Epidemiology of oral cancer from a socioeconomic perspective

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Abstract

Tackling health inequalities is a policy priority. Research on cancer and particularly oral cancer aetiology has somewhat overlooked this area, in favour of pursuing genetic and 'lifestyle' risk factors. The overarching aim of this thesis is to investigate the epidemiology of oral cancer in relation to individual socioeconomic status, area-based socioeconomic circumstances, and socioeconomic inequalities.

To test whether the incidence of oral cancer is continuing to rise in the United Kingdom (UK) and assess if this varies geographically, by sex and age, a descriptive epidemiological study of oral cancer incidence in the 12 UK cancer registries (1990-1999) was undertaken. Poisson regression models were employed to assess trends. There were 32,852 oral cancer cases registered (1990-1999). Statistically significant increases in incidence of 18% and 30% were seen in males and females respectively ($p<0.01$). The trend was observed in both younger (<45years) and older (45+ years) age-groups ($p<0.01$) with 3.5% and 2.4% average annual increases respectively. These increases were consistent for the majority of regions in the older group. For the younger group the increases in incidence were more rapid (although not significantly so) and differed geographically. Incidence remains significantly higher in men than women, in older compared with younger groups, and in northern regions. These findings provide evidence of a continuing increase in the burden of oral cancer across the UK.

An investigation of the relationship between socioeconomic circumstances and time trends in oral cancer incidence in Scotland was undertaken. Details of 10,857 patients diagnosed with oral cancer between 1976 and 2002, extracted from the Scottish Cancer Registry, were examined. The Carstairs index of socioeconomic status was derived from national census data (1981,1991, 2001). Poisson regression models were employed to assess trends. Over the study period there was a constant 50% excess incidence in males compared to females, with statistically significant rises in incidence observed for males and females at all ages. The risk of oral cancer was significantly associated with increasing levels of deprivation – a relationship which remained unchanged when controlling for age, sex, and year of diagnosis. For males, the 'socioeconomic gap' became increasingly wide over time, accounted for by a marked differential rise in incidence in the most deprived quintile. The picture was less clear for females.

A systematic review and meta-analysis of the world literature was undertaken with the aim of quantitatively assessing the association between socioeconomic status (SES) and the

incidence risk of oral cancer. Studies were included if they reported odds ratios and corresponding 95% Confidence Intervals (CI) of oral cancer with respect to SES or if the estimates could be calculated or obtained. Published and unpublished estimates of the SES risk related to oral cancer were included. Meta-analyses were performed on subgroups: SES measure, age, sex, global region, development level, time-period, and lifestyle factor adjustments; while sensitivity analyses were conducted based on study methodological issues. Forty one studies with a total of 15,344 cases and 33,852 controls met the inclusion criteria. Compared with individuals who were in high SES strata, the pooled odds ratios for the risk of developing oral cancer were: 1·85 (95%CI 1·60, 2·15; n=37 studies) for those who had low educational attainment; 1·84 (1·47, 2·31; n=14) for those with low occupational social class; and 2·41 (1·59, 3·65; n=5) for those with low income. Subgroup analyses showed that low SES was significantly associated with increased oral cancer risk in high and lower income-countries, across the world, and remained when adjusting for potential behavioural confounders. Oral cancer risk associated with low SES is significant and comparable to the risks associated with lifestyle risk factors.

An investigation was undertaken to assess the association between socioeconomic factors and selection and participation biases in a population-based case-control study of head and neck cancer conducted in the city of Glasgow, UK. General Medical Practices (GP) of the case-subjects were the sampling frame from which age- and sex-matched controls were randomly selected. Participant and non-participant postcodes of cases and controls were linked to the area-based Scottish Index of Multiple Deprivation (SIMD). Comparisons of study selection and participation were made with the Glasgow study-base population. Cases were from significantly more deprived areas than controls. Overall participation was low for both cases (34.9%) and controls (34.7%). The overall control sample did not represent the general population of Glasgow having ‘over selected’ from deprived areas. However, individuals from more affluent areas were more likely to participate, providing a set of interviewed participants reflecting the socioeconomic distribution of Glasgow. In conclusion, low participation rates in case-control studies remain a problem and socioeconomic factors strongly affect participation. Selecting controls from case GP practices is not appropriate for cancers with a skewed socioeconomic distribution. A control sample selection biased in one direction was offset by participation bias in the opposite direction – fortuitously providing a representative control sample.

A population-based case-control study using face-to-face interviews in Glasgow, Scotland was undertaken. Participants included: 103 people aged 24- to 80-years diagnosed with cancer of the head and neck between April 2002 and December 2004; and 91 controls

randomly selected from general practitioner lists. Interviews were carried out in the subject's homes and topics included: smoking; alcohol; diet; education; and occupational history. Odds ratios (OR) and 95% Confidence Intervals (CI) were computed using logistic regressions. Age and sex adjusted ORs for the risk of head and neck cancer in relation to socioeconomic circumstances found significant increased risks associated with: residence in the most deprived areas OR = 4.66 (95% CI 1.79, 12.18); and experience of unemployment OR = 2.27 (95% CI 1.21, 4.26); in addition to a decreased risk associated with high levels of educational attainment OR = 0.17 (95%CI 0.05, 0.58). However, significance was lost when adjusting for smoking and alcohol behaviours. Smoking remained the only significant risk factor OR = 15.53 (95%CI 5.36, 44.99) following multivariate analysis.

Further analytical research is required to tease out the pathways and mechanisms from socioeconomic factors to oral cancer risk. A framework for analysing the relative effects of individual and area socioeconomic factors has been developed. In totality, this thesis suggests that public health policy to address the overall rising incidence of oral cancer needs to acknowledge the complexity of the risk factors and the clear underlying role of socioeconomic circumstances. The results also provide evidence to steer health policy which focus on lifestyles factors towards an integrated approach incorporating measures designed to tackle the root causes of disadvantage. Health professionals and policy makers need to consider advocating for socioeconomic change in addition to behaviour change.

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Preface

It has taken me a long time to get here, but it feels like the journey has only just begun.

In a previous life, when I was a junior trainee in oral and maxillofacial surgery, I experienced at first hand the abundant suffering and grief that came to patients and their families with the diagnosis and treatment of oral cancer. It struck me that a better understanding of the disease process was needed. A prevention approach had to be better than the heroic 'commando' surgery, but yet almost hopeless prognosis that seemed inevitable following an oral cancer diagnosis.

Now, working in public health, the complex puzzle of oral cancer aetiology still presents an intriguing set of questions. Viewed through a public health perspective, the aetiology takes on an even broader dimension with regard to the role of social and economic factors and inequalities. How these socioeconomic factors 'get under the skin' (Taylor *et al.*, 1997; Marmot and Wilkinson, 2006) seems to be the most fundamental question of all in seeking to understand the causes of oral cancer.

The underlying aim of this work is not to look at socioeconomic associations in relation to oral cancer for their own sake. As the philosopher Durkheim (1893) wrote 'Although we set out primarily to study reality, it does not follow that we do not wish to change it…'. Echoed by and to paraphrase Clemessen (1965), one of the founders of the Danish Cancer Registry, 'the aim of every form of cancer epidemiology study is to prevent it'.

Epidemiology's duel role of both describing and analysing inequalities in health and disease within a population is essential for: public health; distributing resources; planning and targeting health care / improvement services; identifying new and emerging health problems; assisting in the discovery of aetiological risk factors; and for formulating and developing and evaluating effective health and social policies. Further, there is an ethical obligation, related to principles of justice and fairness, underlying these roles.

The association between socioeconomic status and health or rather disease – including cancer – is so well accepted that it is almost unheard of to investigate cancer risk factors without adjusting for socioeconomic status (Berkman and Macintyre, 1997). This thesis, however, aims to investigate risk from an alternative point of view – to focus on socioeconomic status, circumstances, and inequalities as the fundamental risk factors of cancer: in this case oral cancer.

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Author's Declaration

Parts of the research work included in this thesis has been published or submitted with co-authors, including:

Chapter 2: Conway DI, Stockton DL, Warnakulasuriya KAAS, Ogden G, Macpherson LMD (2006) Incidence of oral and oropharyngeal cancer in United Kingdom (1990-1999) – recent trends and regional variation. Oral Oncol; 42: 586-592.

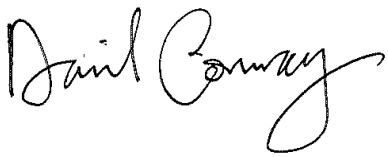
Chapter 3: Conway DI, Brewster DH, McKinney PA, Stark J, McMahon AD, Macpherson LMD (2007) Widening socioeconomic inequalities in oral cancer incidence in Scotland, 1976-2002. Br J Cancer; 96: 818-820.

Chapter 4: Conway DI, Berthiller J, Hashibe M, Marlborough H, Petticrew M, Macpherson LMD. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis. Int J Cancer; *In Press*.

Chapter 5: Conway DI, McMahon AD, Smith K, Taylor J, McKinney PA. Socioeconomic factors, selection and participation in a population-based case-control study of head and neck cancer in Scotland. J Clin Epidemiol; *In Press*.

Chapter 6: Conway DI, McMahon AD, Smith K, Black R, Robertson G, Devine J, McKinney PA. An exploratory study of the components of socioeconomic risk of head and neck cancer: results from a population-based case-control study in Scotland. Submitted to Oral Oncol.

I declare that the thesis is my own composition and has not been submitted in part or whole for any other degree.



David I Conway
Glasgow, November 2007.

Abbreviations

AICR	Association for International Cancer Research
ARCAGE	Alcohol Related Cancers and Genetic-susceptibility in Europe study.
CDC	Centers for Disease Control and Prevention
CHI	Community Health Index number
CHP	Community Health Partnership
CI	confidence interval
CONSORT	CONsolidated Standards Of Reporting Trials
CT	computerised tomography
DCO	death certificate only (cancer registrations)
DEPCAT	Carstairs Deprivation Category
EASR	European age-standardised incidence rate
EC	European Commission
ETS	environmental tobacco smoke
EU	European Union
GP	General (Medical) Practitioner
HIV	human immunodeficiency virus
HSV	herpes simplex viruses
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
IAOO	International Academy of Oral Oncology
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
INHANCE	International Head and Neck Cancer Epidemiology consortium
IPD	individual patient data
ISD, NSS	Information Services Division, National Services Scotland
MOOSE	Meta-analysis Of Observational Studies in Epidemiology group
MRI	magnetic resonance imaging
NCI	National Cancer Institute (US)
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NI	Northern Ireland
ONS	Office for National Statistics
OR	odds ratio
OSC	occupational social class
PET	positron emission tomography
RCT	randomised controlled trial
RGSC	Registrar General's Social Classification
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SEG	Socio-economic Group
SES	socioeconomic status
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UK	United Kingdom
UKACR	United Kingdom Association of Cancer Registries
UN	United Nations
UNICEF	United Nations Children's Fund
US	United States (of America)
WHO	World Health Organisation
WCRF	World Cancer Research Fund

1 Introduction

This chapter aims to provide the historical and policy perspectives; to review the literature in the fields of epidemiology, oral cancer, socioeconomic circumstances and inequalities; and to discuss the current debates, issues and knowledge gaps in these areas.
Section 1.1: provides the background – including a general introduction, historical perspective, and policy context.
Section 1.2: describes the roles of and techniques involved in epidemiology – including the advantages, disadvantages, strengths, and weaknesses of descriptive, analytical, and meta-analytical observational epidemiological studies; in addition to exploring the emergence of social epidemiology.
Section 1.3: discusses socioeconomic circumstances, poverty, and inequalities – including social theory and measurement issues, with an exploration of the issues around measuring socioeconomic circumstances and inequalities.
Section 1.4: covers oral cancer from the clinical aspects to the descriptive and analytical epidemiology of the disease – including issues of how oral cancer is defined, and an exploration of the vast literature on aetiological factors.
Section 1.5: details the thesis hypotheses.
Section 1.6: describes the thesis objectives.

1.1 Background

1.1.1 General introduction

Oral cancer is a horrible, insidious disease.

'Horrible' – in the words of John Diamond (1998, 2001), a journalist who so vividly documented his suffering and death from oral cancer, as he described it as 'like being on death row' (Diamond, 2001, p.244). Although most of his writings, beautifully reviewed by Crossley (2003), were an example (in his own words) of 'chirpy positivism and its imminent injunction to live on the bright side' (Diamond, 2001, p.275), the disease cast a dark shadow. As his brother-in-law later described: 'his public never knew just how black his moods could become, how great his physical pain, how deep his mental torment' (Diamond, 2001, p.6). Although this represents the experience of one individual, John Diamond was able to articulate the so often unheard patient-voice.

'Insidious' – because, despite killing more people in Scotland than either malignant melanoma or cervical cancer, oral cancer receives much less attention than these two diseases (Macpherson *et al.*, 2000, Scottish Cancer Registry, 2007). Consequently, there is low public and professional awareness (Warnakulasuria *et al.*, 1999; McCann *et al.*, 2000).

Oral cancer is cancer of the mouth. It is also generally defined as malignant (invasive) cancer – usually squamous cell carcinoma i.e. cancer that begins in the squamous cells that form the surface lining tissue. The main anatomical subsites considered in oral cancer are the lips, oral cavity, and oropharynx. The oral cavity is usually defined to include the front two-thirds of the tongue, the upper and lower gums, the lining of the cheeks and lips (buccal mucosa), the floor of the mouth under the tongue, the 'bony' top of the mouth (hard palate) and the small area behind the last (wisdom) teeth (retromolar trigone). The oropharynx includes the part of the throat at the back of the mouth, and also includes the 'soft' back of the top of the mouth (soft palate), the back one-third of the tongue (base of the tongue), and the tonsils (National Cancer Institute, 2007a).

Epidemiology, formerly defined as the study of 'epidemics', is more commonly appreciated by its literal meaning translated from its Greek components 'epi' meaning 'on'; 'demos' – 'people'; and '-ology' – 'the study of' (Mawson, 2002). It is now widely recognised as the tool used to measure the public health impact of disease, including (oral) cancer, and is the basic science of preventive medicine involving studying (large) groups of people rather than individuals (MacMahon and Pugh, 1970; Last, 2001). The purposes of cancer epidemiology are to: (i) describe the burden of the disease in various human population groups; (ii) generate and test hypotheses on its cause (aetiology); and (iii) support cancer prevention activities, including testing effectiveness of treatments and interventions (Rothman and Greenland, 1998). The key motivation behind this branch of science is to answer a central question: How do various behaviours, environments or genes influence the frequency of specific cancers? (Adami *et al.*, 2002).

Inequalities in health can be defined in a multitude of ways (Gakidou *et al.*, 2000), in terms of the differences, variations, or disparities across population groups: in health, wellbeing, and disease, as well as life-expectancy, and mortality, by a wide-range of factors including: age, gender, ethnicity, sexual orientation, geographic location, and socioeconomic class or circumstance (Braveman and Gruskin, 2003). For the purposes of this body of work, inequalities will be considered primarily in terms of the socioeconomic dimension; and consideration of age, sex, and geographic determinants will mainly be in terms of their interaction with socioeconomic inequalities. Such inequalities can also be value-laden

(although they are also termed ‘inequities’ for this purpose) and often viewed through a belief system that describes them as, in Whitehead’s widely quoted terms, ‘unnecessary, avoidable, and unjust’ (Whitehead, 1990). It is well recognised that inequalities in health exist across the world (Kunst *et al.*, 1995), in the USA (Krieger and Fee, 1996), Europe (Dalstra *et al.*, 2005), the UK (Acheson, 1998), and in Scotland (Macintyre, 2001). The terms ‘inequality’ and ‘inequity’ are both used interchangeably across the world and particularly in the UK and Europe (Whitehead, 2007), although in the US the term ‘disparity’ is almost exclusively used (Braveman, 2006).

1.1.2 Historical perspective

1.1.2.1 Epidemiology

The history of epidemiology has been documented by Lilienfeld (1978) and more recently by Winkelstein (2000). Lilienfeld (1978) investigated the origins of epidemiology, and described it as the coming together of clinical and statistical sciences. The establishment of epidemiology as a science was also shown to have progressed in tandem with public health developments according to Winkelstein (2000). In summary, the science of epidemiology was ‘born’ by the clinicians when they founded the London Epidemiological Society in 1850. These clinicians included John Snow the ‘father of epidemiology’ who pioneeringly investigated (by plotting cases on a map of the area) the cholera outbreak in Soho London in 1854, and based on his findings took direct action to switch off (or rather remove the handle from) the water pump on Broad Street (Lilienfield, 1978; Ashton, 1994). The first half of the 20th century saw the focus of epidemiology and public health consolidated on monitoring and tackling major communicable diseases, but beginning to move into other areas like cancer research. Epidemiological science and theory became more developed at this time, with the first case-control study being carried out by Lane-Claypon in 1926 in London and Glasgow where she investigated the aetiology of breast cancer (Paneth *et al.*, 2002). The consolidation of methods for both cohort (Doll and Hill, 1950) and randomised control trials followed (Doll, 1992). By the second half of the 20th century, with improved sanitation, vaccination, and antibiotics, attention turned from communicable diseases to chronic diseases: particularly cancer and coronary heart disease. This was symbolised by Doll and (Bradford) Hill’s (1950, 1952) cohort study of UK doctors which established the aetiological link between smoking and lung cancer, and in the US, the Framingham cohort study, which established the risk factors for coronary heart disease (Messerli and Mittler, 1998). Epidemiology continued in this vain, until towards the end of the 20th century and into the third millennium, where it seems to have reached what many commentators have

described as a ‘crossroads’ (Beaglehole and Bonita, 1997). Competing interests have led, on one-hand, to some epidemiologists increasingly pursuing genetic, lifestyle and biomedical phenomena as ‘modern epidemiology’ (Rothman and Greenland, 1998); while others are exploring the wider, social determinants of health and disease (Berkman and Kawachi, 2000). In some quarters, the question ‘epidemiology – is it time to call it a day?’ has even been raised – based on concern about the lack of direction in the field (Davey Smith and Ebrahim, 2000). However, such questioning is not new, and a decline had been predicted before (Rothman, 1981). Despite the recent uncertainties, Pearce (2007) believes the discipline ‘thrives more than ever’ – although he goes on to set out a challenge to create a consensus which broadens the scope of epidemiological research from methodological research to public health, and from a narrow focus to global challenges and issues.

