the rest of your life.
100% chance of immediate death

Definite immediate death
2. You must choose between:
   a. 100% chance of small mouth cancer which will be treated by an operation, after which you will be in hospital for 1 week but will fully recover.
   b. Where you have the choice of having no mouth cancer but take the risk of immediate death

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>100% chance of no mouth cancer for the rest of your life 0% chance of immediate death.</td>
</tr>
<tr>
<td>2</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>99% chance of no mouth cancer for the rest of your life 1% chance of immediate death.</td>
</tr>
<tr>
<td>3</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>95% chance of no mouth cancer for the rest of your life 5% chance of immediate death.</td>
</tr>
<tr>
<td>4</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>90% chance of no mouth cancer for the rest of your life 10% chance of immediate death.</td>
</tr>
<tr>
<td>5</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>80% chance of no mouth cancer for the rest of your life 20% chance of immediate death.</td>
</tr>
<tr>
<td>6</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>70% chance of no mouth cancer for the rest of your life 30% chance of immediate death.</td>
</tr>
<tr>
<td>7</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>60% chance of no mouth cancer for the rest of your life 40% chance of immediate death.</td>
</tr>
<tr>
<td>8</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>50% chance of no mouth cancer for the rest of your life 50% chance of immediate death.</td>
</tr>
<tr>
<td>9</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>40% chance of no mouth cancer for the rest of your life 60% chance of immediate death.</td>
</tr>
<tr>
<td>10</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>30% chance of no mouth cancer for the rest of your life 70% chance of immediate death.</td>
</tr>
<tr>
<td>11</td>
<td>100% chance of a small mouth cancer which will be treated by an operation.</td>
<td>20% chance of no mouth cancer for the rest of your life 80% chance of immediate death.</td>
</tr>
</tbody>
</table>
12. 100% chance of a small mouth cancer which will be treated by an operation.
10% chance of no mouth cancer for the rest of your life
90% chance of immediate death.

13. 100% chance of a small mouth cancer which will be treated by an operation.
0% chance of no mouth cancer for the rest of your life
100% chance of immediate death.

3. You must to choose between:

a. 100% chance of a large, life-threatening cancer in your mouth which will be treated by a major operation which will result in severe changes to your facial appearance and some difficulty in speaking, drinking and eating.

b. Where you have the choice of having no mouth cancer but take the risk of immediate death

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.</td>
<td>100% chance of no mouth cancer for the rest of your life. 0% chance of immediate death</td>
</tr>
<tr>
<td>2</td>
<td>100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.</td>
<td>99% chance of no mouth cancer for the rest of your life. 1% chance of immediate death</td>
</tr>
<tr>
<td>3</td>
<td>100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.</td>
<td>95% chance of no mouth cancer for the rest of your life. 5% chance of immediate death</td>
</tr>
<tr>
<td>4</td>
<td>100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.</td>
<td>90% chance of no mouth cancer for the rest of your life. 10% chance of immediate death</td>
</tr>
<tr>
<td>5</td>
<td>100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.</td>
<td>80% chance of no mouth cancer for the rest of your life. 20% chance of immediate death</td>
</tr>
</tbody>
</table>
6. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

7. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

8. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

9. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

10. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

11. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

12. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.

13. 100% chance of life-threatening cancer which can be treated by having an operation which will result in severe changes to your appearance and effect your speech, eating and drinking.
Appendix 8: Patient Assessment of Quality of life

Patient Consent Form

In addition to monitoring your condition by regular examination we would like to know how you feel to help us in planning treatment.

We have designed a questionnaire which will ask you questions about any changes which may have come about since treatment for mouth cancer.

Some of these questions may not be relevant to your treatment so please do not be alarmed by them.

If you do not understand the question, feel it is difficult to answer, or if you have any comments about the questions please tell the interviewer.

We hope that any information which you provide will be of use in planning care for other patients undergoing treatment.

Your help is therefore appreciated.

If you agree to answering the questionnaire please sign below:

Signed:........................................................................................................

Date:

Interviewer:

Signed:........................................................................................................

Date:
Patient Assessment of Quality of Life

Male / Female Age

Aspect of disease

1. Are you in pain?
   a. Very severe
   b. Moderate
   c. Mild
   d. None *

2. How often are you in pain?
   a. Never *
   b. Less than once a week
   c. Every few days
   d. Daily

3. Do you have a dry mouth?
   a. None *
   b. Only slight dryness
   c. Very dry a lot of the time
   d. No saliva

4. Do your clothes fit the same as before?
   a. Not at all
   b. Very loose
   c. Put on weight
   d. No change *

5. Are you aware of bad breath?
   a. Very unpleasant all the time
   b. Often unpleasant
   c. Occasionally unpleasant
   d. Never unpleasant *

6. Do you have difficulty in eating or swallowing?
   a. Can only manage fluids
   b. Can only manage liquidised foods
   c. Can manage most things (moist food eg pasta/food with sauces)
   d. Normal *
7. Do you
   a. Eat in public places? *
   b. Eat only with the family?
   c. Eat alone?
   d. Normal? *

8. Do you have a bad taste?
   a. Very unpleasant all of the time or no taste.
   b. Most things taste odd
   c. A few things taste odd
   d. Normal *

9. How would you describe your appetite?
   a. None
   b. Very poor
   c. Moderate
   d. Normal *

10. Do you feel tired?
    a. Too tired to do anything
    b. Get tired easily
    c. Get tired some of the time
    d. Normal *

11. How would you describe your social time?
    a. Not going out at all
    b. Only seeing family
    c. Only seeing relatives or close friends
    d. No change than before *

12. How do you spend your day?
    a. Confined to bed
    b. Up at least for part of the day
    c. Up but dont feel like going out
    d. Normal *

13. How would you describe your mood?
    a. Normal *
    b. Low
    c. Very low
    d. Miserable all of the time
14. Do you work?
   a. Able to work as normal *
   b. Able to work part-time
   c. Unable to work
   d. Able to work but not working

15. Can people understand you?
   a. All of the time *
   b. A lot of the time
   c. Sometimes
   d. Never

16. Are you more concerned about your appearance than before treatment?
   a. No *
   b. A little
   c. A lot
   d. Preoccupied

17. Do you have any problems with your personal relationships?
   a. None *
   b. Having minor problems
   c. Considerable problems
   d. Unable to cope

18. Are you more concerned with your health than before?
   a. Not at all *
   b. A little
   c. A lot
   d. Totally preoccupied

Diagnosis:

Treatment:

* these questions were assigned as 0 (no symptoms) for ease of analysis
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Attendance and Compliance at an Oral Cancer Screening Programme in a General Medical Practice

J.A. Jullien, J.M. Zakrzewska, M.C. Downer and P.M. Speight

The purpose of this study was to measure the attendance and compliance rates in a demonstration invitational screening programme for oral cancer. 4348 subjects aged 40 years or over registered at an inner city medical practice in north London were invited for screening by post. The socioeconomic profile of the group was determined by analysis of residential areas. Screening was conducted by one of several dentists and a referral pathway was established for patients requiring follow-up. Attendance rates for screening and referral for follow-up were measured. The response rate was 985/3826 (25.7%) after removing 522 subjects whose invitations could not be delivered or who refused appointments. No reply was obtained for 2841 patients. Attendance for referral of lesions considered to have malignant potential was 67% (8/12), compared to 92% (11/12) for patients requiring referral for incidental benign lesions. The low compliance suggests that oral cancer screening may not be able to achieve the desired benefits of reducing morbidity and mortality, and establishment of such a programme may not, therefore, be cost-effective. Further research is required into how to identify people in high risk groups and motivate them to present themselves for screening.

Keywords: cancer screening, compliance, invitational screening, oral cancer, oral precancer

INTRODUCTION

There are almost 2000 cases of oral cancer each year in England and Wales [1] and over 50% die of their disease within 5 years. The survival rate is comparable to that of invasive cancer of the uterine cervix and melanoma [2], and has not changed for over 25 years although reconstructive surgery and rehabilitation have improved quality of life [3]. One of the main reasons for the poor survival is that over 60% of oral cancer patients present with lesions greater than 2 cm in diameter when prognosis is known to be significantly worse than for smaller lesions [4]. The morbidity associated with treatment of larger lesions is also greater. In the developing world most lesions of oral cancer are preceded by a precancerous stage [5] but there is a lack of knowledge with regard to malignant transformation and progression rates in a Western population (reviewed by Speight and Morgan [6]).

Screening for oral cancer is simple and involves a systematic visual examination of the soft tissues of the mouth [7]. The aim of screening is to detect lesions more frequently during the pre-invasive stage or at an earlier stage of invasive disease than is usual in clinical practice [8]. Since oral cancer would seem to meet many of the criteria for screening as described by Wilson and Jungner [9, 10], and because early diagnosis is associated with improved prognosis, it would seem appropriate to evaluate its suitability for screening. The U.K. Working Group on Screening for Oral Cancer and Precancer recently considered many of these aspects and have made recommendations for further research [11].

The present study, conducted within a general medical practice, is part of a larger demonstration study to evaluate an oral cancer screening programme [12] and was designed to measure compliance rates and to consider the acceptability and feasibility of invitational screening for oral cancer, important factors to consider in evaluating a screening programme [13].

METHODS

The target population was identified from among the registered patients of a large inner city medical practice. All the patients approached were aged 40 years or over since over 95% of oral cancers occur in this age group [14]. Each patient's name, date of birth and address were obtained from the records of the relevant Family Health Services Authority (FHSA). There were 4348 eligible patient names on the list. The distribution of age is shown in Table 1. All patients were invited to attend for mouth screening by postal invitation which included a fixed appointment at the medical practice. This was part of a large health centre with a community dental clinic on site. Patients were also offered an alternative open screening appointment during the day at a nearby dental clinic.
hospital, an open evening at the medical practice or the opportunity to change the time by telephone, if their hospital, an open evening at the medical practice or the appointment was not convenient. To minimise anxiety [15] the letter was sent from the medical practice and explained that the subject's name had been obtained from their general practitioner as part of a mouth screening study for all patients aged 40 years or over. The letter also included an information leaflet explaining the screening process and outlining the benefits of a healthy mouth and the importance of early diagnosis of oral cancer.

After the first round of invitations had been completed a second invitation was sent out in a slightly different format to the 3167 subjects who had failed to respond to the initial invitation. These remaining subjects were randomly divided into two approximately equal groups. One received only a reminder and an appointment card, whereas the other group received an appointment and an additional information leaflet. This was published by the British Dental Health Foundation (BDHF) [16], and contained more explicit information about mouth cancer, including risk factors and the importance of early diagnosis. The frequency of attenders and non-attenders in each group was compared to see if the information leaflet had any effect on compliance. The decision to have two rounds of invitations was to allow for holidays and to follow the frequency of attenders and non-attenders and to follow the 3167 subjects who had failed to respond to the initial invitation. These remaining subjects were randomly divided into two approximately equal groups. One received only a reminder and an appointment card, whereas the other group received an appointment and an additional information leaflet. This was published by the British Dental Health Foundation (BDHF) [16], and contained more explicit information about mouth cancer, including risk factors and the importance of early diagnosis. The frequency of attenders and non-attenders in each group was compared to see if the information leaflet had any effect on compliance. The decision to have two rounds of invitations was to allow for holidays and to follow the custom of other screening programmes.

The screening procedure and the referral process has been described in detail elsewhere [12]. Briefly, all patients received an interview questionnaire about their lifestyle habits. Informed consent was obtained and any questions were answered regarding the nature of the screening process [17]. Each subject was examined independently by a dentally trained screener and a specialist. There was a total of four screeners but only one specialist who examined all the subjects. The specialist provided the definitive diagnosis for each subject. Evaluation of the concurrent validity of the screening test has been described previously [12].

If a subject was considered to be negative according to the definitive diagnosis (no precancer or cancerous lesions were detected), they were told immediately. All smokers and heavy drinkers were advised of the risk of oral cancer from their habits. All patients requiring treatment or further follow-up were advised of this and given an appointment to attend at the dental hospital where they were reviewed by the specialist and a consultant oral physician. The group requiring referral contained both positive subjects and subjects classified as negative for oral cancer and precancer, but who required treatment for benign pathology. No follow-up was arranged for subjects screened negative but all participants were advised to attend their dentist on a regular basis.

The postcodes of all patients were analysed by “ACORN” which is a commercially available service which provides a classification of residential neighbourhoods [18, 19]. This information was used to obtain a socio-economic profile of the invited practice population. The frequency distribution in each ACORN group for non-attenders and attenders was compared statistically.

### RESULTS

#### Uptake of screening

Of the 4348 invitations sent out, there were 522 notified non-attenders and 2841 subjects who did not respond at all. Of the 3826 eligible attenders 985 (25.7%) accepted the invitation for mouth screening. There was no significant difference between the numbers or proportions of males (479; 21%) and females (506; 24%) who attended. The breakdown of attendance by age group is shown in Table 1. The 522 notified non-attenders are detailed in Table 2, these included those who could not be contacted and those who refused for reasons of ill-health, immobility or other, unspecified, reasons.

ACORN classified the patients of the medical practice into four (A, C, E, F) of the six (A-F) possible classifications (Table 3), with over 98% of the population being in either group C or F. Groups A and E were excluded from any analysis since the numbers of patients in each group were small. The true proportion of attenders in each ACORN group

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total</th>
<th>Acceptance</th>
<th>Response rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>609</td>
<td>139</td>
<td>22.8</td>
</tr>
<tr>
<td>45-54</td>
<td>1069</td>
<td>246</td>
<td>23.0</td>
</tr>
<tr>
<td>55-64</td>
<td>939</td>
<td>260</td>
<td>27.7</td>
</tr>
<tr>
<td>65-74</td>
<td>873</td>
<td>211</td>
<td>24.2</td>
</tr>
<tr>
<td>75-84</td>
<td>562</td>
<td>109</td>
<td>19.4</td>
</tr>
<tr>
<td>85-94</td>
<td>241</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>95-104</td>
<td>50</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>105-114</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>115-124</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All groups</td>
<td>4348</td>
<td>985</td>
<td>25.7*</td>
</tr>
</tbody>
</table>

First mailing = 659; second mailing = 326; total = 985.

*Corrected for 522 notified non-attenders (985/3826).

#### Table 2. Details of the notified non-attenders

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to sender</td>
<td>329</td>
</tr>
<tr>
<td>Dead</td>
<td>36</td>
</tr>
<tr>
<td>Other reasons*</td>
<td>65</td>
</tr>
<tr>
<td>Not interested</td>
<td>65</td>
</tr>
<tr>
<td>Visits dentist</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>522</td>
</tr>
</tbody>
</table>

*Other reasons includes patients who could not attend due to ill health or immobility.

#### Table 3. ACORN classification of the invited subjects compared to that of the United Kingdom

<table>
<thead>
<tr>
<th>ACORN</th>
<th>Defining factors</th>
<th>Study %</th>
<th>U.K. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Thriving, wealthy achievers, prosperous pensioners</td>
<td>0.2</td>
<td>19</td>
</tr>
<tr>
<td>B</td>
<td>Expanding, affluent families</td>
<td>0</td>
<td>10.4</td>
</tr>
<tr>
<td>C</td>
<td>Rising, prosperous urbanites</td>
<td>46.5</td>
<td>9</td>
</tr>
<tr>
<td>D</td>
<td>Settling, skilled workers, mature home-owners</td>
<td>0</td>
<td>24.5</td>
</tr>
<tr>
<td>E</td>
<td>Aspiring, white collar, better off ethnic areas</td>
<td>0.7</td>
<td>13.9</td>
</tr>
<tr>
<td>F</td>
<td>Striving, low income, high unemployment</td>
<td>52.3</td>
<td>23.1</td>
</tr>
</tbody>
</table>
or tagging patient notes have been reported as more successful than unsystematic opportunistic programmes [27]. In a com­
people who do not attend the doctor or a dentist on a regular attendance rates it may achieve a wider coverage among those cervical cancer [26].
screening programmes have compliance rates in the region of present invitational study. Other comparable invitational the present figure. A similar oral cancer screening study in the achieve compliance rates of about 50% which is greater than screening is offered on site and encouraged by the company, studies in the United Kingdom for invitational screening of compliance was in the range of 60-76% for opportunistic screening groups, only 1 (referred for a denture related condition) failed to attend; 2 with leukoplakia and 2 with erosive mouth were normal or who might have benign pathology with no recognised malignant potential. All subjects who were considered to require further follow-up or treatment were referred to an oral medicine clinic to be seen as soon as possible. 12 patients were referred with positive lesions. 4 subjects failed to attend; 2 with leukoplakia and 2 with erosive lichen planus. 12 subjects required referral for benign pathology including 1 lipoma, 1 sebaceous cyst, 1 trigeminal neuralgia, 2 polyps and 7 denture related conditions. Of the 12 subjects, only 1 (referred for a denture related condition) failed to attend.

DISCUSSION

During the period of screening almost 1000 individuals accepted the invitation for screening, giving an overall compliance rate of 25.7%. Ikeda et al. [20] also found low compliance following postal invitations for oral cancer screening in Japan. In their study a compliance of 12.2% was measured for postal invitations to subjects over 60 years, but compliance was in the range of 60–76% for opportunistic screening among company workers. There are no published studies in the United Kingdom for invitational screening of the mouth, although some industrial companies offer screening to their employees [21, 22]. These programmes, where screening is offered on site and encouraged by the company, achieve compliance rates of about 50% which is greater than the present figure. A similar oral cancer screening study in the United States [23], used an opportunistic method to obtain high risk subjects, but this study is not comparable with the present invitational study. Other comparable invitational screening programmes have compliance rates in the region of 70%, for breast [24], 50–55% for colorectal [25], and 30%, for cervical cancer [26].

Although invitational screening may result in generally low attendance rates it may achieve a wider coverage among those people who do not attend the doctor or a dentist on a regular basis. Systematic approaches to screening, either by invitation or tagging patient notes have been reported as more successful than unsystematic opportunistic programmes [27]. In a com-
puter simulation model of opportunistic screening in a general practice, it was calculated that it could take up to 12 years to screen 90% of the population [28]. The type of invitation offered may also be important. In a recent osteoporosis study [29], a fixed appointment time produced 75% attendance compared to 65% for confirmable and 54% for open appointments. Similar studies of breast cancer screening programmes have shown a 10% higher level of compliance by sending invitations with fixed appointments [30]. However, fixed appointments can result in a waste of resources due to lost appointment slots [31]. In the present study, wastage was reduced by sending large numbers of invitations for each appointment time. All letters were personally signed by the screener to encourage attendance, as recommended by Turnbull et al. [32], and the address of the medical centre and a contact number were given. Posters and information sheets were displayed in the waiting rooms throughout the screening period to help increase awareness of oral cancer and the mouth screening programme. In the second round, invitations were mailed to arrive at least 2 days in advance of the fixed appointment time [33].

It is of interest to note that there was a significant difference in attendance, in the second mailing, between those subjects who were, or were not given the BDHF leaflet; those who did not receive the leaflet showed a better attendance. Although the actual numerical difference was small it is possible that the leaflet, which was quite explicit about oral cancer, may deter some individuals from wanting to be screened. Further research is needed to identify the reasons for non-attendance and in particular, to further evaluate the effectiveness of different types of educational material.

A disadvantage of screening for oral cancer appears to be a lack of public knowledge of the disease and this may have contributed to the overall low compliance. In a recent investigation in the same medical practice it was found that only 65.8% of subjects questioned were aware that cancer can affect the mouth [34]. Lack of knowledge about oral cancer may also account for the lower attendance among those individuals referred with positive lesions compared to those with benign lesions. Although the numbers are small, anxiety and fear about the nature and treatment of the disease may have been the cause.

There was an obvious problem regarding the accuracy of the FHSA list of registered patients’ names and addresses. The computerised system is, however, currently being modernised, and this should avoid problems such as a patient who would have been 121 years old remaining on the register. This is a particular problem in London compared to most other parts of the country and arises from high population mobility [35]. There are several studies evaluating the disadvantages and inaccuracies of using age/sex registers from family practitioner lists for screening programmes. In screening studies for cervical and breast cancer, up to 69% [36] and 35% [35] of the invitational letters have been found to be inaccurate or inappropriate. Bickler and Sutton [37] demonstrated that the accuracy could be increased from 73% to 92%, by checking the family practitioner register against the electoral role and inviting only those whose names appeared on both lists.

The socio-economic status of the population selected for screening must also be taken into account. The population of the medical practice in the present study was not typical of the United Kingdom as a whole, although it may be quite representative of many inner city practices. Majeed et al. [38]
have shown that the uptake rates for cervical smears can vary from 16.5% to 94.1%, depending upon a number of variables, including the socio-economic profile of the population and the type of medical practice. Further studies in areas with different socio-economic profiles are necessary to determine uptake rates for oral screening in other population groups. ACORN, or other similar techniques, may be of use in targeting individuals by encouraging uptake in areas where the disease is likely to be more prevalent. Cervical cancer screening, for example, shows low response rates in inner city areas [39] where the incidence of the disease is greatest.

The low compliance rate found in this study suggests that an invitation screening programme for oral cancer may not be cost-effective. Low compliance, particularly when associated with a disease of relatively low prevalence, would result in a markedly reduced detection rate in a screening programme [40]. It would seem more appropriate for screening for oral cancer to be done opportunistically during routine dental or health check-ups. However, the population coverage would depend on the age of the patients and the frequency of visits to health professionals. For example, it is known that in the over 55 year age group, the frequency of visiting the doctor is over twice that to the dentist [41]. Since only 50% of the adult population are currently registered with a dentist [42], a large proportion is not going to be screened and it is arguable that the non-attenders are likely to be those at higher risk of oral cancer. In a recent review, Smart [43] recommended that oral screening should be part of both routine dental and general health check-ups.

Before such programmes are introduced, however, it is essential to increase public awareness of oral cancer, particularly the benefits of a regular oral examination and the need to seek treatment as early as possible.