The branch of epidemiology known as systematic reviews and meta-analysis has a relatively recent history. Reviewed by Petitti (1994), the subspecialty arose from Cochrane (1971) amongst others’ first descriptions of the statistical techniques involved in combining data from different studies. These early studies focused on the synthesis of experimental data, and the method was taken up by epidemiologists in their quest to increase the numbers of subjects in clinical intervention trials and subsequently randomised control trials (RCT) (Cochrane, 1971). By the late 20th century there was growing movement towards ‘evidence-based healthcare’ which culminated in the establishment of the Cochrane Collaboration in Oxford in 1993, whose remit was (and remains) to establish an evidence base through undertaking systematic reviews of health care interventions in various fields. This has expanded to be a global network and movement with branches and centres in all continents (Cochrane Collaboration, 2007). A key element of this development has been a corresponding focus on systematic review and meta-analysis methodologies. Development in systematic reviews and meta-analysis of observational (analytical) epidemiological studies have followed those for clinical interventions, however, there has not been the same methodological progress (Petitte, 1994).

The history of the topic of cancer epidemiological research has been intricately detailed by dos Santos Silva (1999), where she noted that the concept of cancer incidence as a formal topic for scientific study is relatively new in the scheme of scientific endeavour, although awareness of cancer and hypotheses about its causes can be found as early as in the writings of Hippocrates in 600BC (dos Santos Silva, 1999). However, until the nineteenth and twentieth centuries, cancer was a relatively rare occurrence, which Lilienfeld (1978)

proposed as being largely explained by the dominant association with age – where cancer mainly occurs in older people. He noted that at the beginning of the 19th century in Europe, life expectancy was around 35-years. Thus, many of those who may have got cancer later in life had died at earlier ages from the 'big killers' of the day: infectious diseases, malnutrition, or accidents. By the 20th century the pathology of cancer was being studied extensively, and epidemiology, which sought both to describe the distribution of the disease in populations and to analyse potential causes was beginning (dos Santos Silva, 1999).

The history of cancer descriptive epidemiology follows that of cancer registration, which has also been well rehearsed in the literature (Wagner, 1991; Terracini and Zanetti, 2003; Parkin, 2006). Global descriptive epidemiology data on cancer incidence (including oral cancer), have been pulled together from cancer registries from across the world by the World Health Organisation (WHO) under the auspices of the International Agency for Research on Cancer (IARC) since the 1960s. A series of, now, eight volumes of monographs entitled *Cancer Incidence in Five Continents* has been published every five years since the first volume in 1966, which included data from 32 registries from 24 countries (Doll *et al.*, 1966). This has expanded to 186 registries from 57 countries, contributing data to the eighth volume in 2003 (Parkin *et al.*, 2003). The ninth volume, planned for late 2007, will contain data from almost 300 registries (Steliarova-Foucher, 2007). In the UK, regional cancer registries have been collecting population-based cancer incidence data since the 1960s (Department of Health, 2007). In Scotland, data on cancer (including oral cancer) mortality and incidence have been available since 1911 and 1959 respectively (Boyle *et al.*, 1990).

While the beginnings of analytical epidemiology of cancer can be traced back in time (Buck *et al.*, 1988; dos Santos Silva, 1999), it came of age in the mid 20th Century, largely driven by research into the aetiological role of smoking and tobacco (Greenwood, 1988). This began with the work of Doll and Hill (1950), whose prototype case-control study (Doll and Hill, 1952) and subsequent cohort study, which first reported results in 1964, demonstrated an increased risk of lung cancer among smokers (Doll and Hill, 1964). Many cohort and case-control studies followed on the same and similar themes – where clinicians and statistical epidemiologists interfaced to elucidate aetiological risk factors for cancer (Buck *et al.*, 1988). Methodologically, analytical epidemiology on cancer continued to be refined towards the end of the century (Breslow and Day, 1980; 1987).

1.1.2.2 Socioeconomic inequalities

'there are but two families in this world, the haves and the have-nots' Don Quixote (de Cervantes, 1615, p.589).

Inequalities are not such a new concept or a new problem either. In the UK, measuring and monitoring differences in mortality by socioeconomic status has been a function of the General Register Office (GRO) since its establishment in 1837. The Office for National Statistics (ONS) now carries on this tradition (Rose and Pevalin, 2001). In Scotland, the General Register Office for Scotland (GROS) has been producing similar data in 'Annual Reports' since 1855 (GROS, 2007). Similarly, in the US, they have been documented almost since vital records registration began – however, this was not until the 20th Century in most States (Krieger and Fee, 1996). Inequalities research has a history embedded in the development of social epidemiology. Berkman and Kawachi (2000) provide an excellent description of the history of social epidemiology in which the social perspectives of epidemiological investigation are detailed. They showed that despite a longstanding curiosity of social issues being related to health, described as early as the nineteenth century, it was not until much later that the social determinants became a focus of epidemiologists' attention. This highlights the paradox outlined by Krieger (2001a) – that while all epidemiological research seems inherently a 'social' endeavour (studying groups of people or populations), the direction of travel had veered more towards the individual and the biomedical, rather than the social and the community. By 1950, according to Berkman and Kawachi (2000), social epidemiology was emerging as a distinct branch, which distinguished itself by explicitly investigating the social determinants of population distributions of health, disease, and wellbeing, rather than considering social determinants merely as background to biomedical factors. The emergence of social epidemiology and its struggle for recognition strikes at the heart of the debate on future direction for epidemiology, and is a topic worthy of further exploration (see Section 1.2.5).

The rationale and importance of studying socioeconomic factors and inequalities in relation to cancer are convincingly set out in articles by Pearce (1997), and Kawachi and Kroenke (2006). They both outline the need to better describe and explain the social distributions in cancer – to enable public health action to be undertaken. Historically, inequalities in relation to cancer are under-researched, with the epidemiological research on (particularly oral) cancer inequalities generally limited to ecological studies describing the socioeconomic gradients or distributions mainly in mortality (Faggiano *et al.*, 1997).

Correspondingly, such inequalities are under-acknowledged and, therefore, little has been done to address them.

1.1.2.3 Oral cancer

Oral cancer is not a new disease. The first description appears in an ancient Indian surgical text, *Sushruta Samhita,* around 600BC. Some of the first hypotheses on oral cancer were recorded, also in India, in 1902 where betel quid use was suspected to play a role (Boyle *et al.*, 1990). By 1911, the first descriptive and case-series study investigating the aetiology of oral cancer was being undertaken. Singer (1911), in London, described the mortality rates of cancers by site including oral cancer; and also in the same paper looked at a series of over 700 patients with oral cancer. He noted that the vast majority were male and that many were also suffering from syphilis and gout. He also reported occupational differences, with those from unskilled and manual occupations bearing the greatest burden, and only a small minority being from the 'professional' or 'leisured' classes. Despite these stark social differences, he was far more interested in the rate in the professional classes whom he combined and classified with those from 'alcohol-related occupations' such as Publicans (but who comprised only 15 % of his sample). This group, he noted, were also generally predisposed to gout, and he postulated that excess liquor could also therefore have a role in oral cancer (Singer, 1911). By 1920, Broders seemed to have undertaken one of the first case-control studies published, which investigated the association between pipe smoking and lip cancer. However, he failed to adequately describe the control group. Nevertheless, in the same paper he did begin to describe the first numerical system for histologically grading cancer (Broders, 1920). Eight years later, the first fully detailed case-control study of oral cancer had been carried out by Lombard and Doering (1928), where not only was an association between pipe smoking and oral cancer discovered, but they also were the first to detail the epidemiological methodology of selecting an age- and sex-matched cancer-free control group (Paneth *et al.*, 2002). In 1962, the Royal College of Physicians of London (1962) had concluded in their landmark document on smoking and cancer, which reviewed 23 case-control studies, that 'smoking…may be a contributing factor in cancer of the mouth'. Since then there has been an accelerated interest in both the descriptive and analytical epidemiology of cancer, with oral cancer being no exception. Notably these include: (i) Rothman and Kellers' landmark study in 1972, which was the first to note a synergistic effect relationship between multiple risk factors – when they described the greater than additive effect of tobacco smoking and alcohol consumption on increasing oral cancer risk (Rothman and Keller, 1972); and (ii) Blot with co-workers who undertook the first major (in terms of size) case-control study investigating oral cancer in

over 750 cases from across the US through the 1980s (Blot *et al.*, 1988). Up-to-date, recent developments in oral cancer epidemiology include the establishment of the International Head and Neck Cancer Epidemiology (INHANCE) Consortium – who are a network of epidemiologists from across the world, coordinated by IARC. They have begun to pool together all the data from nearly three decades of case-control studies in the field (INHANCE, 2007).

1.1.3 Policy context

1.1.3.1 Global

Inequalities in health and society are a global issue. This concern began to be acknowledged in 1978 in the 'Health for All' *Declaration of Alma-Ata* – a global strategy developed by the World Health Organisation (WHO), which proposed 38 targets to reduce inequalities in health (WHO, 1978). This was taken a step further, in 1986, by the WHO's *Ottawa Charter* which set out key community development steps required to begin to address them (WHO, 1985; 1986).

More recently, the WHO revisited this issue as a global challenge in light of the stubborn and worsening challenge of inequalities in health both within and between countries. These include a life expectancy spread of 48-years between countries and of around 20-years within countries; and a wealth (for want of a better word) of evidence linking inequalities to social and economic determinants. Firstly, *The Solid Facts* were produced which reviewed the evidence regarding the nature, determinants and means of reducing within-country inequalities in Europe (Wilkinson and Marmot, 2003), and secondly, the WHO *Commission on Social Determinants of Health* was launched in 2005. This group is continuing to review the evidence, debate the issues, and intends to recommend policies to address health inequalities at the global level (Marmot, 2005). Postscript, the 'interim report' has recently been published, which has reviewed much of the evidence, while the recommendations for action are expected in the final report in 2008 (Commission on Social Determinants of Health, 2007).

In addition to the WHO (and its regional offices), a plethora of international agencies attempt to work in partnership on the challenges of global health. These organisations include: United Nations agencies such as The United Nations Children's Fund (UNICEF); the Centers for Disease Control and Prevention (CDC) in the US; and the European Union

(EU) and European Commission (EC). Further agencies working in this arena include the World Bank, as well as governments, universities, and industries from across the world.

The EC is worthy of particular mention with regard to inequalities policy. With the establishment of a new European Expert Working Group on Social Determinants of Health Inequalities, plans are afoot to produce 5-yearly reports on health inequalities in Europe. The Working Group will complement the European Union's Programme on Community Action in the Field of Public Health 2003–2008 (European Commission, 2002) which already has the reduction of health inequalities as a key aim.

The International Agency for Research on Cancer (IARC) is the lead cancer agency of the WHO (IARC, 2007a). IARC's remit is to: monitor global cancer occurrence, identify causes of cancer, elucidate mechanisms for carcinogenesis, and develop strategies for cancer control. To these ends, lifestyle and genetic factors are given prominence and investigation of social determinants is not an identified priority area, although, they have in the past conducted a wide-ranging review of the evidence of social inequalities in relation to cancer (Kogevinas *et al.*, 1997). IARC, on behalf of the WHO, recently published the *World Cancer Report*, which provides a global view of cancer: documenting trends in cancer incidence and mortality; and reviewing the known causes of human cancer. The report contains an up-to-date overview of cancer prevention, including screening programmes for early diagnosis, but socioeconomic determinants are notable by their almost negligible presence (WHO, 2003).

Recently, global inequalities have officially begun to be acknowledged as important in relation to oral cancer. The WHO sponsored the *Crete Declaration on Oral Cancer Prevention* in 2005, which reiterates the importance of epidemiological information and emphasises the importance of a prevention approach, and of the need for research into the 'biological, behavioural and psychosocial factors' associated with oral cancer (WHO, 2005). This has already harnessed the support of key international clinical and research associations in the field, including the International Academy for Oral Oncology (IAOO, 2007).

1.1.3.2 UK

The establishment of the National Health Service (NHS) in the UK on 5 July 1948 was seen as a major step towards redressing health inequalities through the universal provision of health care. 'It will be a great contribution towards the wellbeing of the common people

of Great Britain' declared Aneurin Bevan, Minister of Health at the time of its debate in the House of Commons (Bevan, 1946).

Since then, Wilkinson and others have shown that, while inequalities in access to health care have narrowed (to some degree), inequalities in health (and disease) have persisted and even widened (Mackenbach *et al.*, 1989; Davey Smith and Morris, 1994; Wilkinson, 2005).

The Conservative government policy throughout the 1980s and much of the nineties ignored the existence of inequalities in health, euphemistically referring to them as 'variations', which were explained away as statistical artefacts or the fault of those who suffered as a result of them (Marmot, 2001). Furthermore, the value and underlying meaning of the difference was ignored – exemplified by the persistent refusal to acknowledge the findings of the 'Black Report', and by attempts to bury it by publishing it on the August bank holiday in 1980 and producing only 260 copies (Department of Health and Social Security, 1980; Shaw 2005).

With the election of the Labour Government in 1997, there was a considerable policy shift in terms of public health – health inequalities were back on the agenda. In *Modernising Health and Social Services*, the intention was set out to shift the focus of health policy to include the broader impact of social and environmental factors on people's health (Department of Health, 1998a). There also followed the *Independent Inquiry into Inequalities in Health* – 'The Acheson Report' – which reviewed the evidence of the most effective action to reduce health inequalities (Acheson, 1998). This review informed, in UK policy terms, the 1998 *White Paper Saving Lives: Our Healthier Nation* (Department of Health, 1998b), which was the first government report to explicitly acknowledge the existence of health inequalities and the evidence that they were widening. It pledged to 'improve the health of everyone and the worst-off in particular'.

In 1999, devolution to Scotland and Wales began the process of divergence in health policy within the UK (– see below). In England, the *NHS Plan*, which aimed to improve health and reduce health inequalities, was produced (Department of Health, 2000). Repeated governmental initiatives followed, including: a 'national consultation' (Department of Health, 2001); a *Cross-cutting Review* (Department of Health, 2002); in addition to an independent fiscal review 'The Wanless Report' (Wanless, 2002); and its follow-up 'The Wanless 2 Report' (Wanless, 2004). Despite the repeated acknowledgement by Ministers in the Department of Health in England of the existence of

health inequalities and even of the wider social and structural determinants, the public health white paper which was produced – *Choosing Health* (Department of Health, 2002) redirected responsibility back to the individual (Shaw *et al.*, 2005a). This direction was taken whilst evidence was showing that the inequalities in health and life-expectancy between the most and least well off, which emerged in the 1980s and 1990s had continued to widen into the 21st century (Shaw *et al.*, 2005a). Targets were set to reduce health inequalities (mainly in the distribution of health behaviours) in *Tackling Health Inequalities: A Programme for Action* (Department of Health, 2003). However, progress on addressing the multitude of health inequality targets has been limited. The *Programme for Action* S*tatus Report*, produced by an expert panel chaired by Marmot (Department of Health, 2005), pointed to a lack of progress and highlighted the intrinsic difficulties in trying to tackle the complex issue of health inequalities. It also led to, what has been described in some quarters, as the Labour government's 'Black Report moment' as they tried to suppress its publication (Shaw *et al.*, 2005b).

1.1.3.3 Scotland

Devolution for Scotland came on 6 May 1999 with the election of the Scottish Parliament. Devolved legislative powers were substantial and included: health, education, local government, social work, housing, planning, the environment, sport, arts, agriculture, forestry, and fishing. Some aspects of law, home affairs and transport were also devolved. Powers which were reserved to the UK legislature in Westminster included: social security, economic and fiscal powers, trade and industry, employment, equal opportunities, constitutional issues and defence (The Scottish Parliament, 1998).