Acknowledgements—The authors would like to thank all the staff at the Finsbury Health Centre, particularly Dr Lemonsky and the dentists involved in the project. This study was supported financially by the Department of Health in England and by the Europe Against Cancer Programme of the Commission of the European Communities under item B34300 of the General Budget, file number SOC 93 101728.
Evaluation of screening for oral cancer and precancer in a company headquarters


Abstract – Oral cancer and precancer appear to fulfil many of the criteria for a disease suitable for mass screening. Several commercial organisations in the UK have introduced screening for their employees. One program has been formally evaluated over the course of 1 yr. Of 553 company headquarters staff aged ≥40 yr, 292 (53%) responded to the well-publicised screening invitation and received a simple clinical examination of the oral mucosa from one of two company dentists. In addition, 17 staff were screened from a separate company work-site. After screening, subjects were examined independently by an oral medicine specialist with access to the relevant diagnostic aids. The dentists' screening decisions were validated against the specialist's definitive diagnoses (the 'gold standard'). The true prevalence of subjects with lesions diagnosed as positive (white patch, red patch or ulcer of greater than 2 weeks' duration) was 17 (5.5%). Overall, sensitivity was 0.71 and specificity, 0.99. The compliance rate to screening among headquarters subjects in seven occupational categories did not differ significantly from the occupational profile for all headquarters personnel. Estimates of relative risk of a positive diagnosis were calculated by logistic regression for five independent variables; gender, age, moderate smoking, heavy smoking, and smoking combined with greater than low risk alcohol consumption. Only heavy smoking (>20 cigarettes per day) produced a significant odds ratio (3.43, \( P < 0.05 \)).

Key words: compliance; oral cancer; oral precancer; relative risk; screening; sensitivity; specificity

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There are some 2000 new cases of oral cancer reported in England and Wales each year with an overall incidence of 4.5 per 100 000 per annum. Approximately 60% of patients die from their disease within 5 yr (1). In the industrialized world it is considered the eighth most common cancer, representing between 1 and 2% of total malignancies, and there is evidence that incidence and mortality are increasing (2). Although cancer often apparently arises de novo, there are also a number of clinically identifiable precursor lesions which constitute a detectable preclinical phase (3). Pre-malignant lesions such as leukoplakia, and other conditions associated with a high risk may be present in up to 5% of the population over 40 yr of age (4-6).

Treatment of oral cancer, especially advanced lesions, is associated with significant physical and psychological morbidity whereas small lesions are relatively easy to detect and treat effectively. Poor survival is in part due to a failure to detect small lesions since over 60% of patients present with lesions over 2 cm in diameter, by which stage prognosis is significantly worsened (3, 7). Yet it is recognised that a simple clinical examination can detect asymptomatic disease and result in treatment being instituted early (8). It seems timely therefore to consider the feasibility of screening for oral cancer and precancer. A recent report (9) concluded that oral cancer met most of the criteria of Wilson & Jungner (10) for a disease suitable for screening but found insufficient evidence to recommend a national screening program without further research.

In India, where the incidence of oral cancer is high, large scale primary preventive programs aimed at reducing tobacco usage have been evaluated (11). However, few studies have attempted specifically to validate clinical screening for oral cancer and precancer. Nevertheless there is evidence that satisfactory sensitivity and specificity levels can be
achieved both by dentists (12) and, in developing countries, by primary health care workers (13).

IKEDA and coworkers (12) conducted their screening among factory and office workers in Japan. The workplace offers an ideal opportunity for screening (14-16) and although a number of companies have now instituted oral cancer and precancer screening for their employees (17), there have been no formal evaluations of work-site oral screening programs in the United Kingdom. The purpose of this project was to establish the sensitivity and specificity of a screening test for the detection of oral cancer and precancer, and to evaluate a pilot screening program in a workplace environment.

Material and methods

The screening program – Screening was carried out in the London headquarters of a large commercial company. All staff aged 40 yr or over were invited to attend for an oral screening in the surgeries of the on-site company dental practice. The program was widely publicised through the company house magazine, a video screen in the entrance hallway, and by means of an information sheet explaining the importance of mouth screening in the detection of cancer and the nature of the examination. Screening was conducted at dedicated sessions and was carried out by two general dental practitioners who had not received any specific training except for instruction in the screening procedure and the criteria for a positive or negative test.

The screening test consisted of a thorough, systematic visual examination of the lips and mucosal surface of the mouth and oropharynx. It was carried out under a dental operating light using two mouth mirrors to retract and visualise the soft tissues and a gauze swab to manipulate the tongue. The test was recorded as positive if a white patch, red patch or ulcer of greater than 2 weeks’ duration was detected. However, these criteria were further qualified by defining lesions or conditions regarded as malignant or premalignant and therefore screened positive, and by indicating lesions which might have a similar appearance but should be regarded as negative (Table 1). An apparently normal mucosa was also classified as negative. Findings were entered on a simple report form. In addition, each subject screened was asked to complete a brief, confidential questionnaire designed to identify high risk lifestyle factors, notably smoking and alcohol consumption habits. Questions covered the amount and type of tobacco used and the duration of use, and the amount, frequency and type of alcoholic drink consumed.

The program was designed to continue long term, and a pathway was established for patients requiring referral. Also all participants were given preventive advice stressing the risk factors for oral cancer and the benefits of a healthy lifestyle.

Evaluation and analysis – After screening, each subject was independently examined by a specialist in oral medicine who was unaware of the findings of the screener but who had the subject’s completed lifestyle questionnaire available for scrutiny. The reference criterion (“gold standard”) for calculating sensitivity and specificity was the definitive diagnosis by the specialist who had access to any relevant diagnostic aids, including biopsy if considered necessary.

Sensitivity and specificity were computed for each screener separately and for their combined results. Uptake of the program among staff was recorded, and the classification of screened subjects by occupational group was compared for goodness-of-fit with the occupational profile of all eligible staff on the headquarter’s payroll. Seven occupational staff grades were used for classification purposes. Logistic multiple regression analysis estimating relative risk was carried out using the specialist definitive diagnosis, classified as negative or positive, as the dependent variable. Personal data items and responses from the lifestyle questionnaire, each aggregated and expressed in binary form, represented the independent risk factor variables. The variable, age, was entered as a continuous independent measurement. The cut-points for the dichotomized variables were (1) any use, (2) moderate or (3) heavy usage of tobacco, and (4) higher than safe use of alcohol. The criteria are specified in Table 5.

Results

There were 553 eligible staff aged 40 yr or over on the headquarters payroll and 292 (53%) were screened during the 1-year evaluation period. Seventeen staff were also screened from a separate worksite of the company and included in the analysis. Of those screened, all but 12 were registered patients of the practice.

Table 1 presents a contingency table for frequencies of subjects classified as positive and negative according to the screening test and definitive diagnosis. Seventeen positive lesions were diagnosed by the specialist amounting to a prevalence of 5.5% in the screened popula-

<table>
<thead>
<tr>
<th>Test findings</th>
<th>Positive</th>
<th>Negative</th>
<th>True prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive diagnosis</td>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Test prevalence</td>
<td>2</td>
<td>290</td>
<td>292</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>295</td>
<td>309</td>
</tr>
</tbody>
</table>

Sensitivity=0.71 (95% CI, 0.46–0.96), specificity=0.99 (95% CI, 0.98–1.00).
Table 3. Comparison of uptake of the screening programme by headquarters staff according to occupational grade, with the occupational profile of all headquarters staff aged 40 yr or over

<table>
<thead>
<tr>
<th>No.</th>
<th>M/F</th>
<th>Age</th>
<th>Occupation group</th>
<th>Diagnosed lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>52</td>
<td>Middle manager</td>
<td>Erosive lichen planus</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>57</td>
<td>Service staff</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>Middle manager</td>
<td>Reticular lichen planus</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>55</td>
<td>Middle manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>61</td>
<td>Service staff</td>
<td>Reticular lichen planus</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>45</td>
<td>Assistant manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>57</td>
<td>Clerical staff</td>
<td>Reticular lichen planus</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>56</td>
<td>Senior manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>53</td>
<td>Senior manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>42</td>
<td>Middle manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>42</td>
<td>Middle manager</td>
<td>Erosive lichen planus</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>55</td>
<td>Assistant manager</td>
<td>Reticular lichen planus</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>48</td>
<td>Service staff</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>55</td>
<td>Assistant manager</td>
<td>Reticular lichen planus</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>55</td>
<td>Senior manager</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>54</td>
<td>Senior manager</td>
<td>Atrophic lichen planus</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>41</td>
<td>Middle manager</td>
<td>Leukoplakia</td>
</tr>
</tbody>
</table>

Table 5. Logistic multiple regression analysis with definitive diagnosis as dependent variable and gender, age and reported life style factors as independent variables

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>b coefficient (SE)</th>
<th>P</th>
<th>Odds ratio</th>
<th>95% confidence interval for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.21 (0.53)</td>
<td>&gt;0.05</td>
<td>1.23</td>
<td>0.43–3.51</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.03 (0.04)</td>
<td>&gt;0.05</td>
<td>1.03</td>
<td>0.95–1.11</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>-0.39 (0.79)</td>
<td>&gt;0.05</td>
<td>0.68</td>
<td>0.14–3.21</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1.23 (0.60)</td>
<td>&gt;0.05</td>
<td>3.43</td>
<td>1.06-11.11</td>
</tr>
<tr>
<td>Drinker</td>
<td>-6.09 (37.55)</td>
<td>&lt;0.05</td>
<td>0.00</td>
<td>2.48×10⁻³-five</td>
</tr>
<tr>
<td>Smoker &amp; drinker</td>
<td>-0.84 (46.68)</td>
<td>&gt;0.05</td>
<td>0.43</td>
<td>7.91×10⁻⁴⁻2.35×10⁻⁹</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.72 (2.22)</td>
<td>&gt;0.05</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Key

<table>
<thead>
<tr>
<th>Variable</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male=1, female=0</td>
</tr>
<tr>
<td>Smoke</td>
<td>Current smoker of tobacco in any form or regular smoker within last 10 yr =1, non-smoker =0, current smoker, else=0</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>Current smoker of less than 20 cigarettes or equivalent per day =1, non-smoker =0</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>Current smoker of 20 or more cigarettes or equivalent per day =1, non-smoker =0</td>
</tr>
<tr>
<td>Drink</td>
<td>Consumer of more than 21 standard units of alcohol (male) or 14 units (female) per week =1, drinker of less than the specified amount =0</td>
</tr>
</tbody>
</table>

Each screener saw only those subjects who presented for screening at their own scheduled sessions whereas the specialist was in attendance at every dedicated screening session and saw the screened subjects of both dentists. One screener returned a sensitivity of 0.75 (95% CI, 0.50–1.00) and the other, a value of 0.60 (95% CI, 0.17–1.00). Both had specificity values of 0.99 (95% CI, 0.98–1.00 and 0.97–1.00 respectively).

In Table 3, the composition of the headquarters group who presented themselves for screening according to occupational grade, is compared with the occupational profile of all eligible headquarters staff. The personnel department graded the staff as service (skilled and semi-skilled manual workers); clerical or secretarial; assistant, middle or senior management; and board members. The composition of the screened group by occupational grade did not differ significantly from that of all headquarters staff (P>0.05). However, there was a trend towards an over-representation of assistant managers and an under-representation of service personnel.

Table 4 examines the subjects who were diagnosed as positive according to their gender, age, occupational grading, and type of lesion diagnosed. There were nine cases of leukoplakia (2.9%), and eight cases of lichen planus (2.6%). There were no cases of squamous cell carcinoma. In establishing the definitive diagnosis, five patients were biopsied; two showed epithelial dysplasia, two hyperkeratosis without dysplasia and one, erosive lichen planus.

Table 5 presents the logistic multiple regression analysis producing estimates of relative risk among those screened with five independent variables included. The only independent variable which was statistically significant (P<0.05) was heavy smoking. This produced an odds ratio (estimating relative risk) of 3.43 (95% CI, 1.06–11.11) of a positive diagnosis for those who smoked 20 or more cigarettes or equivalent per day. The regression coefficients for the other independent variables were non-significant (P>0.05). In testing for goodness-of-fit.
of the model, the chi-square value for \( -2 \log \text{likelihood} \) with all conditions included was 124.35 \( (P=1.00) \) and for goodness-of-fit, 292.13 \( (P=0.50) \), upholding the null hypothesis that the model did not differ significantly from a "perfect" model.

**Discussion**

The response rate over the course of 1 yr to the offer of mouth screening for oral cancer and associated precancerous lesions amounted to 53% of all head-quarters staff of 40 years of age or over. This appears rather low compared, for example, with the workplace screening program of Ikeda et al. (18), who recorded attendance rates of 77% and 60% in factory and office workers from 2 Japanese companies. However, the present figure represents some under-estimation of true compliance. A number of staff who were screened will not have been included in the evaluation since they were unable to attend at one of the dedicated sessions and were therefore not examined by the specialist diagnostician. The lower compliance rate in the present study may be due to the nature of the publicity material given to staff which was fairly forthright in its emphasis of the dangers of oral cancer, and uncompromising in its reference to the risk factors. A higher compliance might have been achieved with a more bland invitation to undergo general mouth, as opposed to oral cancer, screening. This would place a positive emphasis on the benefits of a healthy mouth rather than following a more negative approach centered on the detection of disease.

The overall sensitivity of the screening test in the hands of the two company dentists amounted to 0.71 and compares with the value of 0.48 reported by Ikeda et al. (12) and 0.95 reported by Warna­kulasuriya & Pindborg (13) in their Sri Lanka study using primary health care workers. Two factors may have accounted for the comparatively low sensitivity achieved in the current study. First, there was no specific training and standardization of the screeners nor assessment of their performance before commencement. They were simply given the criteria for a positive or negative screen (Table 1) and instructed on the conduct of the evaluation and how to complete the recording forms. This was done purposely to test the ability of dental practitioners without special training to screen for oral cancer and precancer. Secondly, 96% of those screened were registered patients of the practice and the two practitioners were therefore aware that the patients were under continuing supervision. This may have made them cautious in designating a patient as positive. It is evident that thorough training in oral soft tissue screening is essential for those involved in any substantive program.

In contrast to sensitivity, specificity values were very high. There was thus a low to negligible frequency of false-positive decision making which is of some psychological importance to those screened and potential economic importance to providers of follow-up secondary care services (19). Of the five false-negative screening decisions, 3 were reticulor-lichen planus. Only two cases, apparently missed, were potentially serious conditions, one of erosive lichen planus and one of leukoplakia.

The occupational profile of the screened subjects did not differ significantly from that of the eligible head-quarters population. Nevertheless, there was a degree of over-representation of the lower management grade and under-representation of service personnel. This reflects the pattern of uptake of oral care services generally where it is found that people in the professional and managerial social classes consistently have the higher asymptomatic attendance rates. Special efforts should be made in work-site screening programs for oral cancer to encourage staff in lower occupational grades to participate since some may be at heightened risk to the disease (20).

The logistic regression analysis, estimating the relative risk of having a positive lesion, incorporated five independent variables concerned with known risk factors. The cut-points were derived from a consideration of documents responding to government targets for reducing dependence on smoking and alcohol (21, 22). It produced a significant regression coefficient only in those claiming to smoke 20 or more cigarettes per day who had an estimated risk more than three times greater than non-smokers. However, the numbers involved in the analysis were small and quantification of the independent variables depended upon self-reported behaviour, which may be a doubtful reflection of actual behaviour.

The study has highlighted some of the difficulties of conducting a rigorous research program in a real life setting. Ideally, all those involved in data collection in a field research study should be unfamiliar with the subjects of the investigation. A larger study among dental hospital patients and subjects recruited from a medical practice list, currently being undertaken by the investigative team, should overcome this shortcoming. Despite the relatively small numbers, a quantifiable risk from heavy smoking was detected. Also a need was identified for specific training in the theory and practice of screening in order to maximize sensitivity while at the same time maintaining a low false-positive rate.

In conclusion, the study afforded a pragmatic evaluation of a screening program which is already established, and provided a useful pilot exercise for gaining practical experience and expertise in further investigations of the feasibility, suitability, and cost effectiveness of screening for oral cancer and precancer.

**Acknowledgement** — The authors are grateful to Ms Antvia Petrie for her valuable advice on the statistical analysis.

**References**

Evaluation of a screening test for the early detection of oral cancer and precancer

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Oral Cancer Screening Group, Eastman Dental Institute for Oral Health Care Sciences, London, UK.

The purpose of this study was to establish the sensitivity and specificity of a clinical examination for the detection of early oral cancer and precancer. A screening programme was conducted over a period of one year and 2027 subjects aged 40 years and over were examined. Screening took place at two sites; opportunistically in outpatient departments at a dental hospital and by postal invitation at an inner city medical practice. The screening procedure included a questionnaire on habits and an oral examination by two independent dentists. The first examining dentist (the screener) was either a general dental practitioner, a community dental officer or a junior hospital dentist. There were 24 dentists in the screener group. A second single examining dentist (a specialist) provided the definitive diagnosis, or ‘gold standard’, with which the screeners’ results were compared. A screen was defined as positive if a white patch, a red patch, or an ulcer of longer than two weeks duration was detected. Each subject was categorised as either positive or negative by both the screener and the specialist. The screener and specialist were unaware of each other’s findings. The prevalence of disease according to the specialist was 2.7 per cent. The results for all 24 screeners were pooled and gave an overall sensitivity of 0.74 (95 per cent CI, 0.62 to 0.86), specificity of 0.99 (95 per cent CI, 0.985-0.994) and positive and negative predictive values of 0.67 and 0.99 respectively.

Key words: oral cancer and precancer, screening, sensitivity, specificity

Introduction

There are approximately 2000 newly diagnosed cases of oral cancer in England and Wales each year, with an incidence of 4.5 per 100,000 (Office of Population Censuses and Surveys, 1994). Although there have been many advances in surgical techniques and rehabilitation for oral cancer patients, the OPCS statistics indicate that the incidence to mortality ratio remains 1.68 (tongue, female) compared to 2.1 for invasive cancer of the uterine cervix and 3.56 for malignant melanoma (female), both of which have comparable incidence rates to oral cancer. Evidence from a large European oral cancer study (Platz et al., 1986) suggests that small oral cancer lesions have a better prognosis than large lesions. For example comparing two patients aged between 50 and 70 years with lesions differing only in size, the median survival time is reduced by over four years for the patient with a lesion greater than 4cm in diameter.

Screening for oral cancer is simple and involves a systematic visual examination of the oral soft tissues (Mock, 1985; British Postgraduate Medical Federation, 1991), with the aim of detecting cancer at an earlier stage than is usual in clinical practice (Shapiro, 1992). Also, because oral cancer may be preceded by a clinically detectable precancerous lesion, usually a leukoplakia (Pindborg et al, 1991) screening may also offer the opportunity to reduce the incidence of invasive lesions. Since oral cancer complies with many of the principles of screening described by Wilson and Jungner (1968), it would appear appropriate and timely to evaluate oral cancer as a disease suitable for a screening programme. A United Kingdom working group on screening for oral cancer and precancer (Speight et al., 1993), has considered the feasibility of oral screening and has made a number of recommendations for priority areas for future research.

Previous studies of oral mucosal conditions have sought, in the main, to establish the prevalence of oral cancer and precancer (Bouquot and Gorlin, 1986; Hogewind and van der Waal, 1988; Kleinmann et al., 1991) and the effects of primary intervention (Gupta et al., 1986). Although several industrial firms in the United Kingdom have initiated screening programmes for their employees (Downer et al., 1995; Feaver, 1990), few studies have attempted to evaluate the effectiveness of oral cancer screening in terms of sensitivity (proportion of true positives) and specificity (proportion of true negatives).

The purpose of this study was to measure the sensitivity and specificity of a simple oral examination for the detection of lesions which may be associated with oral cancer or precancer and to estimate the relative risk for oral cancer and precancer from tobacco smoking and drinking alcohol. It is part of a larger project which is evaluating a number of aspects of an oral cancer screening programme.

Materials and methods

The screening programme

The screening took place at two separate sites; a dental hospital and an inner city medical practice. At the dental hospital there were specific screening sessions where subjects were recruited by the screener or the specialist from the various out-patient departments of the hospital. This group consisted of patients in the defined target group (people aged 40 years or over) and also included eligible relatives and
friends attending on that day. For the medical practice, a list of registered patients was obtained from the Family Health Services Authority (FHSA). This contained details of the name, address, and date of birth of each patient. Subjects were invited by postal invitation to attend for screening at the practice. The subjects at both sites received the same information leaflet explaining the nature of oral cancer, its associated risk habits, the screening method and the advantages to the subject of being screened. At both sites, posters and information leaflets advertising screening sessions and their times were displayed at all patient reception areas.

The screeners were advised of the diagnostic criteria which should result in a positive or negative screen but apart from this no formal training or standardisation was undertaken. A lesion was defined as positive when a white patch, a red patch or an ulcer of longer than two weeks duration was detected. A number of well defined clinical entities which might have this appearance were designated as positive including lichen planus, submucous fibrosis, lupus erythematosus and actinic keratosis. Prior to screening, all subjects completed a questionnaire concerning their age, gender, smoking and drinking habits, and dental attendance, and provided informed consent. The screening test comprised a thorough visual examination of the surface of the oral mucosa (British Postgraduate Medical Federation, 1991). The examination took place in a dental chair, using two mouth mirrors and a good light. The results were recorded on a standard pre-numbered form.

Each subject was examined independently by a second dentist (the 'specialist'), who was able to refer subjects for further tests or review as appropriate. The results were also recorded on a standard form which was collated with the screeners’ form only after completion. All subjects diagnosed as positive by the specialist or requiring treatment for benign lesions were referred to an oral medicine or oral surgery clinic where they underwent biopsy and treatment as appropriate. The specialist provided the definitive diagnosis or ‘gold standard’ for each subject. This was used to assess the sensitivity and specificity of the screeners.