Tackling health inequalities and improving health was given highest priority in Scotland – outlined in the white paper *Designed to Care – Renewing the NHS in Scotland* (Scottish Office, 1997). Following this, a national consultation document *Working Together for a Healthier Scotland* (Scottish Office, 1998) placed an emphasis on: community development approaches to health improvement, community involvement, and addressing socioeconomic inequalities. In 1998, a comprehensive report looked at health and health services in Scotland through an inequalities perspective (McLaren and Bain, 1998). Focusing on NHS data, it highlighted that all the major health issues (mental health, coronary heart disease, stroke, and cancer), and the services in place to address them, demonstrated substantial inequalities both in the distribution of disease and access to health care – with those from the most deprived communities fairing poorest (McLaren and Bain, 1998). The subsequent green paper and white paper – *Towards a Healthier Scotland*

(Scottish Office, 1999a) – acknowledged the impact of socioeconomic circumstances on health and highlighted the need for public health policies to tackle the wider determinants of health, although it somewhat disappointingly dropped 'Working Together' from the Green paper title – perhaps a metaphor for the inherent difficulties in the challenge of moving public, private, community, and voluntary sector organisations into truly meaningful collaborations.

In 2000, the newly established and now devolved Scottish government administration, the Scottish Executive, set out plans to rebuild the NHS in Scotland in *Our National Health: A Plan for Change* (Scottish Executive, 2000). While a strategy was outlined to modernise the delivery of health services, there was also an attempt to reorientate the health service to improving health and reducing health inequalities. This was reinforced by the development of a *Health Improvement Fund* (Scottish Executive, 2001a), and the subsequent establishment of joint health board and local authority funded Social Inclusion Partnership areas, which aimed at targeting money directly into local communities. At this time health policy was increasingly being incorporated into the 'social justice' agenda (Macintyre, 2001). By 2003, lessons from this work were being rolled out nationally. Partnership working was revisited and now seen as vital to the success of health improvement activities and the tackling of health inequalities (Scottish Executive, 2003a). This included the evolving development of Community Health Partnerships (CHPs) (Scottish Executive, 2004a). However, at the same time, there seemed to be a slight change in health policy direction (not as extreme as in England – as described earlier) particularly in health improvement policy. *The Challenge* document (Scottish Executive, 2003b) re-emphasised individual responsibility and set out action on tackling lifestyles and behaviour change at its core. Nevertheless, 'community-led' aspects were also set out as a key strand of activity (although not integrated throughout the policy). In addition, the Scottish Executive's (2003c) social inclusion policy *Closing the Opportunity Gap* took health inequalities targets beyond the sole remit of health services and also recognised the fundamental importance of community involvement in tackling health inequalities. Consequently, a joint Ministerial Task Group on the theme of community-led health improvement was established in late 2004. This cumulated in a series of national reports produced in 2006/07, which highlighted the importance of the community and neighbourhood perspectives and which made recommendations back to Government about how best to harness community approaches for health improvement (Community-led Supporting and Developing Healthy Communities Task Group, 2006).

In the meantime, health services are being developed in Scotland broadly in-line with the proposals in the *Kerr Report* (Scottish Executive, 2005a) and in the Scottish Executive's response *Delivering for Health* (Scottish Executive, 2006a) – which placed a focus on anticipatory and preventive care – to prevent inequalities occurring, although it followed a medical model of prevention as opposed to a wider social model approach. The emphasis was more on health outcomes. In parallel, for dentistry, a national *Dental Action Plan* set out the direction of travel to improving oral health and modernising dental services (Scottish Executive, 2005b).

Further change in health improvement and public health activity in recent years in Scotland worthy of mention was the merging of the Health Education Board for Scotland and the Public Health Institute for Scotland in 2003 into NHS Health Scotland, which has an overarching aim of reducing health inequalities (NHS Health Scotland, 2007). This characterises the change in national health activity from educational health promotion approaches to one which incorporates a public health approach, embracing public health sciences including epidemiology and acknowledging the wider determinants of health. In Glasgow, the establishment of the Glasgow Centre for Population Health in 2004 aims to work in the areas of research, policy, and implementation to develop new ways of understanding and addressing health inequalities focused in Glasgow – but with implications for many cities (Glasgow Centre for Population Health, 2007).

Postscript, at the time of writing, the direction of health policy in Scotland is not fully certain, with the election of a new (minority) Scottish National Party-led Scottish Government in May 2007. Early indications seem to be suggesting that there will be no let up, and perhaps even revived vigour towards addressing the key challenge of health inequalities (Sturgeon, 2007), with inequalities at the heart of their current discussion document: *Better health, Better care* (Scottish Government, 2007). However, the challenge, as always, remains: turning words and good intentions into sustainable action to redress and not widen inequalities in health.

1.1.3.4 Cancer policy

For England and Wales, the national public health strategy, *Saving Lives: Our Healthier Nation* (Department of Health, 1999), set targets of reducing cancer mortality although there was limited mention on the inequalities in deaths or diagnoses. Although the *National Cancer Plan* (Department of Health, 2000) does acknowledge inequalities in cancer care, there is limited detail in this area of the strategy.

Similarly, in 2001, Scotland's cancer strategy *Cancer in Scotland: Action for Change* was launched with a primary focus on changing the way cancer services are planned and managed. While prevention was acknowledged as a key area for action, and reducing inequalities were given a headline priority, there was no clear definition of inequalities nor were actions specified either in terms of access to care or prevention of cancer (Scottish Executive, 2001b). In 2004, *Cancer in Scotland: Sustaining Change* (Scottish Executive, 2004b), looked at progress since 2001, and outlined the next steps to ensure continuing improvements in cancer services in Scotland. However, there was limited mention of progress on addressing inequalities, in fact they were barely mentioned, and notably described as 'variations'. The overarching health policy in Scotland (until May 2007) was *Delivering for Health* (Scottish Executive, 2006a) within which cancer services and cancer prevention activities were to be guided to an anticipatory care model, although the impact on inequalities are uncertain. The *Dental Action Plan* also sets out specific targets for oral cancer in Scotland, including improving the five-year survival, but makes no mention of inequalities in this regard (Scottish Executive, 2005b).

1.1.4 Key points

Against the back drop of a political agenda dominated by health inequalities, research in this area is also clearly a priority. This also needs to be viewed together with the widely held acceptance that cancer is a major public health concern – and health policy in general is also strongly focused on tackling cancer. However, there is an apparent dissociation of cancer policy from full integration with the health inequalities agenda.

A robust evidence base, both in terms of identifying the problems and also for developing potential solutions, is a pre-requisite to informing policy and decision makers in this area. A call was made by Blamey and colleagues (2002), from the (then) Public Health Institute of Scotland in a comprehensive review of inequalities research in Scotland: emphasising the 'need for more independent research tackling and explaining health inequalities'. It seems that a potential direction of travel for epidemiological research in the 21st century – towards investigating health inequalities and social determinants, could place epidemiological research as a key tool to deliver on this research agenda.

1.2 Epidemiology

1.2.1 Definitions

Epidemiology is difficult to define, exemplified by Alexander Gillian's comment 'epidemiology is what epidemiologists do' (Sartwell, 1972). While this statement sounds rather obvious, it reveals the issue that, even to those immersed in the subject – it is often difficult to define and explain.

Nevertheless, it is probably still best defined in the words of epidemiologists. According to Buck *et al.* (1988) the first published use of the word was the Spanish 'epidemiologia' in a study of bubonic plague in Spain in 1598; and it was derived originally from the Greek word 'epidemion', a verb meaning 'to visit' used in connection with human illnesses in the writings of Hippocrates. Originally used as the term for the study of epidemics, epidemiology is a continually evolving discipline evidenced by the changing definitions and emphasis.

All epidemiologists would generally agree that it concerns itself with populations rather than individuals, thus sitting within the discipline public health rather than clinical (medical) practice (Detels, 1997). The basic definition of describing and analysing disease and health in the population also has broad agreement (Detels, 1997). Through the historical development of epidemiology (as detailed earlier), not only have the subjects of interest (diseases and health conditions) grown through time, but the range of factors which the epidemiologist considers in the search for disease distribution and determinants has also markedly expanded. In this quest to describe and understand the causation of disease patterns in populations, a wealth of scientific methodology has developed in parallel (Susser, 1985; Rothman and Greenland, 1998). However, remaining constant is the basic assumption in epidemiology – that the distribution of disease observed in a population is not random. The patterns of disease observed in a community are often caused by interaction of several factors in a multiple causation or multi-factorial aetiology of disease (Detels, 1997), although there are the exceptions that may be associated with specific toxins (e.g. thalidomide).

Within these broad definitions, epidemiological approaches boil down to: describing the natural history of specific diseases in populations; and analysing the aetiological determinants of disease (Last, 2001). In addition, communicable disease epidemiology is still concerned with identifying epidemics in the population; while interventional (or

experimental) epidemiology is focused on testing in controlled trails, either clinical or ‘community’ interventions (Buring and Hennekens, 1997; Hoffmeister and Mensink, 1997).

In relation to cancer, epidemiology remains important for several reasons. Understanding causes and the proportion of cases due to each cause is essential for developing cancer prevention programmes, aimed primarily at preventing the onset or first manifestation of cancer, through strategies for risk reduction (Rockhill and Weed, 2006). Epidemiology can also inform therapeutic interventions to prevent the progress of the disease or its recurrence. However, with the human genome now sequenced, a huge challenge looms large – to understand the complex interactions between genes, environment, and behaviours, together with the increasing recognition of the influence of wider social determinants – in the causation of cancer.

Three main branches of epidemiology adopted in this thesis – descriptive, analytical, and meta-analysis will be considered in turn, with the concept of causality reviewed within the analytical epidemiology section. Meta-analysis as an epidemiological statistical tool will be assessed with regard to analytical (observational) studies; while emergent social epidemiological approaches will be reviewed to capture the socioeconomic context which is the focus of this thesis.

1.2.2 Descriptive epidemiology

1.2.2.1 Definitions

Descriptive epidemiology aims to describe the distribution of disease in terms of ‘time, place, and person’ factors of disease (Last, 2001) – these correspond to the questions: ‘when?’, ‘where?’, and ‘who?’. In addition ‘what?’, and ‘how many?’ are investigated within descriptive epidemiology (Rothman and Greenland, 1998). These questions relate to the aims of descriptive epidemiology, which are to: describe the extent and spectrum of disease; describe the natural history of disease; (begin to) identify disease aetiological factors through generating hypotheses for further study; predict disease trends; identify health needs of a community; and evaluate public health intervention programmes (Detels, 1997).

A series of methods have been developed for: study design, statistical analyses, data collection, classification, tabulation and presentation, followed by inference, and

interpretation (Rothman and Greenland, 1998). The advantages of descriptive epidemiology include their efficiency both in terms of time and cost – particularly as they utilise existing or routine data (e.g. cancer registries) without the need to individually contact study subjects (dos Santos Silva, 1999), however, the disadvantages are related to the limited data on exposures (risk factors) available, and to the strength of evidence and conclusions which can be drawn from such studies (Detels, 1997).

Nevertheless, descriptive epidemiology has an important surveillance role, particularly in terms of cancer surveillance which provides a useful first step in the usual sequence of study design – by providing insights which inform and develop hypotheses which can be testing using analytical study designs.

The major concepts in the descriptive epidemiology of cancer will be reviewed, including: cancer registration, measures of the burden of disease, and descriptive epidemiology study design.

1.2.2.2 Cancer Registration

Jensen *et al.* (1991) in their defining text on cancer registration on behalf of IARC, describe it as the systematic collection, storage, analysis, interpretation, and reporting of data on subjects – performed by cancer registry organisation.

There are two broad categories of cancer registry: hospital-based cancer registries and population-based cancer registries. While hospital-based registries focus on recording information on patients with cancer from one particular hospital, their purpose is primarily for planning, administrating, and monitoring hospital resources and clinical services, and they are less suited to epidemiology – as it is generally not possible to define the population-base catchment area for a hospital (Jensen *et al.*, 1991). Population-based registries on the other hand collect data on all new cases in a defined geographical area and together with information on the population-base from which the patients with cancer came from, the data can be used to provide epidemiological statistics useful for public health purposes – including: assessing population need, developing services, research on aetiology, and developing and evaluating cancer prevention activities. Only population-based cancer registries will be considered further here.

The basic data fields included in the cancer registration are: patient related fields, including – date of birth, sex, and address / postcode; together with tumour related fields, including –

incidence date, basis of diagnosis (e.g. microscopic), cancer site, morphology, behaviour, and source of information (Jensen *et al.*, 1991).

Robust cancer registries ensure the validity, accuracy and reliability of incidence rate data. Prerequisites for reliability include a census of the entire population by age and sex, universal access to diagnostic facilities, with, ideally, histological confirmation, and complete as well as timely notification of all newly diagnosed ('incident') cases to the registry (Davies and Williams, 1994). Cancer registry efficiency and reliability depends on numerous factors such as precise and prompt diagnosis, coding and reporting (Izquierdo *et al.*, 2000).

Cancer registries focus on providing cancer incidence and survival data, and occasionally mortality data – there is an ongoing debate on the relative merits of incidence and mortality data in relation to describing disease burden which will be discussed in the following section (Parkin, 2006).

The general advantages of utilising cancer registries for epidemiological research were documented by Bain *et al.* (1997). They include: (i) the relative low cost; (ii) the potentially large numbers in the study sample; (iii) the population coverage; and (iv) the prolonged time period coverage. The same article also documents the limitations of such routinely held health data, which are mainly concerned with factors that influence data quality, including: completeness, accuracy, and timeliness, of the data. Evidence of high quality data is a further pre-requisite to the use and interpretation of registration data, but it is essential that high quality data are not just espoused, but rather active steps to continually monitor and improve quality are taken (Jensen *et al.*, 1991). The iterative and dynamic nature of cancer registry data should also be taken into account when assessing quality (Parkin, 2006).

Weighing these strengths and weaknesses, it seems that despite the potential limitations, cancer registry incidence data should not be underestimated as a prime epidemiological population tool for measuring the impact or 'burden' of cancer on society. Through descriptive epidemiological studies of cancer registry data, information on cancer can readily and uniquely be conveyed, from which hypotheses for further analytical research can be taken forward, and prevention programmes can be developed, and assessed directly (Harris *et al.*, 1998).

Globally, cancer registration data are pooled and published via IARC through their programme of *Cancer Incidence in Five Continents* series, currently running to eight but imminently nine volumes (Steliarova-Foucher, 2007). In the US, cancer registration is known as cancer surveillance and is coordinated via the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) which collects and publishes cancer data from 18 city or state registries covering approximately 26 percent of the US population (SEER, 2007). In the UK, 12 cancer registries cover the whole population and cooperate together within the United Kingdom Association of Cancer Registries (UKACR) (UKACR, 2007). The Scottish Cancer Registry is a member, covering cancer data from all Scottish residents (Scottish Cancer Registry, 2007).

There is a current and increasing threat to cancer registration globally, in the shape of privacy and confidentiality laws – worryingly described by Parkin (2006). In his account, particular concern was noted in the UK, where interpretation of the Data Protection Act threatened the viability of cancer registration through potentially requesting that informed consent is obtained from all patients before their data are registered.

1.2.2.3 Measures of disease burden of cancer

The ‘burden’ of cancer on society is used to describe the epidemiological quantification of the occurrence of cancer in the population. This is a difficult task – as cancer is a complex and multidimensional problem: impacting on individuals and their families; on the health care services both in primary and secondary care settings; and on the wider community and society (Lagiou and Adami, 2002; Parkin and Bray, 2006).

Recent reviews by Lagiou and Adami (2002); and Parkin (2006) set out the key issues involved in the on-going debate over the relative merits of incidence data (from cancer registries) and mortality statistics (from population registrars) as measures of individual cancer risk. They report that mortality data are more widely available than incidence, but are particularly limited in many developing countries; noting also that mortality data are less accurate, due to poorly specified causes of death on death certificates. The procedures for recording mortality across different countries are described as being highly varied with limited standardisation for mortality reporting. As a comparative measure of risk of disease, mortality data are particularly affected by survival differences, especially for cancers with higher survival, thus the data are influenced by more than risk of developing cancer but also by how it may or may not be treated and the outcomes thereof. In addition, they note that death is a more objective and reproducible event than the more abstract and

less tangible concept of incidence, such that mortality data are less distorted by the effects of incidental or overdiagnosis. By comparison, incidence data from cancer registries are described as holding more detailed information about the patient and their cancer (including, for example site, histological subtype, and stage) than is available on a death certificate. These reviews both conclude by agreeing that while mortality data provides a measure of the risk of dying from cancer and therefore is the single most important outcome measure of the burden of cancer, because not all individuals who develop cancer die from it, mortality has limited utility in describing the overall burden of cancer.

In practice, incidence data provide the best overall measure of cancer burden in a population, but where incidence data are not available an approach which combines mortality and incidence data may be required to assess the burden in different populations over time.

As this thesis is mainly concerned with understanding the aetiology and risk of developing oral cancer, rather than the final (potentially treatment related) outcomes of survival or mortality, this review will therefore focus on the incidence measures of cancer.

1.2.2.4 Incidence

Cancer incidence data is an abstract concept in the sense that it captures information on the development of cancer at an arbitrary point in the natural history of cancer when diagnosis is recorded, in comparison to the finite outcome of death (noted above). Nevertheless, incidence rates perhaps give the clearest measure of cancer frequency at the population level, often described themselves and used interchangeably with the terms ‘burden of cancer’ (Muir and Boyle, 1990). The incidence of cancer is the rate at which new cases occur in a population during a specific period; being in the balance of the frequency and strength of causal or preventive and genetic or environmental or (potentially) social factors either working in synergy or antagonistically (Last, 2001). Thus, it is a measure of the risk of developing cancer. There are several strengths and limitations of cancer incidence data.