The screening sessions were also taken as an opportunity to explain the risk factors for oral cancer and to provide advice on the risks of smoking and alcohol when appropriate. All subjects were advised to attend for a routine dental examination on a yearly basis. The screeners were not given any feedback on their performance until the completion of the study.

Analysis

Since there was a large variation in the number of subjects screened by each screener the results from all the screeners were pooled to calculate the overall sensitivity and specificity of the screening test. This analysis was repeated after excluding the eight screeners who had not seen any positive subjects and the results were essentially unchanged. However, since one third (eight) of the screeners were not exposed to any positive subjects it was not possible to calculate the sensitivity of these screeners individually.

A calculation of relative risk for oral cancer and precancer, was obtained by logistic multiple regression analysis using personal characteristics and lifestyle factors as independent variables. Among these, age was considered as a continuous independent variable with all subjects being 40 years of age or over. Gender (male or female) was included as a dichotomous variable. Dental attenders were those subjects who claimed to have attended a dentist within the past year. Alcohol and tobacco consumption are considered to be risk factors for oral cancer and precancer and subjects were divided into three groups according to levels of use (Table 1). The levels were set according to the recommendations for smoking and drinking levels for males and females in the United Kingdom (Department of Health, 1992). A current smoker was defined as one who smoked now or had done so within the past ten years.

The heavy and moderate groups for both smoking and drinking were compared to the light drinking and non-smoking groups by creating dummy variables for the heavy and moderate groups. Light drinking and non-smoking groups were therefore entered into the analysis as zero for each of the dummy variables. Variables labelled, z1, z2, z3 and z4 were created for the heavy and moderate groups and given values shown in Table 1.

Table 1. Profile of screened population (2027 subjects).

<table>
<thead>
<tr>
<th>Risk</th>
<th>Definition</th>
<th>Proportion of population*</th>
<th>Specification in logistic multiple regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥40 years</td>
<td>Geometric mean: 56.01</td>
<td>Continuous variable</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/female</td>
<td>44% M 56% F</td>
<td>Male:1 Female:0</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>&lt;1 year: 71%</td>
<td>&gt;1 year: 29%</td>
<td>&gt;1 year: 1 &lt;1 year: 0</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>&gt;20 cigarettes/day</td>
<td>8%</td>
<td>dummy variable, z1=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(z1=0 for moderate and non-smokers)</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>&lt;20 cigarettes/day</td>
<td>30%</td>
<td>dummy variable, z2=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(z2=0 for heavy and non-smokers)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>no cigarettes/&gt;10 years</td>
<td>62%</td>
<td>compared to heavy and moderate smokers</td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy drinker (units)</td>
<td>&gt;21 M/&gt;14 F</td>
<td>3%</td>
<td>dummy variable, z3=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(z3=0 for moderate and light drinkers)</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>&gt;5 units &lt; heavy</td>
<td>26%</td>
<td>dummy variable, z4=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(z4=0 for heavy and light drinkers)</td>
</tr>
<tr>
<td>Light drinker</td>
<td>&lt; 5 units/week</td>
<td>71%</td>
<td>compared to heavy and moderate drinkers</td>
</tr>
</tbody>
</table>

(*except for age)
Results

Population profile

The population profile is shown in Table 1. All subjects were aged 40 years or over, the geometric mean average being 56.01 years (95 per cent CI, 55.47–56.48). Forty four per cent of the population were male and 56 per cent female. Seventy one per cent of subjects claimed to have attended a dentist during the previous twelve months. Heavy smokers comprised eight per cent of the screened population and heavy drinkers, three per cent. The light drinking group contained 71 per cent of the screened population and the remaining 26 per cent were classified as moderate drinkers. Non smokers comprised 62 per cent of the screened population and moderate smokers 30 per cent.

Sensitivity and specificity

The results of the screening programme are summarised in Table 2. A total of 2027 individuals received a screening examination of which 1967 were screened negative and 60 screened positive. All subjects were examined by a specialist who provided an independent definitive diagnosis. The true prevalence of positive lesions in the subjects screened was 2.7 per cent (54 lesions). The sensitivity was 0.74 (95 per cent CI, 0.62–0.86), specificity, 0.99 (95 per cent CI, 0.985–0.994) and positive and negative predictive values, 0.67 and 0.99 respectively.

The results from the two sites were similar and are summarised in Tables 3 and 4. Nine hundred and eighty five subjects were screened in the medical practice and 1042 in the hospital. The prevalence of positive lesions was 2.2 per cent (22 lesions) and 3.0 per cent (32 lesions) respectively.

The definitive diagnosis provided by the specialist resulted in 54 positive findings: two cases of squamous cell carcinoma and one of basal cell carcinoma, 18 leukoplakias and 31 cases of lichen planus and two of lupos erythematosus. All the carcinomas were detected by the screeners but fourteen subjects with potentially malignant lesions were missed. These were five with leukoplakia, and nine with lichen planus. There were 20 false-positives, which the screeners recorded as lichen planus (15), ulceration (two), leukoplakia (two) and one pigmented lesion.

Relative risks of smoking and drinking

Age, gender, smoking, drinking and dental attendance were analysed in a logistic multiple regression model to assess the relative risk of oral cancer and precancer for each variable (Table 5). Logistic regression was used to determine which of the prognostic variables, (age, gender, smoking, drinking and dental attendance) could predict the outcome. Only those in the heavy smoking group had a significant risk of 2.36 (95 per cent CI, 1.13–4.93, P<0.05) of being diagnosed positive compared to non smokers (Table 5). Interactions between smoking and drinking were found to be non-significant.

<table>
<thead>
<tr>
<th>Screen</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>955</td>
<td>963</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>963</td>
<td>985</td>
</tr>
</tbody>
</table>

Sensitivity = (14/22) = 0.64 (95 per cent CI, 0.44–0.84)
Specificity = (955/963) = 0.99 (95 per cent CI, 0.984–0.996)
Positive predictive value = (14/22) = 0.67
Negative predictive value = (955/963) = 0.99

Table 4. Agreement between screeners and specialists – hospital subjects.

<table>
<thead>
<tr>
<th>Screener</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>26</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>998</td>
<td>1004</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>1010</td>
<td>1042</td>
</tr>
</tbody>
</table>

Sensitivity = (26/32) = 0.81 (95 per cent CI, 0.67–0.95)
Specificity = (998/1010) = 0.99 (95 per cent CI, 0.984–0.996)
Positive predictive value = (26/28) = 0.68
Negative predictive value = (998/1004) = 0.99

Discussion

The purpose of a screening test is to distinguish individuals who probably have a disease from those who probably do not (Wilson and Jungner, 1968). The test is not intended to be diagnostic but positive findings must be confirmed by a specialist diagnostic procedure. The detection rate (sensitivity) of the test may be determined by the criteria for a positive result. For some tests, for example screening for cholesterol or iron deficiency, the result may be an objective value which can be altered to determine the proportion of individuals to be referred for further investigation. For oral cancer, however, there is no single appropriate test for the detection of malignant or premalignant disease (Zakrzewska et al., 1993) and a simple but thorough examination of the oral mucosa is regarded as the most effective method (Pindborg, 1984; Mock, 1985). However, the criteria for a positive result must depend to some extent on the subjective decision of the examiners and on their ability to recognise aberrations from normal. In an attempt to make the test as objective as possible, it is necessary to define simple and unequivocal criteria for a positive result.

Warnakulasuriya and Pindborg (1990) evaluated a screening programme in Sri Lanka and defined a positive test as the presence of a white or red lesion or an area of ulceration. These criteria can be modified by defining a number of identifiable lesions to be included or excluded as positive (Speight et al., 1992). For oral cancer screening tests to be most

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Table 2. Agreement between screeners and specialist – all subjects.

<table>
<thead>
<tr>
<th>Screener</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>40</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>1953</td>
<td>1967</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>1973</td>
<td>2027</td>
</tr>
</tbody>
</table>

Sensitivity = (40/54) = 0.74 (95 per cent CI, 0.62–0.86)
Specificity = (1953/1973) = 0.99 (95 per cent CI, 0.985–0.994)
Positive predictive value = (40/60) = 0.67
Negative predictive value = (1953/1967) = 0.99
effective it is important to have a high sensitivity to minimise the number of false-negative results. However, in practice, to achieve a high sensitivity usually means a lower specificity and an increase in false positives (Prorok et al., 1990; Chamberlain, 1993). Attempts to increase the sensitivity by changing the criteria for a positive result would lead to more individuals being unnecessarily referred for further diagnostic procedures. Therefore, although an oral screen could be designed to include all mucosal abnormalities, this might result in the referral of a large number of benign lesions, such as fibro-epithelial polyps, which are not associated with cancer. The resulting false positives would be unacceptable because of the cost to the secondary care services as well as the possible psychological trauma for those individuals, unnecessarily screened positive (Marteau, 1990).

In the present study a screen was regarded as positive if a white patch, a red patch, or an ulcer of longer than two weeks duration was evident. The screeners were also instructed to include lesions of lupus erythematosus, submucous fibrosis or actinic keratosis as positive. Also, for the purposes of this study all types of lichen planus were considered to be positive despite the continuing controversy regarding their malignant potential (Eisenberg and Krutchkoff, 1992; Holmstrup, 1992; Eversole, 1992).

The sensitivity and specificity of the screening test in this study were 0.74 and 0.99 respectively which compare favourably with results from other cancer screening programmes. Ikeda et al. (1991) reported that the positive predictive value of an oral examination to detect leukoplakia was 0.73 and the specificity 0.73 with a disease prevalence of 2.5 per cent. In Sri Lanka Warnakulasuriya and Pindborg (1990), using primary health care workers, reported positive and negative predictive values for oral screening of 0.58 and 0.98 respectively. A recent study in a work-site environment achieved a sensitivity and specificity of 0.71 and 0.99 respectively with 5.5 per cent prevalence of positive lesions (Downer et al., 1995). In a study of breast cancer screening which compared the diagnostic ability in reading radiographic films for a radiographer, non-radiologist doctor and a radiologist, the sensitivity and specificity achieved were both in the region of 0.80 (Haierat and Henderson, 1991). A study of cervical cytology screening achieved an overall sensitivity of 0.80 and specificity of 0.99 (Soost et al., 1991). Screening for malignant melanoma by visual examination alone has an estimated sensitivity of 0.75 and specificity of 0.98 (Koh et al., 1991).

Oral cancer is relatively uncommon in the United Kingdom and in this study, the prevalence of malignant and premalignant lesions was 2.7 per cent. However, this should not be construed as representing a true population figure since the sample was self-selecting, although the prevalence of 2.2 per cent in the medical practice population may be close to the population as a whole. The low sensitivity found may be due in part to health care professionals having a low index of suspicion. Nevertheless the results may be indicative of the screening potential of general dental practitioners and community dental officers who constituted over half the screeners employed in this study. It is probable that the detection rate of relevant suspicious lesions could be improved by further training in the specific signs and symptoms of early cancer and precancer. This is supported by the finding that the sensitivity of the screeners in the hospital was higher than in the medical practice. These screeners were generally recruited from junior hospital staff and would be expected to have more current exposure to mucosal lesions than general practitioners.

Eddy (1980) developed a simulation model for breast cancer screening which could reflect the importance of the diagnostic ability of screeners. This model demonstrates that the more training individuals have, the more likely they are to detect lesions when they are small. Thus, a specialist may detect cancer early in its development whereas practitioners, or patients themselves, may be more likely to detect lesions when they are large. Obviously there are many assumptions in this model and the times of detection are only arbitrary since one would expect much variation in diagnosing a lesion between specialists, dentists or individual patients. However, a public education campaign to encourage regular attendance for oral screening, might mean that more lesions could be identified by the dentist at an earlier stage compared to clinicalsurfacing, where the individual presents for treatment with a self-diagnosed lesion.

A further major problem in screening for any type of cancer is the lack of absolute knowledge of progression and regression rates for precancerous lesions (Speight and Morgan, 1993). These lesions must be treated, since a ‘wait and see’ policy would defeat the objective of early detection if a lesion were allowed to progress. Further studies of disease progression are therefore essential in order to truly assess the value of detecting and treating precancerous lesions.

In this study a subject who was a heavy smoker was found to have an increased risk of 2.36 (95 per cent CI, 1.13–4.93) of having a true positive lesion compared to a non-smoker. However, this can only be judged as an estimate since it is generally accepted that people tend to under report their smoking and drinking habits. It may be possible to predict future trends in oral cancer incidence rates from alcohol and tobacco sales figures, or by classifying individuals into heavy, moderate and light smokers, using data from other surveys such as the General Household Survey (1990). Doll (1990)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>b coefficient (SE)</th>
<th>Odds ratio</th>
<th>Confidence intervals (95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01 (0.12)</td>
<td>1.01</td>
<td>0.99–1.00</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>0.33 (0.29)</td>
<td>1.38</td>
<td>0.79–2.44</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dental attendance</td>
<td>-0.21 (0.32)</td>
<td>0.81</td>
<td>0.43–1.51</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>0.86 (0.38)</td>
<td>2.36</td>
<td>1.13–4.93</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>0.54 (0.31)</td>
<td>1.72</td>
<td>0.93–3.19</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>0.78 (0.48)</td>
<td>2.19</td>
<td>0.86–5.60</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>0.46 (0.31)</td>
<td>1.59</td>
<td>0.87–2.91</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
relates the increasing trends in oral cancer mortality to the doubling in alcohol consumption between 1950 and 1980 despite a general decrease in the percentage of the population who smoke. A comparison can be made between the synergistic effect of tobacco and alcohol, and tobacco consumption alone in that the decrease in tobacco consumption is reflected in the decrease in mortality rates for diseases such as lung cancer, with which tobacco consumption is closely related. The relationship between tobacco and alcohol is recognised to be an important factor in the aetiology of oral cancer, although interactions between them were found to be non-significant in this study.

The study has shown that a screening test consisting of a simple oral examination with clear criteria for a positive result, produces a sensitivity and specificity comparable to other cancer screening programmes. No specific training in the diagnosis of relevant malignant or premalignant lesions was given and it is envisaged that with further professional education the sensitivity could be increased. Further research to evaluate the diagnostic ability of dentists before and after training, and to determine the effects of public and professional health education is needed.

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References


The use of artificial intelligence to identify people at risk of oral cancer and precancer.

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Abstract
Artificial intelligence is being used increasingly as an aid to diagnosis in medicine. The purpose of this study was to evaluate the ability of a neural network to predict the likelihood of an individual having a malignant or potentially malignant oral lesion based on knowledge of their risk habits. Performance of the network was compared to a group of dental screeners in a screening programme involving 2027 adults. The screening performance was measured in terms of sensitivity, specificity and likelihood ratios. All subjects were examined independently by a dental screener and a specialist, who provided a definitive diagnosis, or 'gold standard', for each individual. All subjects also completed an interview questionnaire regarding personal details, dental attendance and smoking and drinking habits. The neural network was trained on ten input variables derived from the questionnaire along with the outcome of the specialist's diagnosis. Following training, the network was asked to classify the remaining unseen proportion of the screened population as positive or negative for the presence of cancer or precancer. The overall sensitivity and specificity of the dentists were 0.71 (95% CI, 0.59-0.83) and 0.99 (95% CI 0.99) respectively compared to 0.80 (99% CI 0.55-1.00) and 0.77 (95% CI 0.73-0.81) for the neural network. In view of the potential costs involved in implementing a screening programme, this neural network may be of value for the identification of individuals with a high risk of oral cancer or precancer for further clinical examination or health education.
Introduction

In the developed world, oral cancer is the eighth most common malignancy and is more common than cervical cancer (1). Although less frequent in the United Kingdom (2) it still represents just over 1% of all malignancies with an annual incidence of about 4 per 100,000. In England and Wales there are approximately 2,000 new cases each year compared to 4,500 cases of cervical cancer, 27,000 of breast cancer and nearly 40,000 lung cancers (3). These figures suggest that oral cancer is a relatively small health care problem but mortality from the disease remains high with over 60% of patients dying as a result of their oral lesions (4,5). There is also evidence that oral cancer is increasing in the United Kingdom (2,6,7) and throughout Europe (8).

Oral cancer is the only fatal disease which dentists have to deal with on a regular basis and these worrying statistics have been the cause of increasing concern among the profession, resulting in calls for improvements in primary and secondary prevention of the disease (9-14). Recently a UK working group considered the feasibility of oral cancer screening and made a number of recommendations, including the need for further research into methods for screening and the cost effectiveness of screening programmes (15,16).

A recent study of a pilot oral cancer screening programme showed that dental screeners could detect malignant and potentially malignant lesions when these were actually present (sensitivity) in 74% of cases, and would record a negative finding when such lesions were absent (specificity) in 99% of instances (17). However, the attendance rate for screening following a postal invitation to undergo an oral examination was only 25.7% (18). This suggests that an invitational screening programme for oral cancer might not be cost effective and other methods of patient recruitment ought to be considered. Opportunistic programmes, where individuals are examined when they attend a health care professional for some other, unrelated, reason would seem to be a promising method. Because of the relatively low prevalence of oral cancer and precancer, and its association with known risk factors, it might be possible to identify and target high risk individuals for screening from a priori criteria. Since the yield of lesions would therefore be higher, such a programme may be more cost effective.

Artificial intelligence is a relatively new area of computer science which takes as its starting point elements of the micro-structure and functioning of the human brain. Central to this technology is a neural network which is a large number of simple processing units connected together in a complex net-like structure modelling, in a very simplified form, the interconnecting neurones of the nervous system (19). The neural network can 'learn' the answer to a problem by being given repeated individual items of information with a known outcome. Eventually, if data from enough individuals are given, the network will recognise a pattern and will subsequently be able to predict the correct outcome when given information from new individuals. Neural networks are being used increasingly in medicine to aid in diagnosis and to predict the outcome of diseases (20,21).

The purpose of this study was to evaluate the ability of a neural network to predict the likelihood of an individual having a precancer or cancerous lesion of the oral mucosa based on knowledge of their risk habits.
Materials and Methods

The details of the screening programme and the selection of the subjects have been described elsewhere (17). Two thousand and twenty seven adults over the age of 40 years were screened either in a dental hospital or in a neighbouring inner city medical practice. Each subject was examined independently by a dentally trained screener and a specialist who established the definitive or 'gold standard' diagnosis. A screen was defined as positive if a white patch, a red patch or an ulcer of greater than 2 weeks duration was detected. A number of well-defined clinical entities that might have this appearance were designated as positive (Table I). All subjects gave informed consent and completed an interview questionnaire regarding personal details, dental attendance and smoking and drinking habits. This information was collected since age (6), gender (3), and tobacco and alcohol usage (22-24) are known to influence oral cancer risk status.

Preparation of the neural network.

The neural network software was written by one of the authors (AE) in the Turbo Pascal programming language (Borland International Inc, California). The programme was run on a standard 486 desktop PC (Dell Computer Corporation) and was able to input data directly from a commonly used database (Paradox, Borland International Inc, California). The prevalence of positive lesions in the screened population had been determined previously as 2.7% (17) and the computer was instructed to randomly generate two groups of subjects, each with the same prevalence. These comprised a training set of 1662 individuals and a test set of 365 individuals.

For training the network, ten items of personal information relating to age, gender and habits were selected from the questionnaire data (Table II). These ten input variables were given to the network for each of the 1662 individuals in the training set along with the outcome of the specialist oral examination as positive (cancer or precancerous lesion present) or negative. Each variable, except age, was presented to the network in binary form, for example, if the subject was a heavy smoker a value of 1 was entered, but if not, this variable was awarded a value of 0. Age was entered as a continuous variable, between 0 and 1, commencing at age 40 years.

Testing the performance of the neural network

The network was tested by presenting it with the same ten input variables for each of the 365 individuals in the test set. The programme then classified each individual as positive or negative. The sensitivity and specificity of the network’s ability to predict the presence (or absence) of a lesion was calculated using standard methods (25) with the specialist’s diagnosis as the gold standard. The performance of the network was compared to the performance of the dentally trained screeners which had already been determined (17).

The network’s ability to differentiate between positive and negative cases (decision threshold) could be altered by adjusting the weight given to each of the variables. The state of optimum performance was evaluated by plotting receiver operating characteristic (ROC) curves (26). These plot the true positive (sensitivity) against the false positive (1-specificity) rates at different decision making thresholds and determine a test’s ability to differentiate between normal and abnormal.
Assessment of performance (diagnostic accuracy) is represented by the area under the curve (27) where a perfect test gives an area of 1.0 and a random classification produces a value of 0.50. Sensitivity/(1-specificity) is called the likelihood ratio and represents the odds of a positive decision being correct against it being incorrect.

Results

The results of the screening programme have been reported previously (17). Fifty four (2.7%) of the 2027 subjects had a positive lesion, three of which were carcinomas. The sensitivity and specificity of the dental screeners were 0.74 and 0.99 respectively. The performance of the neural network is summarised in Table III. In the test set of 365 individuals there were 10 positive lesions (2.7%). The neural network correctly classified 8 of the 10 positive cases (sensitivity = 0.80) with a specificity of 0.77. This is the same as a detection rate of 80% and false positive rate of 23%. The likelihood ratio relating to positive decisions made by the network was 3.48 while that for the screeners was 74.00. The optimal performance of the network achieved an ROC curve with an area of 0.84 (fig. 1).

Discussion

Use of artificial intelligence and neural networks has increased considerably over recent years. They have been used extensively in many aspects of cancer control (28), for example, as an aid to diagnosing cancer through interpretation of mammographs (29), cervical smears by image recognition (30), ultrasound measurements of hepatic masses (20, 31) and in analysis of laboratory data (32, 33). Neural computing has also been used in cancer outcome prediction (21, 34) and treatment decision making (35).