The primary strength of incidence rates is that they permit insightful comparisons of cancer risk and burden between populations, countries, and time periods compared with mortality and survival measures. As mortality rates are strongly affected by treatment effectiveness and prognosis, while survival rates are associated with the cancer stage at presentation, which is also related to public and professional awareness and access to health care (dos Santos Silva, 1999).

Many factors can affect incidence rate data including cancer registry efficiency in terms of diagnostic intensity, coding, and reporting. These limitations may lead to both under- and overestimation of true incidence and may affect comparisons between population groups and across time periods. For example, screening programmes or new diagnostic technologies may increase diagnostic intensity and lead to artificial elevation of incidence, as observed with the use of prostate specific antigen (PSA) test to detect early prostate cancer (Lagiou and Adami, 2002).

Incidence, therefore, is the primary method of quantifying disease occurrence in populations. To compute incidence a number of prerequisites need clarification: (i) the definition of a case – i.e. an individual with a diagnosis of the disease of interest; (ii) the population from which the case individual comes from; and (iii) the time period over which the data were collected (Rothman and Greenland, 1998).

(i) Defining a case in epidemiology is no easy task, and is not necessarily the same as the clinical (diagnosis) definition – relying on less invasive diagnostic tests than in a clinical setting. Furthermore, it is necessary to standardise the case definition (in cancer registry, incidence data are usually coded to the International Classification of Diseases which codes both the anatomical site and histolopathology). Defining a case is also known as defining the ‘numerator’, so it is important that all cases are included within the population under investigation (Rothman and Greenland, 1998).

Defining a cancer case in histological terms also brings with it serious problems as reported by Parkin (2006): where pathologists define malignancy in terms of the extent of invasion of the tumour – this is inconsistently diagnosed and depends on the methods of pathological examination.

(ii) Defining the population at risk, also known as the ‘denominator’ is important as the number of cases on its own provides limited information. This population-base must be clearly defined and include all those resident in that particular area – i.e. all those potentially at risk of developing cancer (Rothman and Greenland, 1998).

(iii) Defining the time period is also essential as incidence rates vary with time, and time is integral to the definition and computation of incidence (Rothman and Greenland, 1998).

The main types of incidence rate are: crude incidence rates, age-standardised incidence rates, and age-specific incidence rates, and cumulative incidence rates or lifetime risk which will be discussed in turn.

1.2.2.5 Crude incidence rates

The ‘crude’ incidence rate as defined by Last (2001), estimates the number of cases occurring per year (and usually) per 100,000 persons in the population (Equation 1). The units of ‘incidence’ are therefore person-time (usually person-years) at risk. Person-time is an important concept in epidemiology – it is basically defined as the sum of all the time spent by each (study) participant at risk for a disease (Rothman and Greenland, 1998).

Equation 1 Crude incidence rate calculation

$$\text{crude incidence rate per 100,000 person years} = \frac{\text{Number of new cases arising in a defined population in a specific period of time}}{\text{total person-years at risk in that population during that period of time}} \times 100{,}000$$

Crude incidence rates are usually presented separately for males and females, but usually ignore age-subdivisions. The development of cancer, as with most diseases, is strongly influenced by age and correspondingly cancer rates vary greatly with age – ignoring differences in population age structure strongly risks confounding by age (Clayton and Hills, 1993). Thus, the crude rate is heavily influenced by the demographic age structure of the population. Such that if the age-structure of the population were to vary over time then taking the crude rates would not be comparable over that period. Nor would it be appropriate to compare crude rates between different geographical areas or different cancer registries where the underlying population age-structure may differ. Therefore it is essential that these age differences are taken into account. This is done by age-standardisation of the rates (Parkin and Bray, 2006).

1.2.2.6 Age-standardisation incidence rates

There are two main methods of standardisation: direct and indirect (Boyle and Parkin, 1991). Direct standardisation makes allowances for differences in the age-structure of populations and is therefore used to compare incidence rates between different populations or in one population over time. Thus, for a specific cancer site, over a specific time period, and for a specific population, the directly standardised incidence rate is the overall – all ages – incidence rate per 100,000 person-years at risk that would occur in the standard

reference population - where the age-specific incidence rates for the cancer site, time period and population of interest are used (Harris *et al.*, 1998).

Direct standardisation is calculated by taking for each age-group (usually 5-year band) the age-specific (crude) incidence rates and applying them to the age-specific population numbers of people in that particular age-group in a fixed reference 'standard' population of 100,000 people, giving an incidence in that age-group in the standard population. These age-group-specific incidences are then added together to give the overall total incidence in the standard population (per 100,000). Thus, age-standardised rates can be considered as a weighted average of the age-specific rates, the weights being taken from the standard population (Waterhouse *et al.*, 1976).

The choice of standard population is to a degree arbitrary, the two 'standard' populations commonly used in cancer epidemiology are the 'European standard population' and the 'World standard population'. The European standard population represents the average demographic structure of European countries. This has been assessed in relation to the Scottish population (Harris *et al.*, 1998) – where the European standard population was found to be broadly comparable to the Scotland population for men, but the Scotland population had more women in the older age-groups. This was shown to have implications for interpreting incidence rates – where cancer is more common in older age-groups. Thus, crude and European age-standardised incidence rates for males were shown to be similar, but for older females, the age-standardised incidence rates were lower than the crude rates – although in low incidence cancers the differences has been shown to be not materially substantial (Harris *et al.*, 1998).

The average demographic make-up of the whole world is represented in the World standard population, commonly used in the global *Cancer Incidence in Five Continents* series (Parkin *et al.*, 2002). This standard has a greater proportion of younger people and lower proportion of older people than both the European standard population and the Scotland population. Harris and colleagues (1998), investigating the Scottish cancer registry data, found that where cancer rates are higher in older age-groups, using the World standard population for standardising incidence rates would considerably underestimate cancer incidence.

Indirect standardisation is the alternative method and involves calculating the ratio of the total number of cancer cases observed to the total number of cancer cases that would be

expected if the age-specific rates of a standard reference population were applied (dos Santos Silva, 1999). The ratio is known as the standardised incidence ratio.

There has been some debate about which method of standardisation is best (Breslow and Day 1987; dos Santos Silva 1999). In general, the method used will depend on the question being asked and the data available, although there are no hard and fast rules (Parkin and Bray, 2006). Direct standardisation is most appropriate where age-specific incidence data are available, and is the most common method employed for incidence rate comparisons, it is also usually preferred on statistical grounds as it minimises bias (Breslow and Day, 1987). However, it is not suitable where populations in individual age-groups are very small which would give correspondingly unstable or zero age-specific incidence rates. In such cases indirect standardisation should be used. Indirect methods can be used when comparing incidence in small sub-populations, where, for example, the incidence in a small area (e.g. a geographic region of a country) is compared to the expected incidence based on the age-specific rates of a larger population (e.g. a country) (dos Santos Silva, 1999).

1.2.2.7 Age- and sex-specific incidence rates

Age-specific and sex-specific incidence rates refer to incidence rates stratified by age and by sex respectively. They are the foundation of descriptive epidemiological analysis of data on cancer burden (Parkin and Bray, 2006). Age-specific incidence rates are calculated separately for each age-strata (usually 5-year bands) by taking the number of new cases arising in the age-strata in a defined population and time-period, and dividing it by the person-years at risk in that age-strata in the same population and time (and multiplying by 100,000 – to get the rate per 100,000) (Rothman and Greenland, 1998). Plotting these age-specific incidence rates against age gives an age-incidence curve that can provide important insights into the age-distribution of cancer and so to the aetiology (dos Santos Silva, 1999).

Incidence rates are almost always separated out by sex – to provide both male and female rates. This is because of the marked variation in incidence usually observed between the sexes for most cancers.

1.2.2.8 Cumulative or lifetime risk

The terms cumulative or lifetime risk and sometimes ‘cumulative rate’ are often used interchangeably and their use is well covered in the literature (Harris *et al.*, 1998; Rothman and Greenland, 1998; Parkin and Bray, 2006). They are not a ‘rate’ but rather a percentage. The cumulative risk is an alternative method of direct standardisation which avoids the use of a standard population, and provides an idea of lifetime risk. Cumulative risk is the risk an individual would have of developing the disease in question during a specific age period if no other causes of death were in operation. The age-period over which the risk is accumulated had to be specified usually in terms of a ‘lifetime’ – defined as 0-74 years or 0-64 years. It has a number of advantages including: simple to compute, increases intuitive interpretation of risk (with regard to interpreting incidence as risk), and it seems to give a good description of cancer burden.

The Scottish Cancer Registry (2007) has attempted to draw a distinction between the definitions of life-time risk and cumulative rates – based on the methodology used to compute them. The traditional ‘cumulative rate’ method assumes that there are no other competing causes of death (other than the cancer under study), and is calculated by summing the age-specific incidence rates of the cancer up to the specified age. As it does not take into account competing causes of death, it therefore over-estimates the risk as it assumes that the risk of the cancer is the same irrespective of age, with those at birth having the same risk as those in older age. Thus it assumes that the same people are at risk at (say) age 84 as at birth, whereas in practice some of these people will have died of other causes, or will already have developed cancer (Waterhouse *et al.*, 1976).The reality would be that a significant proportion of the population would die from other causes before and up to older age, while those who have developed cancer are also no longer at risk of developing cancer (for the first time).

More recently, calculations have used the ‘lifetime risk’ method, which takes into account those who died from other causes and those no longer at risk following cancer development (Harris *et al.*, 1998). This method is still an approximate, as it is usually based on mortality and incidence rates from the same time-period (e.g. 1990-1999). It does not exactly provide the risk associated with a specific generation’s experience, which would require consecutive calculation of age-specific incidence throughout life; therefore some caution is required in utilising lifetime risk in terms of an individual’s risk.

1.2.2.9 Descriptive study design

Descriptive epidemiological studies are usually studies based on routine data. In terms of descriptive epidemiological studies on cancer, cancer registries are the primary source of data. In general their advantages have been reported as being the speed and low cost with which they can be carried out without necessarily contacting the study subjects, but their main limitations have been described as being the limited number of variables routinely collected through cancer registries (Bain *et al.*, 1997).

Interpretation of findings from descriptive epidemiology needs to be done with caution and all potential sources of bias, confounding, and artefacts in the data need to be explored. To these ends, it is important that the methods of data collection, collation, and processing are understood (dos Santos Silva, 1999).

A range of descriptive epidemiology study designs have been described, including those which utilise individual-level data based on: comparing data from different geographical areas, migration studies based on place of birth or ethnicity, studies based on socioeconomic status or occupation, time-trend studies, record linkage studies; and those based on aggregated population-level data – also known as ecological studies (dos Santos Silva, 1999).

1.2.2.10 Geographical studies

Descriptive epidemiology cancer studies which utilise individual level data are often based on place of residence. These studies compare incidence data from different geographical locations including countries or regional comparisons. Examination of geographical differences can often provide aetiological insights, and stimulate hypotheses warranting further investigation (dos Santos Silva, 1999).

1.2.2.11 Migration studies

A full discussion of the rationale and methodology of migration studies in cancer epidemiology is explored by Parkin and Khlat (1996). In this review, they describe that most of the migrant studies investigating cancer are descriptive epidemiological by design, utilising cancer registry data, where the potential to shed light on environmental or genetic factors in the aetiology of a cancer has been observed. Most studies compare the migrant group with the ‘native’ group or with the group from where they came from. Further

dimensions increasingly seen in these studies are the inclusion of age at or time since migration, and the exploration of ethnicity and place of birth.

1.2.2.12 Socioeconomic status or occupational studies

A review of the descriptive epidemiology studies which examine the relationship between cancer and socioeconomic status has been comprehensively undertaken by Kogevinas *et al.* (1997). The studies included in this review were mainly based on record linkage of cancer registry incidence and mortality rates with measures of social class (including education, occupation, and income) based on census or other health record data. This linkage can be of the form of individual or area-based socioeconomic measures. Such studies have the potential to give important insights into the social context of the aetiology of cancer.

1.2.2.13 Time-trend studies

Adapted from the aims outlined by Coleman *et al.* (1993), time-trend studies in cancer epidemiology attempt to answer the following: (i) how have cancer rates been changing (over time and between populations)?; (ii) why have cancer rates been changing?; (iii) what is likely to happen in the future?; (iv) what can be done to reduce future burden?. In answering these questions one can begin to get an understanding of the underlying determinants; predict future trends; and think about cancer prevention. Hypotheses in time-trend studies can also be tested or confirmed, but more often are generated as a result of the patterns observed.

While descriptive epidemiological studies can compare the burden of cancer between different populations and different geographies, time-trends analysis with changes in incidence data over time can provide greater understanding of aetiological factors, particularly when related to known population-based trends (dos Santos Silva, 1999).

Analysis methods employed include highly statistically sophisticated modelling approaches and were outlined by Clayton and Schifflers (1987a, 1987b) in their two seminal papers, and taken further by Robertson and Boyle (1998a, 1998b). They include modelling (to various levels) the highly inter-related (time factors) of age, period, and cohort effects to explain which of these factors are driving the temporal trends in cancer rates.

Colleagues in Scotland, Roger Black and Diane Stockton, are leading in the utilisation of time-trends studies to predict the future burden of cancer, where they have modelled cancer incidence data based on population projections and age-specific cancer incidence (Black and Stockton, 2001).

1.2.2.14 Record linkage studies

Record linkage studies involve linking cancer registry data with data from other sources – which have included: population census data; mortality record data; medical records – e.g. hospital admission, general practice information, prescribing data; and employment or company records. In Scotland, cancer registry data are routinely linked to the Registrar General's Population and death records (Scottish Cancer Registry, 2007); but with the advent and increasing scope of 'eHealth' – defined as electronic health information and technology, the potential for record linkage of cancer data in the future could escalate.

1.2.2.15 Ecological studies

Ecological study design is reviewed by Greenland and Morgenstern (1989), Walter (1991a, 1991b) and Greenland and Robins (1994). The primary criteria for a descriptive epidemiological study to be ecological in design is that it is one in which aggregated or groups of individuals are used to investigate a possible relationship between exposure and outcome. Thus exposure data are available at the population level and may include demographic, environmental, or lifestyle variables (Walter, 1991a). The analysis of the relationship between exposure and outcome is usually limited to the production of a correlation statistic or to fit a regression line to the data, as described by Greenland and Morgenstern (1989). The former method has been found to be less useful as it can misinterpret the relationship: the wider the range of the exposure variable the greater the correlation and further it can not be translated into a conventional measure of effect so has limited use in epidemiology (Greenland and Morgenstern, 1989). However, regression methods have been shown to be more appropriate: allowing incidence to be predicted as a function of the level or prevalence of the exposure variable, providing an estimate of effect, and being unaffected by exposure variable range (Walter 1991b).

The main limitations of ecological studies are: the 'ecological fallacy' – which implies that a relationship at the population level would hold at the individual level; confounding; measurement errors in exposure and outcome; and the time variation or lag between exposure and outcome (Greenland and Morgenstern, 1989; Walter, 1991b).

1.2.2.16 Descriptive epidemiology: summary of key points

Descriptive epidemiology should not be considered an end in itself but should be regarded as a means of monitoring the burden of disease in the population, in addition to generating hypotheses or highlighting areas for further study and investigation – be that defined by a geographic area or demographic group. These areas could subsequently be explored using methods of analytical epidemiology.

1.2.3 Analytical epidemiology

1.2.3.1 Definitions

Analytical epidemiology takes hypotheses generated by descriptive means and tests them through an analytical approach. The main aim is to determine causality in the form of aetiological risk factors for a disease, through investigation of exposure and disease outcome at the individual level (Last, 2001). Rothman and Greenland (1998) expand on this, describing the objective of analytical studies being to determine whether particular exposure (variables) such as environmental or behavioural factors (including physical, chemical, or biological agents) are associated or not to a disease outcome such as cancer – and further whether this association is independent. Such an association does not necessarily indicate causation, as chance, confounding and bias need to be considered as possible sources of the relationship (Lagiou *et al.*, 2005). The two main analytical study designs are cohort and case-control studies – although there are increasing variations on these two designs (Rothman and Greenland, 1998).

The major concepts in the analytical epidemiology of cancer will be discussed, including causation, study design – with particular reference to case-control studies.

1.2.3.2 Causation

The concept of causality is integral to analytical cancer epidemiology and observational studies, and is well explored in the literature. Reviews by Rothman and Greenland (1998); Lagiou *et al.* (2005); and Goodman and Samet (2006) eloquently explored this complex philosophical and epidemiological issue. Goodman and Samet describe the historical philosophical debate which centres on the premise of the lack of certainty of a ‘cause’ based on the fact that causation can not be directly observed. However, from this age-old problem, came a pragmatic, logical approach often described as ‘counterfactual’ – which

basically describes how the presence (or absence) of an exposure leads to an outcome. Reality dictates that outcomes occur in the absence of some exposures – rarely if one exposure is present does an outcome always occur. Probability theory brought with it mathematical tools for quantifying the uncertainty in the relationship between exposure and outcome. Epidemiologists further built on this thinking by: teasing out spurious or indirect causes described as confounders; by increasing certainty through repetition of observations in different populations; and through developing a better understanding of the underlying biological mechanisms.

The criteria for causation in public health and epidemiology were set down originally by 'Bradford' Hill (Hill, 1965). Hills' nine criteria for associations to be considered as causes were: 'strength, consistency, specificity, temporality, biologic gradient [dose-response relationship], plausibility [biological explanation], coherence [with previous research], experiment [e.g. further evidence from removing exposure], analogy [based on previous findings in other settings]'. This has provided a framework for assessing the evidence for causation. Hill was insistent that they were 'not…hard-and-fast rules of evidence that must be obeyed before we accept cause and effect'. They were also intended only to be applied when a significant association had been observed.

These criteria have been adopted by epidemiologists as a pragmatic approach to assessing associations and causality. However, Last (2001) notes that it is accepted that epidemiological evidence alone is insufficient for establishing causality. These criteria have been criticised more recently as not standing up where complexity is great (as in the example of cancer causality) (Höfler, 2005). Rothman and Greenland (1998) were the first to recognise this limitation and described the 'sufficient component cause' model to provide a framework for considering multiple cause diseases such as cancer. Wherein, each disease has several causes each accounting for a proportion of the cases, while each cause also has several components. If the components are not sufficient then the cause itself would be incomplete. Thus the components themselves can also be considered causal in that they are necessary for the cause to act.

Lagiou *et al.* (2005) revisited the key issues which need to be given due consideration for causality in cancer epidemiology as being: chance, confounding, and bias – to explore non-causal explanations for associations. In summary, the play of chance can be reduced in analytical epidemiology through increasing the numbers of subjects under observation which reduces the effects of random variation and uncertainty – which is inherent to probability theory. In addition, appropriate statistical analysis and interpretation of studies

can also reduce the influence of chance. Confounding is where a spurious or indirect association from another factor is related both to the exposure and disease outcome in question. It can be managed through appropriate statistical analytical methods, and thorough study design to minimise residual confounding – that which is associated with exposures not measured in the study (Rothman and Greenland, 1998). Finally, bias needs to be considered and minimised – this is generally related to study quality, with poorer quality studies leading to greater bias. Bias comes in many forms across the gambit of analytical research (Sackett, 1979) and is a particular challenge in case-control studies where selection bias can be related to: the control subject's participation; the comparability of controls to the cases and to the study population-base; the statistical efficiency; and the general logistics of undertaking a case-control study (Wacholder 1992a, 1992b, 1992c).

The emergent challenges in causal inference in cancer were set out by Goodman and Samet (2006) as: increasing genetic and molecular dimension; and the recognition of the enormous complexity in cancer aetiology research. Pearce (1997) and Krieger (2001b) also set out the challenge to bring a social perspective to understanding the causal pathway of cancer. A further challenge could be seen in bringing these perspectives together.

1.2.3.3 Risk factor terminology

For the purpose of this thesis and literature review, the term 'risk factor' will be used while referring to aetiological, causal factors. Risk factors – are defined as environmental, behavioural, or biological factors confirmed by temporal sequence, which if present directly increase the probability of a disease or condition occurring, conversely if absent or removed, reduce the probability (Last, 2001). Protective factors – are the opposite of risk factors, if present, protective factors directly decrease the probability of a disease or condition occurring, and conversely, if absent or removed, increase the probability. As opposed to aetiological they are considered salutogenic. Previously, separate from risk factors, the term 'risk determinants' has been used – to define social and demographic or background characteristics (Last, 2001). Separated, as they are factors more likely to expose the individual to 'risk factors', and they are considered less amenable to be changed (Beck, 1998). However, these determinants are investigated, analysed, and indeed interpreted in an identical manner and so the distinction is somewhat tautological. Therefore, the term 'risk factors' will be used to capture all components of oral cancer risk, and the potentially more abstract demographic and social factors will be considered on a par with readily conceivable behavioural risk factors.

1.2.3.4 Study design

The basis of analytical epidemiology is through observational rather than experimental research (Rothman and Greenland, 1998). Experimental research either *in vitro* or *in vivo* has limited application to aetiological research. Laboratory experiments involving animal or cellular models, while invaluable in understanding pathogenesis of cancer, are limited in the translation of findings to humans. Experimental trials investigating aetiological factors are constrained by the ethics of allocating potentially harmful agents, and the logistics of the numbers, time, and cost required (Adami and Trichopoulos, 2002).

Thus, there are two primary nonexperimental, observational study designs which are the mainstay of analytical epidemiology – the cohort study, and the case-control study (Rothman and Greenland, 1998).

1.2.3.5 Cohort study

'Cohort' is the Latin word for a division of a Roman army legion (Rothman and Greenland, 1998) and a soldier once recruited to a cohort remains within it until death, but was not replaced until death (Adami and Trichopoulos, 2002). This is the perfect analogous term for how a cohort study design works. In summary, according to Breslow and Day's (1987) comprehensive work on the topic, cohort studies are longitudinal studies, which begin by identifying a group of individuals about whom certain exposure information is collected. This group is then followed forward in time to ascertain the occurrence of the disease(s) of interest, and their individual prior exposure information can be related to the subsequent disease experience. With this basic design, there are also a number of different variations based on whether the design is prospective from the present time into the future, or defines a cohort and their experiences from historic records. In addition comparison groups can be identified from within the same cohort – internal – i.e. those not exposed, or when the whole cohort has similar exposure experience, then an external comparison group is needed (this is particularly used in occupational cohort studies where a cohort from one company or industry, may be compared to those from another company outside the cohort) (Breslow and Day, 1987).

The advantages and disadvantages of cohort studies were detailed by dos Santos Silva (1999). The main strengths are: exposure is always assessed prior to disease development; they can have the power to examine rare exposure events; multiple disease outcomes can be assessed; incidence and relative risk can be assessed in exposed and unexposed. The

main limitations are: the logistical issues of expense and time (particularly in prospective designs); the need to consider changes in exposure status during the time of follow-up (repeated measurements required); and bias – from loss to follow-up (selection bias), and – from outcome information being influenced by knowledge of exposures (information bias). Finally, cohort studies have limited utility in conducting a detailed investigation of risk factors related for outcomes which are rare or have long induction periods, as for oral cancer. In such circumstances, where a cohort study can not be undertaken, the best option is a case-control study (dos Santos Silva, 1999).

1.2.3.6 Case-control studies

Case-control studies are defined as those studies which identify a group of individuals with the disease (the ‘cases’) and those without the disease (the ‘controls’), and compares both groups with respect to whether they have been exposed to the disease’s possible risk factors (Breslow and Day, 1980).

The principal aim of a case-control study is to provide a valid and reasonably precise estimate of the strength of at least one, but in practice often more, hypothesized causal relationships. They are therefore aetiological investigations, the prime objective being the validity of the cause-effect relationship, rather than generalizing results to a population (Breslow and Day, 1980).

Important aspects of case-control methodology are well documented in the standard epidemiology texts (Breslow and Day, 1980; Schlesselman, 1982; Rothman and Greenland, 1998). The important aspects of which are: defining the study hypothesis; definion and selection of cases; definition and selection of controls; measurement of exposures; analyses; interpretation and reporting.

In summary, the study hypothesis – as with all study design, needs to be clearly stated beforehand to avoid ‘data dredging’ in the analysis of multiple exposures and their potential interactions (Crombie, 1996).

A precise and unambiguous definition of what constitutes a case is essential (Breslow and Day, 1980). Inclusion criteria based on age, or sex, or geographic location helps to refine the definition which improves the potential to gain insights from the findings. In cancer case-control studies it is important to define the cases in terms of ICD codes to reduce ambiguity, and selecting newly diagnosed ‘incident’ cases only. Including all prevalent

cases introduces bias as not all cases would necessarily be representative (Rothman and Greenland, 1998).

There is a debate on whether controls should be selected to be representative of the study population or for their comparability with cases. Rothman and Greenland (1998) on one hand argue that representativeness of the population is not so important and that comparability with the cases is the priority. However, the population dimension is increasingly seen as being important on several counts. A population-based approach is concerned with generalisability, and is considered dependent upon selecting a random (or stratified random) sample of that population as controls, with the population defined by the cases, with the further condition that all cases are captured from the population (Wacholder, 1992c). Population controls are also considered more suitable than hospital controls – as they avoid the bias arising from the factors which lead people to use health services – although cost and effectiveness in terms of participation are recognised issues (Wacholder, 1992b). Other sources of controls such as neighbours, friends, or relatives may also be used, although choice of control should always be driven by the hypothesis (Wacholder 1992b).

Exposure variables are ascertained through a range of methods, including: questionnaires, interviews, examination of (health or other) records, and increasingly utilising biomarkers (particular blood or tissue samples for genetic analysis). Correa *et al.* (1994) also note that it is essential that validated tools are used by trained and calibrated researchers in the collection of data, and that such researchers should be masked (where possible) to the disease status of participants – as such knowledge may affect how interviewers influence how hard the cases and controls remember exposures.

Statistical analyses of case-control studies continues to evolve and develop. Thomson (1994) exemplifies this with the change in emphasis in analytical epidemiology away from the p-value to the quantification of the magnitude of effect (of the exposure on the outcome) – the odds ratio, with corresponding confidence intervals (which provides information on the precision of the estimate). Further, analysis methods which include controlling for confounding, evaluation of interactions, and systematic pre-determined (not data dredged) logistic regression methods for multivariate analysis have also been emphasised (Rothman and Greenland, 1998). An outstanding issue in case-control analysis includes developing techniques which take into account error in measurement or missing data (Thomson, 1994). However, sensitivity analysis has been proposed as one way of

addressing these biases associated with missing data or missing confounders (Rothman and Greenland, 1998).

Interpretation of results of case-control studies should be undertaken in full acknowledgement of the potential biases in the form of selection bias in the choice of cases and controls, information bias in the collection of data, and failure to fully consider confounding factors (Lagiou *et al.*, 2005). Ideally, a high quality case-control study can provide informative results, if cases and controls can be selected independently of the exposure and controls are selected at random from the same defined study population as the cases came from – the results would be unbiased and equivocal to a cohort study. Returning to the issue of causality criteria, the temporal sequence issue needs to be considered. Due to the nature of case-control design and data collection, it is sometimes difficult to fully determine whether the outcome was a result of the exposure or whether 'reverse causality' had occurred (dos Santos Silva, 1999).

As with Consolidated Standards of Reporting Trials (CONSORT) guidelines, which were widely adopted and improved the quality of clinical trial reporting internationally (Moher *et al.*, 2001), a group of epidemiologists in Europe have begun to develope similar guidelines with similar aims for reporting observational studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (STROBE, 2007), due for full publication in late 2007, will set out standards for reporting of observational studies, including case-control studies – which will include acknowledging all the issues covered above.

The major strengths of a case-control study have previously been documented (Rothman and Greenland, 1998; dos Santos Silva, 1999). They include its direct application to humans, and its 'informativeness' and efficiency, such that one study can simultaneously evaluate multiple hypotheses and interactions – albeit with caution as noted above. Confounding factors can also be investigated. Another advantage of case-control studies is that they allow the evaluation of casual significance, even with relatively low risk factor exposure or disease prevalence. Even the major cancers in the world (lung, breast, and colon) are relatively 'rare', but the more rare the cancer the greater the relative effect (Breslow and Day, 1980). Rare diseases with a wide-range of potential risk factors are also particularly suitable for case-control design. They are also considered relatively quick, cost-effective, and easy to perform, and there is 'no loss to follow-up' (Rothman and Greenland, 1998).

The limitations of case-control studies are also well considered (Rothman and Greenland, 1998, dos Santos Silva, 1999) and have been discussed to some degree (above) in the methodological design issues. The major concern is their susceptibility to bias (Breslow and Day, 1980). Sackett (1979) attempted to define bias and pulled out 30 different types of bias to which observational studies were potentially susceptible. Rothman and Greenland (1998) argued that it was difficult to fully determine the differences in these, and concluded that bias fell into three broad categories: recall (information) bias, selection (including response) bias, and analytical bias (including confounding effects).

Recall bias – where the case subjects have a differential ability to remember details about their past life history is a potential problem. It has been suggested this is perhaps related to their perceived need to focus on a cause (Rothman and Greenland, 1998). John Diamond's search for a 'reason' exemplifies this from the patient's perspective (Diamond, 1998).

Selection bias relates to the way cases and controls are selected – if they are not representative of the population from which the cases come, then the results are likely to be distorted. Therefore approaches to select population-based controls are less inclined to bias – however, response rates and participation bias also need to be closely monitored with this approach (Wacholder, 1992b).

Analytical bias issues include the potential problems of lack of precision and validity. Precision, or lack of random error of results can be improved by increasing sample size (utilising a pre-study power calculation), and by improving study design, and study efficiency (including matching control group e.g. by age). Internal validity, or lack of systematic error, in case-control designs, relates to the accuracy of measurement, while external validity relates to the generalisability of findings. The major potential analytical bias is that which is associated with confounding – design and analytical steps can be taken to control for their effect, including sensitivity analysis of bias (Rothman and Greenland, 1999).

Finally, confounding is the most important consideration in the analysis and interpretation of case-control studies. Basically, confounding is a confusion of effects of the exposure of interest. In general, a confounder must be associated both with the exposure and with the outcome under investigation.

It seems that socioeconomic factors are generally considered as confounding factors (Rothman and Greenland, 1998). This seems to have limited the ability to assess their explanatory and causal role in cancer aetiological studies.

1.2.4 Systematic review and meta-analysis in epidemiology

1.2.4.1 Definitions

The term ‘meta-analysis’ combines the word ‘analysis’ with the Greek word ‘meta’ meaning ‘after’ which, when used as a prefix in English, indicates ‘beyond, above, at a higher level’ – denoting abstraction from another concept (Oxford English Dictionary, 2007). It was first coined by Glass (1976) to mean ‘analysis of analyses’ to distinguish it from primary analysis of original research data and secondary or re-analysis of the same data (Glass, 1976; Oxford English Dictionary, 2007). In practice, meta-analysis comprises a set of statistical analysis methods for quantitatively summarising the ever increasing epidemiological literature. Lagiou and colleagues (2005) draw a helpful distinction between ‘meta-analyses’ and ‘pooled analyses’ (which are often used interchangeably) whereby meta-analysis is used where published results are combined, while pooled analysis combines individual patient data (IPD) from the original studies. This notation has also been taken up by the Cochrane Collaboration (Higgins and Green, 2006).

There is still some debate about the terminology and somewhat confusingly the terms ‘systematic review’ and ‘meta-analysis’ are used interchangeably (Davey Smith *et al.*, 1997a). In general, ‘systematic review’ denotes the overall approach of a comprehensive review in which specific methods have been undertaken to search and retrieve data, and review findings with an unbiased approach. Such methods can include a meta-analysis, together with assessment of the studies. Therefore meta-analysis is a component (albeit an integral one) of systematic reviews; and together they are recognised epidemiological methods for the formal, thorough process of synthesising information from (all) relevant studies – both published and unpublished, on the same topic.

1.2.4.2 Background

Traditional narrative literature reviews have inherent biases as a result of the subjectivity of the ‘expert’ reviewer and are heavily criticised in the literature (Davey Smith *et al.*, 1997a; Torgerson, 2003). The main problems described, are: they are not governed by any ‘rules’ and inclusion of studies tends to be on the basis of whether they have positive

results which support the authors opinion. Even a ‘fair’ review, which captures all published literature, generally adds up the number of studies supporting one side of an argument and compares this to the number supporting the other side – with the greatest total prevailing in the argument. Such an approach is obviously biased in that it fails to take into account numerous factors about the study, including: study design, sample size, and effect size. Although it is argued that qualitative narrative reviews still have a place, particularly in that they, rather than draw conclusions based on potentially false precision of a meta-analytical summary result, set out all the arguments and allow the reader to make the interpretation on overall synthesis (Shapiro, 1994). However, systematic reviews are now well established epidemiology methods that have on the whole replaced the narrative review – which no longer is viewed as either a simple or reliable method of distilling and summarising epidemiological research (Rothman and Greenland, 1998).

1.2.4.3 Aims

Broadly, from the benchmark writings of Chalmers and Altman (1995), Lipsey and Wilson (2001), and Petticrew and Roberts (2006) the aims of systematic reviews and meta-analyses are: (i) to refine and reduce large quantities of information (usually of varying quality) into a manageable finding; (ii) to improve research efficiency – by distilling information quickly, perhaps preventing unnecessary research, but also by identifying research gaps; (iii) to increase reliability – a systematic approach prevents the haphazard and perhaps biased or at least inaccurate literature reviews of the past; (iv) to obtain greater power and precision than could be achieved from a single study – with greater numbers a more precise estimate can be obtained; (v) following from all of these aims – to enable better research transfer through the ability to generalise results and iron out or explore inconsistencies in individual study findings.

1.2.4.4 Methodological issues

A wealth of literature on conducting systematic reviews has also developed for assessing clinical interventions (Centre for Reviews and Dissemination, 2001; Higgins and Green, 2006). In summary the key steps in carrying out a systematic review and meta-analysis include: (i) planning the review: identifying the need, defining the question, developing the proposal and protocol; (ii) conducting the review: identifying the research (literature), selecting studies, study quality assessment, data extraction, and data synthesis – with, where possible, meta-analysis, tests for heterogeneity between studies, subgroup and sensitivity analyses; and (iii) reporting and dissemination.

While this broad outline would seem to be a sensible approach, similar detailed guidelines do not exist for systematic reviews of observational studies. However, guidelines for reporting such studies were recently produced by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group (Stroup *et al.*, 2000) – which seem to have partly filled a niche – given the almost 500 citations they have received in the world-wide literature (ISI Web of Science, 2007).

In terms of the literature search, generic guidance on systematic reviews is also worthy of noting. McManus and colleagues (1998) report the importance in contacting experts in the field to help maximise the literature obtained. Lemeshow *et al.* (2005) outline the importance of searching multiple databases, particularly for obtaining observational studies. And Grégoire *et al.* (1995) point to the importance of not imposing a language restriction on the search to avoid linguistic publication bias.

1.2.4.5 Potential for systematic reviews and meta-analyses

The world of systematic reviewing and meta-analysis has generally focused on analysis of the effectiveness of interventions from trials (usually randomised control trials) – be these clinical interventions (Cochrane Collaboration, 2007), or 'social' interventions (Campbell Collaboration, 2007). In both fields they have been used widely and effectively and increasingly, meta-analysis is being used to synthesise aetiological observational studies (e.g. case-control or cohort studies), where their potential is yet to be fully realised (Petitte, 1994).

The potential advantages of systematic reviews and meta-analyses are well recognised for intervention studies (Davey Smith *et al.*, 1997a) and similarly are noted for observational studies (Dikerson, 2002): (i) they are cost-effective – particularly in relation to undertaking a single large study; (ii) they may help contribute to the generalisability of study findings – through demonstration of repeated findings in different populations and settings; and (iii) they are more transparent than traditional reviews in terms of studies included and conclusions drawn – as they are based on the data in the studies rather than the abstract or conclusions presented in the papers.

The strengths of meta-analysis, summarised from Lipsey and Wilson (2001), are that it is a sophisticated mechanism for synthesising research findings which gives appropriate weight to study results based on the relative merits of that study – be they design, quality, or

sample size. It also provides an organised approach for handling and interpreting a large number of studies and data.

1.2.4.6 Limitations of systematic reviews and meta-analyses

The limitations of systematic reviews and meta-analyses are well documented (Davey Smith *et al.*, 1997a; Rothman and Greenland, 1998). In general terms, the limitations of systematic reviews are mainly focused on which studies should be included – these translate to potential for publication bias, or other biases in the location of data (poor search strategy), or to biases in selecting studies for inclusion in a meta-analysis (manipulation of inclusion criteria). Publication bias is the biggest of these concerns, where the review only includes published studies, and ignores those that have been unpublished. While studies are not published for a variety of reasons, one particular concern is that they are unpublished because of their findings – e.g. they do not show positive results, or only demonstrate equivocal relationships (Easterbrook *et al.*, 1991).

'Overconcluding' is also a recognised limitation, with large meta-analysis appearing more precise – however, conclusions can only be drawn having fully considered the quality and source of the underlying data, and following this, caution is usually indicated (Rothman and Greenland, 1998).

Lipsey and Wilson (2001) offer general limitations of meta-analyses, suggesting that, compared with traditional qualitative narrative reviews, they are more time-consuming, and require more effort and expertise, including statistical skills. They also consider them potentially over-structured and mechanical (although this they note this is also a potential strength). Finally, the main weakness of meta-analysis is overcoming the heterogeneity between studies.

1.2.4.7 Meta-analysis of observational studies – validity debate

The remainder of this discussion will focus on the issues involved in undertaking a systematic review and particularly a meta-analysis of observational studies.

The use of meta-analysis in observational studies is recognised as controversial even by those who advocate it (Stroup *et al.*, 2000). The main reasons for this are: (i) recognition of the potential biases in the original studies, relative to the biases in RCTs – these underlying biases may affect the calculation of a single summary estimate of effect of exposure; (ii)

difficulties in comparing the wide range of epidemiological study designs and populations which exist; and (iii) the recognised methodological problems associated with meta-analysis in general, including publication bias, which may particularly affect meta-analysis of observational studies (Easterbrook *et al.*, 1991).

The methodological issues of confounding and biases do not figure in meta-analyses of randomised control trials – leading to them being viewed as statistically sound (Sacks *et al.*, 1987). However, meta-analyses of observational studies are not universally accepted (Shapiro, 1994; Feinstein, 1995) – primarily due to concerns around the ability of meta-analysis to address problems of residual confounding, bias, and variations in results reporting within the included studies. This is considered a particular issue where weak associations and small effect sizes are being synthesised (Shapiro, 1997). Despite the widely held comfort with meta-analysis of randomised control trials, it is recognised that such studies are rarely feasible when investigating risk factors – because they not only may involve exposing subjects to harmful risk factors, but they relate to studying inherent characteristics of the subjects.

In two articles, the same research team were also highly critical of the use of meta-analysis of observational studies (Davey Smith *et al.*, 1997a; Egger *et al.*, 1998). The main thrust of their argument was that confounding and selection bias often distort the findings from observational studies so that there is a danger that meta-analyses of observational data produce very precise but spurious results. They concluded that statistical combination of data should not be a prominent component of reviews of observational studies; rather that careful examination of heterogeneity between study findings should be explored. Other critics found that the approach of a pooled analysis of IPD overcame the heterogeneity (in study design, and populations) inherent between observational studies (Blettner *et al.*, 1999) – but they recognise that this approach is more expensive and time-consuming.

The main counterpoint to these arguments and in particular to Shapiro's (1994) vicious attack on the validity of meta-analysis of observational studies – 'meta-analysis/shmeta-analysis' – was presented by Petitti (1994) in 'of babies and bathwater', where she urged doubters not to dismiss the method without giving it careful consideration. Particularly drawing on Shapiro's 'rubbish in, rubbish out' concern that to reject meta-analysis of analytical epidemiological studies on the basis of the constraints of bias in the observational studies included, should lead to the logical conclusion that we should reject and dismiss as invalid all individual observational studies. Both sides of the argument concluded by agreeing that meta-analysis of observational studies were here to stay, while

in the same debate Greenland (1994a), who was also supportive of meta-analysis of observational studies, offered a way forward. He suggested that refining and evaluating techniques and methods could maximise the usefulness of observational study meta-analysis – acknowledging at the same time that analytical epidemiology was far behind interventional epidemiology in this area, and that epidemiologists had to work harder to overcome the demands that interpreting observational studies brought. Dikerson (2002) picked up on this theme – that analytical epidemiology was lagging behind biomedicine in this area, and thought that it could partly be explained by the polarised debate amongst epidemiologists.

The debate has since moved on and meta-analysis of observational studies has become increasingly used and accepted – at least in part because of the pressure for evidence-based decision making, but also the explosion in the volume of information in the scientific literature and the dissatisfaction with narrative reviews (Stroup *et al.*, 2000). It has taken time to develop methodological guidelines and for critics to be won round. Interestingly, some of those most critical of meta-analysis of observational studies have been turning to it themselves of late (Davey Smith *et al.*, 2007).

Some of the main concerns around the meta-analysis of observational studies have begun to be addressed through adopting similar approaches to those taken in interventional study reviews (Higgins and Green, 2006). These include: the introduction of quality or methodological assessment of studies; through the use of a systematic approach to the meta-analysis including thorough sub-group and sensitivity analyses; as well as performing random effects modelling to take into account study heterogeneity.

However, some these methods themselves remain controversial. The use of arbitrary quality scores is open to debate (Juni *et al.*, 1999). Nevertheless, there is broad consensus that some form of methodological quality assessment is needed and should form part of the sensitivity analysis (Juni *et al.*, 1999; Higgins and Green, 2006).

The random effects model assumes that the size effect in each study is randomly distributed and includes a term in the statistical model for variability between studies, and is an important tool where there is significant heterogeneity between included studies. By contrast, the fixed effects model assumes that the true size effect is the same for all studies (Normand, 1999; Higgins and Green, 2006).

Despite these statistical approaches, concern that underestimation of chance variation and consequent over-estimation of statistical significance can be born out of meta-analysis (Greenland 1994b) remains valid – and interpretation with caution is advised (Stroup *et al.*, 2000).

In terms of the potential problem of bias, MOOSE guidelines offer an informative approach: advising the adoption of broad inclusion criteria for studies and then performing sensitivity analyses (when the data permit), relating suspected sources of bias and variability to study findings (Stroup *et al.*, 2000).

Despite these challenges, systematic reviews with meta-analyses of observational studies continue to be one of the few objective methods for interpreting the wealth of analytical epidemiology literature, and they are being published in increasing numbers (Dikerson, 2002). The MOOSE guidelines have evidently enabled this through the provision of a framework for undertaking and reporting these meta-analyses.

The next step in synthesising studies is to pool the individual patient data from various studies, rather than published results (Blettner *et al.*, 1999). In analytical cancer epidemiology, one of the pioneers of this approach is the International Head and Neck Cancer Epidemiology (INHANCE) Consortium – led by high level collaboration between the International Agency for Research on Cancer in Lyon, and the National Cancer Institute (NCI) in Washington DC (INHANCE, 2007). They are beginning to pool data on head and neck cancers from multicentre studies from around the world, to permit high powered, in-depth fully adjusted analyses of risk factors (Hashibe *et al.*, 2007).

1.2.5 The emergence of social epidemiology and beyond

As described earlier (Section 1.1.2.1), epidemiology had evolved throughout the 20th century. Susser and Susser (1996a, 1996b) detail the shifting emphasis in their account of the role of epidemiology in public health. From the era of miasma theory and ‘sanitory epidemiology’ through to the germ theory and infectious disease epidemiology of the first half of the century; and on to the ‘black box’ and ‘web of causation’ models, which defined chronic disease epidemiology towards the latter half of the century. The ‘black box’ metaphor was used to define the approaches of chronic disease epidemiology which focus on individual risks, but which lack deeper understanding of the aetiological pathways involved, while the ‘web of causation’ metaphor began to acknowledge the multiple risk factor nature of chronic diseases. While these approaches remain the prevailing models for

what is termed ‘modern epidemiology’ (Rothman and Greenland, 1998), Susser and Susser (1996a) sensed that this ‘present era of epidemiology is coming to a close’ and that the focus of risk factors at the individual level is no longer adequate in itself. This position was echoed by Pearce (1996) in his critique on modern epidemiology as being increasingly reductionist and individual focused to the extent that it is using ‘more and more advanced technology to study more and more trivial issues.’ He also noted that despite the increasing body of work demonstrating wide (and widening) socioeconomic inequalities in health, ‘modern epidemiologists rarely consider socioeconomic factors and the population perspective, except perhaps to occasionally adjust for social class in the analysis of the health effects of tobacco smoke, diet, and other lifestyle factors.’ The results of such an approach, he concluded, were that the major social causes of disease are ignored while individuals are blamed for their ‘lifestyle’ and their condition. Krieger (1994) was also critical of the ‘web of causation’ model as, rather than providing a seemingly complex model of causality, it was somewhat flat and two dimensional. It inhibited exploration of deeper and wider aetiological factors and had limited theoretical basis, while being overly constrained by a biomedical individualist approach.

The ‘modern’ epidemiologists have responded to these criticisms by continuing to ignore social factors from their research. For example, the major research in the field of cancer aetiology continues to overlook socioeconomic factors, considering them only confounders, from Doll and Peto’s (1981) work on ‘the causes of cancer’ in the US; to Danaei *et al.*’s (2005) ‘causes of cancer in the world’; and more recently IARC’s (2007b) ‘attributable causes of cancer in France’. Peto (2001) reiterates this view in a recent review article: ‘most cancers are in principle preventable and many could be avoided by a suitable choice of lifestyle and environment’ with no acknowledgment of social factors. However, there have also been some direct responses, most notably from Rothman *et al.* (1998), in which they provide comments such as: ‘however well motivated, epidemiologists cannot rid the world of poverty’; that public health professionals ‘do not have a license to tinker promiscuously with society’; and that such studies are ‘too political’ (Rothman *et al.*, 1998).

Pearce (1997) argues that such positions against epidemiology investigating social factors are themselves political points of view. He also describes these views as following a ‘politically acceptable’ path and avoiding the big public health issues which are inherently political issues.

Rothman *et al.* (1998) go on to argue that public health approaches are more effective when they focus on determinants 'most proximal to disease occurrence' i.e. the molecular and biochemical determinants and even behavioural factors, rather than the social political or economic 'upstream' factors. However, they do not provide evidence to support this assertion – instead they argue that there is no evidence to support upstream public health action. Further, they fail to acknowledge that such individual approaches have the potential to cause harm, by shifting the problem rather than properly solving it. As an example of this potential, Pearce (1996) suggests that the individually focused epidemiological research on the dangers of smoking, which has provided public health approaches (such as education, and awareness) have been disproportionately taken up by more affluent groups in society leading to harm in the form of widening health inequalities, and similar global inequalities – with tobacco companies shifting their emphasis to developing countries. He, therefore, argues that a more holistic approach to the problem of smoking would have been to focus on and tackle the production side rather than consumption.

Out of the debate on the future of epidemiology has emerged the discipline of social epidemiology, defined by its focus on explicitly investigating the wider social and economic determinants of the distributions of population health and wellbeing as well as disease (Krieger, 2001a). By the beginning of the 21st century the first text book on the topic entitled – *Social Epidemiology* – was published (Berkman and Kawachi, 2000), which sets out the guiding concepts of social epidemiology as: a population perspective, social context of behaviour, multilevel analysis approach, and a life course perspective. Theories underpinning social epidemiology have become better articulated: in response to the restrictive (2-dimensional) 'web of causation' (Krieger, 1994). Krieger (2001b) also sets out the eco-social model to encapsulate the multilevel thinking and also acknowledges the other developing theories of psychosocial influences and socio-political production of disease. The nature of causality in social epidemiology has recently come to the fore with Greenland (2005) arguing that only modifiable factors should be considered as 'causes' (suggesting social factors are not modifiable), while Susser and Schwartz (2005) recognise the modifying potential of social factors and recommend that they are treated in the same way as other factors.

In parallel, genetic and molecular epidemiology has developed at a pace – partly in response to the criticism of the 'black box' approach of not fully investigating the aetiological pathways, but also related to the massive investment and expansion of human genetics (Butler, 2001). Thus, genetic epidemiology has almost replaced traditional observational modern epidemiology, as it aims to understand heritable aspects of disease

risk, individual susceptibility to disease, and molecular pathogenesis (Davey Smith and Ebrahim, 2003). However, almost before it has begun to develop, some have argued that genetic epidemiology is ‘a misguided and hopeless quest for the philosopher's stone’ given the complexity of causality and of risk inference, never mind the potential difficulties translating this to preventive interventions from genetic data (Buchanan *et al.*, 2006). Others have argued that cause is not the aim of genetic epidemiology, rather to better identify and potentially influence interacting environmental risk factors (Khoury *et al.*, 2005).

With the establishment of these diverse disciplines, the debate, in many ways, has taken epidemiology to the ‘crossroads’ (Beaglehole and Bonita, 1997; Davey Smith and Ebrahim, 2001; Weed 2006). The future directions for epidemiology seem to be a molecular and genetic path or the social path. The division is almost polarised: exemplified by statements such as ‘It's all genetic’ (Ebrahim, 2006), and ‘Is not all epidemiology, after all, "social" epidemiology?’ (Krieger, 2001a); and by the ferocious: ‘social epidemiology? No way!’ (Zielhuis and Kiemeney, 2001) vs. ‘social epidemiology? Way!’ (Kaufman, 2001) debate which seemed to boil down to an argument over terminology.

Weed (2006) proposed a ‘third way’ as potentially the path forward. He called for a coming together of perspectives, not one way or other, but for both approaches to complement each other – after all he eloquently argues there is much in common. All research endeavours to explain and understand the world, while all epidemiology aims (ultimately) to improve the public’s health.

1.3 Socioeconomic status, circumstances, and inequalities

The literature in the field of socioeconomic status, circumstances, and inequalities is vast. Definitions of the terms and concepts remain open to controversy and debate – partly because the science is still evolving (Kawachi *et al.*, 2002).

This section aims to discuss the issues around these definitions and concepts through an exploration of socioeconomic theory, social and economic trends, measurement of socioeconomic circumstances and inequalities, and how socioeconomic circumstances and inequalities relate to health.

1.3.1 Socioeconomic theory

Socioeconomic theory, or more commonly social theory, has been reviewed by Susser (1997), and Lynch and Kaplan (2000). While these are thorough accounts, the pace of change in the field, the explosion in research, and the need to set the theoretical context for this research, indicates that revisiting some of these fundamental issues is warranted.

The following subsections will focus on summarising the most recent discussions and positions on a number of key areas and issues including: the definition and utility of social theory; the continued influence of Marx and Weber theories in terms of the stratification of society; the definitions and concepts of poverty and deprivation; the meaning of inequality with respect to health and socioeconomics; the perspective of those experiencing poverty and inequality; and finally the global dimension, with particular focus on these issues in developing countries.

1.3.1.1 Definition and purpose

According to Harrington (2005), social theory is a set of views and ideas about how society works. Interestingly, he points out that the term ‘theory’ comes from the Greek ‘theoria’ – originally meaning ‘contemplation and reflection’, but which developed into critical thinking and research based approaches. Such theories allow for both a description and an explanation about a particular aspect of society – and ‘sociology’ is the systematic study of social life (or environment).

There are many different sociological theories dealing with many aspects of society, almost all agree with the fundamental assumption that the world is organised by social constructs: that people live together in societies (Harrington, 2005). However, some do disagree with this concept, most notably articulated by the former UK Prime Minister Margaret Thatcher. In her infamous ‘sermon on the mound’ speech to the General Assembly of the Church of Scotland, Edinburgh, in 1988, she set out her conviction that ‘there is no such thing as society’ – although the direct quote is from an interview in *Women’s Own* magazine around the same time (Thatcher, 1987; 1988). However, even from this standpoint of individualism, it is difficult to argue that we live in isolation – it is inevitable that individuals have to live and work together and in cooperation. Further, almost all social theories also agree that we need to observe individuals within the wider context of their circumstances and positions in society (Harrington, 2005). Sweeney *et al.* (2003) describe how it is sociological theories which provide the lenses through which to

observe individuals within society; which provide a picture of how society works so that individuals can be observed living and being members of society. They also note that it is important to understand sociological theory so as to appreciate that there are aspects about society which are not so obvious or apparent. Therefore, sociological theory provides some of the tools to view the world from different and deeper perspectives from the 'common' (sense) view of the world.

According to Sweeney *et al.* (2003), there are two main sociological theories which are important to achieve an understanding of an individual's position in society. These are those of Marx – 'society as conflict', and Weber – 'social action and interaction'. In addition, Lynch and Kaplan (2000) consider the more modern 'Functionalist' theories of Durkeheim are also worthy of consideration.

1.3.1.2 Marx and Weber: social class and social status

Karl Marx (1818-1883) is seen as the founder of sociological thinking in terms of the study of 'social power' and the power struggles therein (Marx, 1886). By power, Marx primarily means 'economic power'. Thus, the most powerful group in society is that which controls the economy. They consequently also have power within all other social systems including: family, education, work, religion, and politics. According to Marx, society is organised by its economic system into two broad strata: the owners (who Marx refers to as the 'capitalist class' or 'bourgeoisie') and the non-owners (referred to as the 'working class' or 'proletariat'). Society, according to Marx, is constructed whereby the owners always benefit while the workers suffer. Therefore, the Marxist view generally stratifies society by 'class', generally only into two classes, and emphasises the struggle between them. However, Marxist theories struggle with modern social phenomena such as the rise of the 'middle class', although it may highlight possible causes of inequalities in society (Sweeney *et al.*, 2003).

One of the most famous critics of Marx was Max Weber (1846-1920). Weber argued that Marx placed far too much prominence on 'class' groups within society and on structural deficiencies of capitalism which created them (Weber, 1914). Weber proposed other groups are important, such as 'status' groups which, to some degree, go beyond class, and which were developments within the system where these groups of individuals share a sense of identity and common purpose. Individuals see themselves from the perspective of the group rather than from the perspective of a 'social class'. Weber (1914) was also interested in how people interact with each other and he argued that society was based on

'patterns of interactions' between individuals. Therefore, Weberian social theory broadly stratifies society by social position and status which are used interchangeably. Further, according to Weber (1914) whose work was thoroughly reviewed by Liberatos (1988), social status or position is based on three dimensions: (i) class – incorporating ownership and the economic dimension, (ii) status – prestige or honour in the community, and (iii) power – political influence. Weber described these dimensions as 'life-chances', being more about distribution of 'opportunity' than about 'exploitation'.

The Functionalist theory is most associated with Émile Durkheim (1858-1917). Its main thrust is that society is complex and made up of many systems (e.g. political, economic, education, religious, and family), but that it works through 'consensus' and co-dependencies, with each individual seen as having an equal role in society (Durkheim, 1893). Such thinking, according to Lynch and Kaplan (2000), builds on both Marxist and Weberian traditions, arguing that social stratification and resulting inequality are the 'natural' result of meritocracy in a capitalist society, but they add little to definitions of social strata themselves.

All of these theories exert an ongoing influence on sociological thinking. Weberian theories focus on individual's 'life-chances' (opportunities), and the ability for researchers to readily measure these via education, occupation, and income, has led health and epidemiology research in particular to broadly adopt a Weberian framework (Liberatos *et al.*, 1988). The US Marxist author Erik Olin Wright is one of the few to have attempted to directly capture the exploitative aspects of socioeconomic status, although application of his formulation is limited (Lynch and Kaplan, 2000). That is not to say that a Marxist approach, which takes a structural view, could not be readily applied to health outcomes and inequalities – as it has been in research on other social 'inequalities' e.g. racism, sexism (Sweeney *et al.*, 2003). A quick search of Medline revealed that there has been a considerable body of work in Russian and Eastern European journals and languages considering public health issues (particularly communicable diseases) through a Marxist framework, and one senses it is or has been a cultural reluctance to utilise these theories and approaches in the West which has seen Weberian theory prevail. Forbes and Wainwright (2001), in their damning critique on the philosophical vacuum in health inequalities research, agree that the Marxist perspective has been broadly overlooked.

A further area which these theories underpin is the terminology used to describe the social and economic factors which determine social stratification.

1.3.1.3 Socioeconomic status and socioeconomic circumstances

Part of the difficulty in this area of research is the shifting terminology. Lynch and Kaplan (2000) report the vast range of terms used in the epidemiological literature, including 'social class', 'social stratification', 'social inequality', 'socioeconomic position' and 'socioeconomic status'.

The move from 'social' to 'socioeconomic' which encapsulates more explicitly Weber's economic dimension has been a helpful addition to the terminology. Lynch and Kaplan (2000), following Krieger *et al.*'s (1997) earlier suggestion, opt for the term 'socioeconomic position', describing it as meaning 'the social and economic factors that influence what position(s) individuals and groups hold within the structure of society' – they, and others on their behalf (Muntaner *et al.*, 2004) argue that it is 'neutral with respect to relational / ordinal distinction'. But is this not the very point of studying socioeconomic factors and inequalities? – to assess the effects of socioeconomic hierarchical relationships and differences. Further, a view of social stratification in terms of 'status' remains valuable terminology, for it not only describes an individual's position in society, but captures 'standing', and one's own 'value and importance' (de Botton, 2004).

Therefore, somewhat against the grain, the terminology 'socioeconomic status' (and its acronym SES) will be used in this thesis to encapsulate the social, and economic factors that affect not only an individual's position but their standing – with 'status' better describing the hierarchy of societal positions.

In recent years, it has also become apparent that the ecological, or social environmental aspect of society are becoming important considerations particularly in relation to health – with an explosion of literature in this field (Marmot and Wilkinson, 2006). Thus, when considering both 'area' or 'place' and the individual's socioeconomic status, the phrase 'socioeconomic circumstances' will be used as it seems to encapsulate the multidimensional and complexity of the social and economic factors which influence health.

Social mobility is also an important concept and has been reviewed by Susser (1997). He describes that neither socioeconomic status nor socioeconomic circumstances are completely static dimensions, with individuals able to move both up and down social strata. However, he notes it is only over time that life chances of entire classes can change.

He also describes how monitoring the effect of social mobility on disease and vice versa may contribute to a better understanding of the distributions and causes of disease.

1.3.1.4 Poverty and deprivation

Poverty is a much debated issue, with multiple terminologies, definitions, theories and explanations, as described in an excellent discussion piece by Mooney (2003). The study of poverty, he argues is a politically motivated activity. This translates to the language, terminology and definitions employed to describe people defined as poor – often in condemning and derogatory tones: from the: 'rogues', 'vagabonds', 'idle', and the 'disreputable poor' of the 19th Century; to the 'problem families', 'dysfunctional communities', 'feral youth', 'neds and chavs', and 'underclass' of the late 20th and early 21st centuries. It may be argued that to challenge the use of such terms may seem like 'political correctness', however, such language is obviously loaded with perceptions of the causes of poverty – where the poor are on the whole blamed for their own situation.

Given the politically charged nature of this area of study, there is common agreement around the need to acknowledge the difficulty of defining poverty, both in terms of objectivity and complexity (Scott, 1994; Mooney, 2003; Mowafi and Khawaja, 2005). Simplistically, how it is defined will generally reveal an opinion on the way to address it. For example, if poverty is seen as the result of individual actions or limitations such as 'laziness' or 'failures', then policies which force employment and cut welfare benefits would be pursued. Alternatively, if poverty is viewed as a result of societal structural failures and injustice, then redistributive policies would be pursued. The complexity of poverty is highlighted by the multitude of sub-definitions.

Poverty can be defined in 'absolute' and 'relative' terms, and a brief appreciation of the historical context of the study of poverty helps with an understanding of these definitions.

The history of the study of poverty is thoroughly described by Scott (1994). He records that poverty has been studied, from as early as the beginnings of the industrialisation and urbanisation of Britain in the 19th century. The political debate which followed the early studies was also significant in that it focused on how to deal with 'the problem poor' and the 'slums' of the expanding cities. The studies which were most notable during this time were Booth's surveys of poverty in London, which found that one third of the population of London lived in poverty – and in which he was the first to define the 'poverty line' as a minimum income for a family to live on. At the same time, Rowntree (the confectionary

manufacturer) was investigating poverty in York. He studied several working class families and also defined the absolute minimum costs of living at the time. Within these studies there were emerging definitions including: the 'respectable poor', who were poor as a result of factors outwith their control; and 'the disreputable poor', who were themselves to blame for their poverty. This resulted in concepts of 'good' and 'bad' poor which perhaps still exist in some form today – and explain some of the terms outlined above.

Absolute poverty has been defined by a 'poverty line' since these early studies. It is defined by Mowafi and Khawaja (2005) as the 'set of economic resources to maintain a minimum standard of living for survival'. It has gained and maintains prominence in international agencies and human rights organisations – where poverty eradication policies usually refer to absolute poverty measures (World Bank, 2007). It has the advantage that it can be readily used to quantify a group or proportion in need and can be used to monitor the effect of policies on such a group. It is also an intuitive and readily understood measure – providing a clear tangible cut-off point for poverty. There remains considerable debate about the level at which the poverty line should be drawn.

Absolute poverty, with its poverty line, has become highly criticised as being a too narrow and almost meaningless term, with a biased definition of the minimum required for human survival (Novak, 1995). Particular criticisms centre on the real difficulty of those on the border line or just over the line and how they are perceived. Further, it is recognised as failing to acknowledge the spectrum of poverty – tending to define the poor as a distinctive group in isolation from the wider structural factors and wider determinants (Marmot and Wilkinson, 2006).

Relative poverty. Poverty is increasingly recognised and defined as a 'relative concept' after Abel-Smith and Townsend (1965) who described it as – 'saying who is in poverty is to make a relative statement – rather like saying who is short or heavy'. Relative poverty is defined by Mowafi and Khawaja (2005) as 'how worse off an individual or household is with respect to others in the same society'. They convincingly argue that relative poverty can also be seen as having a 'poverty line' – drawn so that the lowest fifth of a population are considered relatively poor, compared to the top fifth who are considered affluent.

Much debate persists over the relative merits and faults of both a relativist and absolutist perspective on poverty and its impact on health – exemplified by the *BMJ* global health debate between Judge (1995) arguing for the importance of absolute poverty, and

Wilkinson (1995) for the relative and inequalities perspective. An alternative critique of these polarised positions (which is often a circular argument) is emerging, with the interconnectedness of the definitions observed, as well as the futility of the debate. Thus, the United Nations definition of deprivation encompasses the multiple dimensions of poverty (United Nations, 1995) – although such ideas are not new (Sen, 1983).

Townsend led in the exploration of this concept of relative poverty in the UK, and in his account of 'Poverty in the United Kingdom' sets out a compelling case for defining poverty in terms of relative deprivation (Townsend, 1979). Although the terms 'poverty' and 'deprivation' are used interchangeably, it is often argued that a distinction between them should be made (Mooney, 2003).

Deprivation is a term that has flowed from a relative view of poverty, and is described as more than simply a lack of income, but as a failure to fully participate in society (Townsend, 1979). To capture this, Townsend constructed a deprivation index (initially an individual level index) which incorporated some 60 items: including material possessions as well as activities based on lifestyles and attitude surveys. While this index acknowledges that poverty is more than insufficient income, and begins to consider wider structural issues and inequalities, it has limitations in not taking into account wide diversity of lifestyles in modern Britain (Mooney, 2003). Although this index continues to be updated (Gordon *et al.*, 2000), one further criticism is that the relative measure employed confuse poverty and inequality (Mooney, 2003). However, this criticism seems to somewhat miss the point that both are connected.

More recently, deprivation has begun to be defined at multiple levels, encompassing relative income or material resources and social deprivation – and being observed not only related to individuals, but also to places, areas or environments (Macintyre and Ellaway, 2000). This concept of multiple deprivation has led, in the UK, to the development of several indices to measure this, for example, the Townsend and Carstairs Indices of deprivation, and, more recently, to the Indices of Multiple Deprivation (see Section 1.3.3.6).

Social exclusion (and the converse social inclusion) has also followed the concept of multiple dimensional deprivation and the acknowledgement that poverty is more than a lack of income. It focuses on marginalisation (Mowafi and Khawaja, 2005) and brings in a wide range of issues including social, economic, cultural, political, and environmental that prevent full participation in society. Research has begun to explore the relationships

between social capital or cohesiveness, income inequalities, and health inequalities (e.g. Marmot and Wilkinson, 2006). Policy has mirrored and partly driven the changing terminology in this field – particularly in Scotland (see Section 1.1.3.3).

1.3.1.5 Inequality

Socioeconomic inequality is best defined through examples:

'7:84' is the name of a Glasgow Theatre Company with a social justice ethos. The name describes the wealth distribution in Britain of the 1960s at the time when it was established – when 7% of the population owned 84% of the UK's wealth (7:84 Theatre Company, 2007). More recent and official treasury data (from the mid 1970s to present), from National Statistics (UK) reveal that such inequalities persist unchanged from the 1970s, with the country almost split in half – 'the haves and have-nots' (de Cervantes Saavedra, 1605) – with 50% of the population owning over 90% of the wealth, although at the most extreme end, the most wealthy 10% 'only' own just over 50% of the wealth (National Statistics, 2007a).

Another example of social and economic inequalities is the research by Conyon (2002) on the difference in pay between company directors and workers between 1994 and 2001 in the UK. He showed that the median annual company director's pay (or 'compensation' as he somewhat ironically calls it after the US English) increased from £201,000 to £416,073 over the period, an increase of 107%. The median employee pay in the same companies rose from £19,272 to £25,223 over the same seven year period – an increase of just 31%.

Globally, the picture of income inequalities is equally stark. Data from the World Bank (2007) for 2005, show that of the $45 trillion global gross domestic product (GDP), $39 trillion (86%) was held by high and upper-middle income countries, and only $6 trillion (13%) by low and lower-middle income countries – where 75% of the world's population live (World Bank, 2007).

Mooney (2003) argues that poverty and inequality are often seen as being 'inextricably linked' and that this is a result of analysis and interpretation rather than the underlying processes. Further, he notes that it is possible to have 'inequality with no poverty' but not possible to have 'poverty and no inequalities'.

Some (including the UK Conservative government of the 1980s and 90s) have argued that rising inequalities can have the positive effect of raising living standards for everyone, occasionally termed the 'trickle down effect' (after the economic theories of Kuznets (1955)). However, the reality has shown widening inequalities, leaving some falling further and further behind (Pantazis and Gordon, 2000). The positive effects of the trickle down theory are widely viewed as a 'myth' in developing countries as much as in developed countries (Arndt, 1983). Therefore, in response to Mooney's call for a clear distinction between poverty and inequality, the 'possibility' to have 'inequality with no poverty' seems remote. Poverty and inequality – in wide socioeconomic terms – seem to go hand in hand: poverty is relative afterall.

Therefore, the term inequalities, sits with relative poverty and relative deprivation as ways to define the 'gap' or the difference between the rich (affluent), and the poor (deprived) in society. It is also important to acknowledge both the social and economic dimensions to these differences.

Health inequalities follow from socioeconomic inequalities. Kawachi *et al.* (2002) provides a helpful glossary of the terminology in this field, defining health inequalities as the differences in health of individuals and groups most commonly associated (but not exclusively) by socioeconomic factors. Inequalities and socioeconomic inequalities in health are almost synonymous, such that other non-socioeconomic related inequalities usually require further definition (e.g. age- or sex-related inequalities).

Forbes and Wainwright (2001) have criticised the dearth of philosophical and theoretical thinking behind the research on health inequalities, even with regard to addressing the question 'what is inequality?' They argue that the definitions of and overall objectives related to health inequalities (research and policy) are not explicitly articulated. Anand (2002) takes this further suggesting that health inequalities need to be defined as 'inequality of what' and 'inequality among whom'. Arguing from a welfare economics perspective, he attempted to make a clear distinction between inequalities in wealth and inequalities in health – arguing that we should be more averse to the latter than the former. However, this relates to the dimension of how far 'upstream' one is willing to go in pursuit of causes, and politically, in measures to tackle such inequalities.

It is not that a theoretical basis does not exist, rather that it has not been cohesively described. Krieger (2001b), from a social epidemiology perspective, has begun to document the three theoretical frameworks employed in relation to inequalities in health –

psychosocial, social production of disease / political economy of wealth, and the emerging multi-level ecosocial approach – arguing that the last of these theories offers a potential way forward in that it encapsulates all multidimensions and factors.

The measurement of socioeconomic status and circumstances, poverty, and inequalities and their effects on health will be discussed in more detail in Sections 1.3.3, and 1.3.4.

1.3.1.6 The perspective of people who experience poverty and inequality

As with the need to ensure that epidemiology does not lose sight of the patient's experience, it is important that, from a sociological and inequality perspective, the people's perspective views and experiences of poverty are not overlooked – especially when considering more abstract concepts such as inequality. However, the people's perspectives are not overly explored in the literature.

In relation to people's perception of poverty and socioeconomic inequality, the Joseph Rowntree Foundation (Green, 2007) recently undertook a detailed investigation – 'Voices of people experiencing poverty in Scotland.' The main findings were that low income and access to services were the predominant issues, with participants often having to make choices between items and services which most people would consider essential (such as food choices, heating, and electricity).

In relation to socioeconomic inequalities and poverty, other non-scientific examples are also worth turning to, and three such pieces will be considered here. The first is the travel writer and photographer Nick Danzinger's (1996) graphical account of his journey among the 'other British…the excluded and marginalised people of Great Britain'. His time among the unemployed of the ruined manufacturing 'no-go' areas of Glasgow was enlightening if not harrowing. For example, in a conversation with Catherine, a community worker in the East end of the city, she paints a picture of despair following the industrial decline and the poverty vacuum and inequality that has replaced it: "Look at the way things are going. There's nothing for us. My granda sweated to build them ships…Now they've closed the yards. The yuppies have moved in. I'm greetin' [crying]…The lottery is our only hope." (Danzinger, 1996, p.119).

The second, is by Guardian journalist Polly Toynbee (2003), who, in 2002, spent some time living in one of the poorest council estates in London and took work on the minimum wage (then £4.10 per hour). She describes how the low paid are often caught between low

pay and job insecurity, while all around is a culture of consumerism and the corresponding temptation to borrow money. She observes how the poor are being increasingly left behind, despite 'average wealth' increasing. However, it is her descriptions of the dire conditions of the jobs she takes, such as a cleaner and care-worker, within the NHS and other public services, which are most stark and make uncomfortable reading.

Of course George Orwell (1933, 1937) had gone before them in 'Down and out in Paris and London' and 'The Road to Wigan Pier'. In the former he describes the retched poverty of London at the beginning of the 20th century. He provides enlightening insights into the dehumanising nature of poverty at that time, but spends much of the book tearing down the myths surrounding the poor and humanising the individuals: 'the rich and the poor are differentiated by their incomes and nothing else, and the average millionaire is only the average dishwasher dressed in a new suit.' (Orwell, 1933, p.107).

Evidence of people's perceptions in relation to health inequalities comes mainly from qualitative research. Popay *et al.* (1998) has led this research in the UK, with her important studies of lay belief systems and values, elucidating the mediating role of stress related to illhealth and behaviours harmful to health (Popay *et al.*, 2003). An earlier ground-breaking study by Graham (1987), investigating smoking among poor women, began to uncover that the reasons they smoked were as coping mechanisms and as a brief respite from the tough caring roles and social disadvantage they endured. Blaxter (1997) reviewed the literature in this field and highlighted the interesting perspective that people did not view their disadvantaged positions in society as affecting their health. Similar work in relation to cancer has found that people from lower socioeconomic groups have more fatalistic health beliefs (Price and Everett, 1993).

However, recent work in this area has begun to challenge the perceived health belief views of people from more deprived backgrounds as being fatalistic. Davidson *et al.* (2006) noted in an extensive piece of qualitative research in the north of England and Scotland that people were acutely aware of the effects of socioeconomic hierarchies on their health.

Further, renewed interest in this area has come through research by the Glasgow Centre of Population Health (GCPH) under their programme of work on 'people's stories and community engagement' (GCPH, 2007). As part of this research they have focused on how personal experience and socioeconomic circumstance influence uptake of health promotion advice in relation to cancer. Their findings also suggest that fatalistic health beliefs were not so prevalent in poorer communities, but rather there is an increasing acknowledgement

of the role of genetics and socioeconomic circumstances in cancer, in addition to the increasing complexity of health information which were the main factors affecting uptake of health behaviour orientated information related to cancer prevention (Rowa-Dewar *et al.*, 2007).

Wainwright and Forbes (2000) are as critical of this area of research as they were in relation to health inequalities research in general – in terms of the lack of theoretical basis, and particularly for the focus on health beliefs, while ignoring the wider structural aspects of health inequalities.

1.3.1.7 The global perspective

The global persepective on inequalities is a massive area, but the one topic which will be discussed briefly here is globalisation and its impact on societies and on global inequalities.

Globalisation, according to Giddens (1999), in social and economic terms, basically means that society is not confined to one particular country's borders. This globalised society is driven not only by the nature of international markets and financial institutions, but more by the electronic communication revolution.

Literature from the field of political science on the effects of globalisation on poverty and inequality was critiqued recently by Kiely (2005). There seems to be much debate about the effects of global inequality: with some arguing that the effects are on the whole positive and particularly that absolute poverty has reduced (Giddens, 1999), while others detail evidence that socioeconomic inequalities both within and between countries have widened since the 1980s (Kiely, 2005; Basu, 2006). However, debate remains about the causality pathway between globalisation and inequality, and on the adverse effects of global inequality. On one side, neo-liberal economies have been shown to have both higher income inequality, and higher proportions of people living in poverty compared to Christian or social democratic political economies (Navarro, 1999). On the other side, Giddens is the main advocate for theories around the acceptance of the neoliberal global dominance and the positive effects and potential of economic growth for both poverty and inequality reduction (Giddens, 1999).

The language of globalisation and global development is also important. Countries are no longer viewed as industrialised or developing, with the accepted definitions of

development status being those of the World Bank (2007): high, upper-middle, lower-middle, and low income countries.

The global strategy of the World Bank is economically focused towards poverty eradication in lower income countries rather than explicitly on the inequality between high and low income countries. It is driven by a set of targets led by the United Nations adoption of the Millennium Development Goals which aim to reduce by half the number living in extreme poverty (defined as those living on a dollar or less a day) by 2015 (United Nations, 2007). The World Bank (2006) also reviewed the evidence in relation to global poverty and inequality, acknowledging both inter- and intra-country inequalities in wealth. It concluded that life-chances and opportunities were most important, and that policy, in economic terms, needs to remain focused on reducing absolute poverty in countries, but also needs to support countries in maximising their potential income. This approach was criticised by Basu (2005) in a recent article, where he argued that such global economic policy and globalisation, which aims to increase the per capita income level of low income countries and reduce inter-country inequalities will only increase the inequalities within a country, as the incomes of unskilled labour will lag further behind skilled labour.

The World Health Organisation have also been criticised for defining and measuring health inequalities without fully considering the socioeconomic dimension of inequalities within and between countries (Szwarcwald, 2002).

In addition to the effects of globalisation on inequality, another major effect of globalisation which warrants some brief discussion is the issue of ‘cultural hybridisation’. Robertson (1992) described this phenomenon as when a country’s culture increasingly evolves with influences from that of other countries through migration. Food is a good example to illustrate this concept as pointed out by Sweeney *et al.* (2003), and is particularly apt for Scotland, and particularly for Glasgow and the West of Scotland. The preferred foods in these parts have changed over time, moving from traditional ‘mince and tatties’ (potatoes), and fish and chips (although the latter itself was imported with early Italian migrants – Devine (2006)), to curries (from India), pizzas (from Italy), and kebabs (from Greece and Turkey). It is somewhat unfortunate that the more ‘healthy’ aspects of these diets – the high fruit and vegetable intake renowned in the Mediterranean diet, and the generally vegetarian diet of the Indian subcontinent did not assimilate to quite the same degree.

1.3.2 Social and economic trends

This section reviews briefly the social and economic trends in society with a focus on Scotland, with an aim of setting the context to both measuring and relating socioeconomic circumstances and inequalities to health.

Following on from the snap shot of global inequalities presented above, socioeconomic trends have seen the world's wealth increasingly concentrated in fewer countries, and within countries in fewer individuals. Data from the United Nations Development Programme (UNDP) over the past three decades showed that the proportion of global income of the poorest 20% of countries fell from 2.3% to 1.4% while that of the richest 20% grew from 70% to 85% (UNDP, 1996). Analysis of the more recent data from the World Bank (2007) shows that these trends may be slowing with low-income countries' share of global GDP increasing very slightly from 2.5% in 2000 to 3.3% in 2006, while high-income countries' share decreased from 81.1% to 75.9% over the same period. However, these headline trends need to be observed in the context of the populations of these countries: low income countries' proportion of the global population grew from 34.4% to 36.9%, while high income countries' share fell from 16.2% to 15.4% (World Bank, 2007).

The economic and social history of recent times in the UK was outlined by Mooney (2003), and a detailed account relating to Scotland was given by Devine (2006). In brief, in the aftermath of World War Two, Beveridge (1942) aimed to purge the UK from the scourge of poverty (in absolute terms) by establishing the welfare state. The economic boom that also followed this time – peaking with full employment in the 1950s – provided a feeling that poverty, at least in Britain, was no more. However, by the mid 1960s, the major industries (ship building, coal mining, steel and iron manufacture) which drove this boom were beginning to slow in the North of Britain and in the big cities. This brought with it unemployment and concerns that the welfare state was not adequate to meet the needs of the poorest in society.

Devine (2006) describes the final quarter of the last century in Scotland as being a period of pronounced structural change, not experienced since the industrial revolution of the early 19th century. The slowdown in the major industries hit Scotland later, but ultimately harder, than in the rest of UK for three reasons (Devine, 2006): (i) these industries in Scotland and the West of Scotland in particular operated on a far greater scale than elsewhere in the UK; (ii) other regions (such as the Midlands, and the South East of

England) had adapted to consumer-based small-scale industries (such as car or electrical goods manufacture) in the early part of the 20th century; and (iii) the two World Wars fuelled industry in Scotland and the West of Scotland – particularly war ship manufacture. While Scotland tried to maintain a grip on these industries well into the 1970s, the 'critical decade', Devine (2006) writes, was the 1980s – a time when 'the old industrial structure literally melted away'. This rapid de-industrialisation process had a major impact on the socioeconomic circumstances of communities built around and on the individuals working in these heavy industries. Some have also argued that this transformation contributed to a wider impact on the Scottish identity, psyche, and confidence (Craig, 2003). However, the outcome, according to Devine's (2006) thesis, is that by the mid-1990s there was the emergence of a diverse service-based economy (such as: tourism, light manufacture, computer-based technology), accompanied by a significant increase in general affluence (demonstrated by average incomes almost tripling over the period). Nevertheless, he notes that inequalities have increased, with a polarisation of unemployment and relative deprivation to communities – which have become saddled with despair, alcohol and drugs replacing the void. To add further interpretation or at least analogy to Devine's (2006) conclusion: it is as if such communities are literally still suffering from a deindustrialisation hangover, and continuing to drink to get through it.

Further interpretation of Devine's (2006) transformation to an 'affluent society', has also come from economists, such as Layard (2005), who attempt to subjectively measure wellbeing of 'happiness' in light of economic or material prosperity. They note that while this affluence may have brought increased wealth and consumer choice, this individualism has been at the expense of community cohesion or 'social capital', and with widening socioeconomic inequality differentials.

Progress on addressing the fall-out of deprivation and social exclusion in Scotland was reviewed by Kenway *et al.* (2002). In 2002, the New Policy Institute pooled the results of a series of studies covering the first five year period of the New Labour government, to assess progress towards addressing poverty. Across 34 indicators of poverty, the report found that: seven showed some improvement; 15 remained unchanged; and six had got worse (with income inequality, low pay, and the risk of low income in this latter category). By the 2006 report, the number of indicators had expanded to 50, with 19 showing some improvement; 21 remaining unchanged or fluctuating; and only four worsening – with income and benefit take-up in this latter category (six new indicators had been introduced in 2006) (Palmer *et al.*, 2006).

1.3.3 Measures of socioeconomic status and circumstances in epidemiology

There have been a number of excellent comprehensive reviews which have extensively discussed the details, strengths, and limitations of the wide-range of measures of individual socioeconomic status (SES) and area-based socioeconomic circumstances (Liberatos *et al.*, 1988; Berkman and Macintyre, 1997; Krieger *et al.*, 1997; Lynch and Kaplan, 2000; and Galobardes *et al.*, 2006a, 2006b). This section will therefore discuss the major individual and area-based measures of socioeconomic circumstance which are readily related to health and disease outcomes and are predominant in the epidemiological literature.

1.3.3.1 Individual measures: socioeconomic status

As reviewed in detail by Liberatos *et al.* (1988), most individual measures of SES reflect the theories of Weber (Section 1.3.1.2) and to a lesser extent those of Marx. Weber stratified SES based on three dimensions, (i) class – incorporating ownership and the economic dimension, (ii) status – prestige or honour in the community, and (iii) power – political influence. It is readily apparent that these three dimensions are inter-related and overlapping. The measurement of SES via the indicators of education, occupation, and income are attempts to gauge both the class and status dimensions. As the socioeconomic domains overlap, it is evident that these three indicators are intertwined: with education generally leading to occupation and so to income. Thus it is these social, economic, cultural, and political dimensions that may impact on health (Berkman and Macintyre, 1997). These can be measured to a certain degree via the traditional individual measures of educational attainment, occupational social class and income, and those will be reviewed, by discussing their: definition, measurement, advantages, disadvantages and uses.

1.3.3.2 Education

Education is defined, in the context of socioeconomic status, as the aspect of ‘formal education’ related to the ‘systematic instruction, schooling or training given to the young in preparation for the work of life’ (Oxford English Dictionary, 2007). Berkman and Macintyre (1997) expand on this, describing it as a broad set of resources including the abiltiy to obtain knowledge and facts, learn concepts and ideas, obtain skills to access information, and gain the ability to critically evaluate information. It is a measure particularly common in Europe and North America; and according to Liberatos *et al.* (1988) it relates to the ‘status’ domain of Weber’s social theory on stratification.

Education can be measured via the continuous variable number of years of education completed, and / or via a categorical variable which includes completion of primary, or secondary, or further, or higher education. Both of these approaches, according to Liberatos *et al.* (1988) are measuring slightly different aspects of education: the continuous variable gives greater importance to the length of time spent in education, while the categorical approach captures achievements and elements of prestige.

The advantages of education as a measure of SES as detailed by Lynch and Kaplan (2000) and Galobardes *et al.* (2006a) are: it is relatively easy to measure; it is not as loaded or controversial a question as other SES measures e.g. income; it can capture SES in the early stages of the life course as it is strongly influenced by parental SES (including education); it is broadly stable across the life course; and it usually predates and to some degree determines employment and the ability to earn income.

The disadvantages, however, are: it is generally fixed in adult life and importantly, for the UK, generally shows little variance. Berkman and Macintyre (1997), discuss the example, that 81% men and 86% of women from England and Wales in the mid-20th century had left school at the statutory minimum school leaving age); it can be affected by broad cohort effects with secular changes to educational experiences being generational; it is not quite so readily transferable between different countries, cultures, and education systems as one would imagine; and it also only provides information on quantity rather than quality of education provided (Lynch and Kaplan, 2000; Galobardes *et al.*, 2006a).

Uses: Education is the most common single measure of SES used, primarily because of the ease of collection and its ready association with health outcomes and behaviours. It is often used as a measure of social class in both mainland Europe and North America. It can be used to indicate childhood socioeconomic status as part of a life course approach (Galobardes *et al.*, 2006a). It also potentially has a major effect on socioeconomic status. Lastly, it has been shown to be a powerful predictor of mortality from all causes (Berkman and Macintyre, 1997).

Effects: Education provides the resources for living, for working, for earning and so may have a powerful overall effect (Berkman and Macintyre, 1997). More specifically it may influence beliefs, attitudes and knowledge in terms of health, accessing health services, locus of control, lifestyle behaviours, coping and problem solving ability (Galobardes *et al.*, 2006a).

1.3.3.3 Occupational social class

Definition: Occupational social class is basically a means of measuring SES based on employment. It is the major historic way of social stratification in the UK and the associated Commonwealth countries. According to Liberatos *et al.* (1988), occupational social class is a reliable measure of 'prestige' which relates to the 'status' domain of Weber's social theory on stratification.

Measurement: In the UK, the system of social classification traditionally used was based on the Registrar General's Social Class (RGSC) scheme which was the official measure of social class in each Census from 1911 to 2001, and was redeveloped and updated in 1990 (Office of Population Censuses and Surveys, 1990).

The occupation groups in each of the strata are shown in Table 1.1. These strata were initially selected to group people with similar levels of 'occupational skill'. In general, each occupational group was assigned *en masse* to a specific social class. There were some conditions applied to the status of 'foreman' or 'manager': where each occupation was given a basic social status, those of foreman status were allocated to Social Class III, while those of managerial status were allocated to Social Class II.

It was also possible, via the RGSC to stratify occupations into Socio-Economic Groups (SEG). This classification aimed to focus on stratifying based on social and economic status of occupations. Seventeen groups were developed and these were based on the 1990 RGSC (Office of Population Censuses and Surveys, 1990).

Table 1.1 Social class based on occupation (RGSC)

Social