In the screening programmes reported here, and in a previous study in a company headquarters (36), the overall performance of the dentists was superior to that of the neural network (Table IV). However, the detection rate of lesions (sensitivity) was similar in all cases, with the network performing equally as well as junior hospital dentists. This is not surprising since the network will have determined that most of the subjects with lesions were smokers and/or drinkers. The specificity achieved by the network was, however, quite low with a false positive rate of 23%, and the odds of having a lesion if classified as positive by the network were only 3.5 compared to over 60 if screened positive by a dentist. This was probably due to the network selecting all those individuals who, from their risk habits, could be considered to have a high likelihood of being diagnosed positive but had not developed lesions. In a preliminary screening procedure such as this, a high false positive rate is not a cause for concern, and indeed may be beneficial since these individuals will be subjected to a further test (oral examination) and can be selected for preventive health education.

The role of neural networks in screening programmes could therefore be as an adjunct in identifying high risk individuals. If the cost of setting up a screening programme and the cost of a dentist’s time is taken into account, then a neural network may prove to be economical since it could make an a priori selection of the high risk individuals that ought to be screened by a clinician. In dental practice, the system could be used to assign a risk status to patients in order to help decide who should receive a detailed oral mucosal examination (Fig. 2).

Although artificial intelligence is relatively new to the field of medicine and
dentistry, its usefulness in clinical decision making is becoming more apparent. This study has shown that a neural network could be used as a filtering system to determine those individuals who should receive a careful examination for oral cancer or precancer. In view of the increasing use of computers in dental surgeries it may be of use to the clinician to incorporate a user friendly risk analysis program to assess patients at risk. Despite this possible use of advanced computer technology in the early detection of oral cancer, it is still of the utmost importance to increase awareness of the disease and its risk factors among both health professionals and the general public. In this respect, the network would also be a useful aid to health education and could identify those individuals who would most benefit from counselling about their risk habits.

In conclusion, the findings of this study suggest that neural networks could have an important role in the primary and secondary prevention of oral cancer, although further research is needed into refining the software, improving the network performance, and producing user friendly systems.

Acknowledgements
This project was funded with the aid of grants from the Department of Health and the European Union (Europe Against Cancer). We would like to thank all the dentists who volunteered to act as screeners in the pilot screening programme.
Table I  Lesions included in the definition of a positive screen.

<table>
<thead>
<tr>
<th>Precancerous conditions</th>
<th>Precancerous lesions</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus</td>
<td>Leukoplakia</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>Erythroplakia</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Submucous fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table II  Input variables obtained from personal information of the screened population

<table>
<thead>
<tr>
<th>Question</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Never smoked or not for over 10 years</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>&lt;20 cigarettes/ day</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>≥20 cigarettes/ day</td>
</tr>
<tr>
<td>Non drinker</td>
<td>Never drinks or &lt; 5 units a week</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>Female ≤14, Male ≤21 units a week</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>Female &gt;14, Male &gt;21 units a week</td>
</tr>
<tr>
<td>Age</td>
<td>continuous variable from 40 years</td>
</tr>
<tr>
<td>Irregular dental attender</td>
<td>has not visited a dentist in the last year</td>
</tr>
</tbody>
</table>
Table III  Specialist result compared with the neural network’s screening result

<table>
<thead>
<tr>
<th></th>
<th>Neural Network</th>
<th>Specialist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>273</td>
<td>275</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>355</td>
<td>365</td>
</tr>
</tbody>
</table>

Positive prevalence: \(\frac{10}{365}\) = 2.74%

Sensitivity : \(\frac{8}{10}\) = 0.80

Specificity :\(\frac{273}{355}\) = 0.77

Likelihood ratio (0.80/0.23) = 3.48
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Dental * Hospital$^{17}$</th>
<th>Medical * Practice$^{17}$</th>
<th>Company Headquarters$^{37}$</th>
<th>Neural Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>1042</td>
<td>985</td>
<td>309</td>
<td>365</td>
</tr>
<tr>
<td>Lesion prevalence (%)</td>
<td>3.00</td>
<td>2.22</td>
<td>5.50</td>
<td>2.74</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.81</td>
<td>0.64</td>
<td>0.71</td>
<td>0.80</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.77</td>
</tr>
<tr>
<td>Predictive value (+)</td>
<td>0.68</td>
<td>0.47</td>
<td>0.86</td>
<td>0.09</td>
</tr>
<tr>
<td>Predictive value (-)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>81.00</td>
<td>64.00</td>
<td>71.00</td>
<td>3.48</td>
</tr>
</tbody>
</table>

* These studies provided the data for the neural network (see text)
References


Case-Control Study of Oral Dysplasia and Risk Habits Among Patients of a Dental Hospital

R. Kulasegaram, M.C. Downer, J.A. Jullien, J.M. Zakrzewska and P.M. Speight

Several studies have investigated risk factors for oral cancer but few have considered precancer. Records accumulated from 1975 to 1993 of dental hospital patients with histologically confirmed oral dysplasia provided the opportunity for a retrospective case-control study of the association between oral precancer and smoking tobacco and drinking alcohol. Seventy sets of case notes were available and each case was matched with records of a control subject, known to be free from dysplasia from another study, for birth date, gender and presumed ethnicity. The relative risk (OR) of having a dysplastic lesion for smokers compared with non-smokers, or ex-smokers for > 10 years, was 7.00. Logistic multiple regression revealed a dose-response relationship for tobacco dependent upon the level of cigarette consumption. Also subjects with moderate or severe dysplasia included a higher proportion of smokers than those with mild dysplasia. No overall increased risk from alcohol was found. However, the proportion of subjects who drank spirits was significantly higher among cases than controls. The study reaffirms the role of dental practitioners in identifying individuals at risk of mucosal disease, the importance of public education about the risk factors, and the necessity for counselling patients with precancerous lesions on avoiding further risk.

Keywords: alcohol, case-control, oral dysplasia, smoking, tobacco

INTRODUCTION

ORAL CANCER is a significant cause of morbidity and mortality and appears to be increasing in adults aged 35–64 years in the United Kingdom [1, 2]. Reducing the incidence of the disease and its morbidity in sufferers is an important goal [2, 3].

Despite advances in treatment and reconstructive surgery, there has been no improvement in oral cancer prognosis for over four decades [4]. 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. Today the future is relatively optimistic for patients whose disease is identified early. However, many of those affected are heavy smokers or consumers of high levels of alcohol and it is important for successful treatment and control to reduce their dependency on these known major risk factors [5].

Macfriean [6] has reviewed extensively the analytical epidemiology linking oral cancer with smoking tobacco and drinking alcohol and concluded that, in industrialised countries, these are the main aetiological factors. The International Agency for Research on Cancer has stated that there is sufficient evidence to show that tobacco is carcinogenic [7], though the precise role of alcohol remains to be established [8, 9]. Both agents are important independent risk factors [10-12] and there is evidence that their combined effect is greater than the sum of the risks from exposure to either on its own [10, 13, 14]. The epidemiological investigations cited were all based on data from oral cancer patients. With regard to potentially malignant oral lesions, Gupta et al. [5] have demonstrated the opportunity for their prevention among populations in India through reducing people’s exposure to risk factors. However, the roles of tobacco and alcohol as risk factors for oral precancer in European populations have not hitherto been investigated.

The present study was concerned specifically with the relationship between these two risk factors and oral precancer among residents of London, U.K. Since 1975 detailed case notes of patients with histologically diagnosed dysplasia have been kept by the oral medicine department of a postgraduate dental teaching hospital. It was considered that this series of records would form the basis for a case-control study. The objective was to quantify and reaffirm the association between tobacco smoking, alcohol consumption and potentially malignant oral lesions based on histologically confirmed dysplasia.
MATERIALS AND METHOD

The investigation was designed as a retrospective case-control study. Eligible cases included all patients who presented with oral dysplasia at the hospital from 1975 to 1993. These were identified from computerised lists held in the oral medicine department and their case notes were then obtained from the medical records department. Controls were selected from among 985 individuals on the list of a neighbouring north London NHS medical practice who had been screened for oral cancer and precancer and had been diagnosed by an oral medicine specialist, in a separate study [15], as being free from oral lesions.

Test and control subjects were matched individually for date of birth, gender and presumed ethnicity (i.e. Asian or non-Asian according to name). Where there was more than one matched control available, the individual whose date of birth most closely approximated that of the test subject was chosen. Except in two instances the control subjects' dates of birth were matched to within 6 months of those of the corresponding dysplasia cases. Anonymity was preserved throughout by identifying each subject only through a unique identification number.

Of the 117 eligible cases, not all could be included since their records were either incomplete, or missing and untraceable. Records of 70 cases were eventually collected for study. For some patients presenting before the early 1980s, information on their smoking habits, and more particularly their alcohol consumption was incomplete and for 19 cases data on type of alcohol consumed was not available. For test subjects the lesions had been histologically confirmed as dysplastic and graded as mild, moderate or severe by a single pathologist.

Data were collected on a standardised form and entered into a computer database for analysis. Each individual's record contained personal information, a note of the referral source for test group subjects, and histories of past or present tobacco use and consumption of alcohol. Tobacco use covered type, daily frequency, duration of habit at presentation and number of years since cessation of smoking if applicable. For those who consumed alcoholic beverages, type and volume per week were recorded.

For analysing the overall risks from smoking and alcohol consumption, the 140 case and control subjects were paired. The paired frequencies were then cast into 4-fold tables, dichotomised for risk status according to Altman's recommended method for paired samples [16]. McNemar tests were applied and odds ratios estimating relative risk and their 95% confidence intervals computed. In order to examine the relationship between smoking and the absence or presence of oral dysplasia and its degree of severity (categorised as mild, moderate or severe) a chi-squared test for trend was performed [16]. In addition, a logistic multiple regression analysis estimating relative risk was carried out with the presence of an oral dysplastic lesion classified as positive or negative as the dependent variable. Personal data and reported exposure to various factors, expressed in binary form, constituted the independent variables. Age was entered as a continuous variable. The investigation was designed as a retrospective case-control study. Eligible cases included all patients who presented with oral dysplasia at the hospital from 1975 to 1993. These were identified from computerised lists held in the oral medicine department and their case notes were then obtained from the medical records department. Controls were selected from among 985 individuals on the list of a neighbouring north London NHS medical practice who had been screened for oral cancer and precancer and had been diagnosed by an oral medicine specialist, in a separate study [15], as being free from oral lesions.

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RESULTS

The mean age of the 70 oral dysplasia cases was 57.0 years (S.D., 13.5), and of the 70 control subjects 60.8 years (S.D., 12.8). Each group consisted of 39 males and 31 females. Of the dysplasia cases, 35 were categorised as mild, 21 as moderate and 14 as severe.

Table 1 shows the self-reported pattern of smoking among dysplasia cases and control subjects. Among the cases, 71.4% were current smokers or had ceased smoking less than 10 years prior to presentation. The corresponding proportion among controls was 37.1%. The differences in frequencies in the four categories of smoking pattern shown in the table between cases and controls were statistically highly significant ($P < 0.001$).

A contingency table categorising pairs of dysplasia cases and matched controls according to smoking risk status is presented as Table 2. The odds ratio, estimating the relative risk of having a dysplastic lesion for current smokers or recent ex-smokers, compared with non-smokers or ex-smokers of 10 or more years' standing, was 7.00. The difference between frequencies according to risk status among cases and controls was statistically highly significant ($P < 0.001$).

Table 3 examines the relationship between smoking and the absence or presence of oral dysplasia and its degree of severity. There was a highly significant trend ($P < 0.001$) towards having any dysplastic lesion, and having a lesion categorised from its histological features as moderate or severe, according to reported smoking status (smokers versus non-smokers, including ex-smokers of more than 10 years' standing). The observed differences in smoking status between the dysplasia groups could be attributed to a linear trend.

Table 4 is a contingency table in which dysplasia cases and matched controls are categorised according to whether or not they reported consuming alcoholic beverages. The odds ratio estimating the relative risk of having a dysplastic lesion for drinkers compared with abstainers was less than unity (0.62). The difference between frequencies according to risk from drinking alcohol among cases and controls was statistically non-significant.

### Table 1. Self-reported pattern of smoking among oral dysplasia cases at presentation and control subjects

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n ($%$)</td>
<td>n ($%$)</td>
</tr>
<tr>
<td>Never (non-smokers)</td>
<td>15 (21.43)</td>
<td>28 (40.00)</td>
</tr>
<tr>
<td>Not for &gt;10 years</td>
<td>5 (7.14)</td>
<td>16 (22.86)</td>
</tr>
<tr>
<td>Ceased within last 10 years</td>
<td>16 (22.85)</td>
<td>8 (11.43)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34 (48.57)</td>
<td>18 (25.71)</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100.00)</td>
<td>70 (100.00)</td>
</tr>
</tbody>
</table>

Chi-squared $= 17.28$, df $= 3$, $P < 0.001$.

### Table 2. Paired comparison of oral dysplasia cases and controls for smokers and non-smokers (including ex-smokers for >10 years) with odds ratio (OR) estimating relative risk and 95% confidence interval (C.I.)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Total pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>22</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>28</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Total pairs</td>
<td>50</td>
<td>20</td>
<td>70</td>
</tr>
</tbody>
</table>

Chi-squared (McNemar) $= 16.53$, $P < 0.001$.

OR $= 7.00$, 95% C.I. $= 2.45-27.50$. 

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Table 3. Frequencies of subjects with no dysplasia, mild dysplasia and moderate or severe dysplasia among smokers and non-smokers (including ex-smokers for > 10 years)

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>No dysplasia</th>
<th>Mild dysplasia</th>
<th>Moderate or severe dysplasia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>26</td>
<td>24</td>
<td>26</td>
<td>76</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>44</td>
<td>11</td>
<td>9</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>35</td>
<td>35</td>
<td>140</td>
</tr>
</tbody>
</table>

Chi-squared = 17.27, df = 2, P < 0.001.
Chi-squared = 15.11, df = 1, P < 0.001.
Chi-squared = 2.16, df = 1, P > 0.05.

Table 4. Paired comparison of oral dysplasia cases and controls for drinkers of alcohol and non-drinkers with odds ratio (OR) estimating relative risk and 95% confidence interval (C.I.)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Drinkers</th>
<th>Non-drinkers</th>
<th>Total pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>41</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Total pairs</td>
<td>49</td>
<td>21</td>
<td>70</td>
</tr>
</tbody>
</table>

Chi-squared (McNemar) = 0.76, P > 0.05.
OR = 0.62, 95%, C.I. = 0.22-1.60.

Table 5 presents a logistic multiple regression analysis producing estimates of the relative risk of having a dysplastic lesion with five independent variables included. The regression coefficients for the two independent variables related to smoking were statistically significant (P < 0.05). Moderate smoking, as defined, produced an odds ratio of 3.76 and heavy smoking an odds ratio of 13.75. The regression coefficients for the remaining independent variables (gender, age and alcohol consumption) were statistically non-significant.

Although overall a heightened risk of having oral dysplasia was not shown among self-reported consumers of alcohol, Table 6 provides some indication that spirit drinking may be more important as a risk factor than beer or wine consumption. The proportion of spirit drinkers among cases amounted to 33.3%, and was significantly higher than that of 12.9%, in the controls (P < 0.01).

**DISCUSSION**

The dose–response relationship between tobacco smoking and oral cancer demonstrated in a number of investigations [10-13, 17-19] is reproduced in this case–control study of patients with a histologically confirmed diagnosis of oral dysplasia. The increase in risk according to the reported number of cigarettes smoked per day (Table 5) would seem to support a causal relationship between smoking and dysplasia rather than just one of association. Among the dysplasia cases, 71%, were smokers compared with 37%, of control subjects and overall, the relative risk of having a dysplastic lesion for smokers was shown to be seven times that for non-smokers or ex-smokers of more than 10 years’ standing (Table 2). Feller et al. [20], reviewing 138 cases of leukoplakia and erythroplakia, reported that 72% were smokers.

Varying frequencies of smokers and non-smokers were found among cases and controls when the subjects were classified according to the absence of dysplasia or the presence of mild dysplasia, and moderate or severe dysplasia (Table 3). The trend towards a corresponding increase in the proportion of smokers was linear and highly significant, offering further support to the notion of a dose response. This trend was apparent despite the fact that the histological grading of dysplasia according to severity is inevitably subjective.

More than 70% of the smokers in the study used manufactured cigarettes as opposed to 18%, who rolled their own, 9% who smoked cigars and 3% who were pipe smokers. In England this implies that the great majority smoked blond tobacco while over half reported using filter cigarettes. Differential relative risks according to type of use, type of tobacco or tar content which, for oral cancer, have been demonstrated by others [14, 21, 22], could not be investigated satisfactorily with this group which used a relatively homogenous range of products.

An independent role for alcohol consumption, and a synergism between drinking and tobacco smoking, which have been shown in several investigations of oral cancer risk [6, 10-13], could not be replicated for these dysplasia cases. A likely reason is that the majority of subjects in both groups drank alcohol yet few admitted to being heavy drinkers. Only three among the cases and two among the controls consumed 30 or more units of alcohol per week, although a high proportion in both groups (70% of the cases and 77% of the controls) reported at least some drinking. At the same time only six cases and 12 control subjects claimed to neither smoke nor drink. With frequencies of this order, a satisfactory examination of alcohol consumption as a risk factor for oral dysplasia could not be achieved.

There was some evidence that consumption of spirits might be more closely associated with oral dysplasia than other types of alcoholic beverage. Thus, the proportion of spirit drinkers was significantly higher among the cases than the controls whereas there were no significant differences in the proportions using the other specified forms of alcohol (Table 6). Blot et al. [12] and Merletti et al. [21] produced evidence that spirits and beer were more important risk factors than wine, although other workers have found the highest risks to be associated with wine consumption [18, 23]. Mashberg et al. [24] and Doll [25] take the view that there is no difference in risk potential between different types of alcoholic beverage.

Grading oral dysplasia according to severity does not provide a reliable guide to the likelihood of malignant change. All patients under the care of the dysplasia clinic were under regular observation and, at the time of the study, only two of the lesions included had progressed to invasive carcinoma. One of these patients (a smoker) subsequently died of lung disease while the other (a non-smoker) underwent marginal resection for the small malignant lesion that had developed.

In conclusion, the results of this case–control study, bearing in mind all the necessary caveats about self-reported behaviour, allow a null hypothesis of no difference between individuals with and without oral dysplastic lesions in respect to tobacco smoking as a risk factor to be rejected. With regard
to heavy smoking, the results support the findings from two other recent investigations by this group [15, 26]. The study also demonstrated a dose–response relationship between smoking and oral dysplasia. With regard to alcohol, the risk of developing a dysplastic lesion associated with drinking spirits was shown to be greater than that from a similar intake of other alcoholic beverages. However, no overall increased risk from alcohol, at least consumed in moderation, was shown. Three-quarters of the dysplasia patients were referred by general dental practitioners, which would be expected for a dental screening programme [15]. This highlights the important role of dental practitioners in detecting oral mucosal lesions and screening their patients who fall into the known risk groups for precancer, and the necessity of counselling patients with dysplastic lesions on avoiding further risk. Although the difficulties of achieving this should not be underestimated [27], the evidence of a reduced risk of oral cancer for ex-smokers who have discontinued the habit for at least 10 years is persuasive [5, 6, 12].


4. Stell PM, McCormick MS. Cancer of the head and neck: are we doing any better? Lancet 1985, ii, 1127.


17. Graham S, Dayal H, Rohrer T, et al. Dentition, diet, tobacco and

\begin{table}
\centering
\caption{Logistic multiple regression analysis with oral dysplasia as dependent variable and gender, age and reported life style factors as independent variables}
\begin{tabular}{|c|c|c|c|}
\hline
Independent variable & \textit{b} coefficient (S.E.) & \textit{P} & Odds ratio \textit{95\%} C.I. for OR \\
\hline
Gender & 0.33 (0.39) & 0.05 & 1.40 & 0.64–3.03 \\
Age (years) & -0.01 (0.01) & 0.05 & 0.99 & 0.96–1.02 \\
Moderate smoker & 1.33 (0.40) & 0.05 & 3.76 & 1.73–8.17 \\
Heavy smoker & 2.62 (0.84) & 0.05 & 13.75 & 2.56–71.08 \\
Drinker & -0.43 (0.43) & 0.05 & 0.65 & 0.28–1.51 \\
Constant & -0.17 (0.96) & 0.05 & 0.99 & 0.31–2.91 \\
\hline
\end{tabular}
\end{table}

Gender: male = 1, female = 0; moderate smoker: current smoker of less than 20 cigarettes per day = 1, non-smoker (currently or for at least 10 years) = 0; heavy smoker: current smoker of 20 or more cigarettes per day = 1, non-smoker (currently or for at least 10 years) = 0; drinker: consumer of alcoholic beverages = 1, non-drinker = 0.

\begin{table}
\centering
\caption{Type of alcoholic beverages consumed by oral dysplasia cases at presentation and control subjects (data not known for 19 cases; categories not mutually exclusive)}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Type of drink & Cases & & & Controls & & \\
\hline
(a) Beer & Yes & 20 & (39.22) & 31 & (60.78) & 29 & (41.43) & 41 & (58.57) \\
(b) Wine & 19 & (37.25) & 32 & (62.75) & 24 & (34.29) & 46 & (65.71) \\
(c) Fortified wine & 8 & (15.69) & 43 & (84.31) & 5 & (7.14) & 65 & (92.86) \\
(d) Spirits & 17 & (33.33) & 34 & (66.67) & 9 & (12.86) & 61 & (87.14) \\
\hline
\end{tabular}
\end{table}

(a) Difference (S.E.) = 2.21 (9.04) \* P > 0.05, 95\% C.I. = -15.51–19.93 \\
(b) Difference (S.E.) = 2.96 (8.81) \* P > 0.05, 95\% C.I. = -14.31–20.23 \\
(c) Difference (S.E.) = 8.55 (5.70) \* P > 0.05, 95\% C.I. = -2.62–19.72 \\
(d) Difference (S.E.) = 20.47 (7.56) \* P < 0.01, 95\% C.I. = 5.65–35.29


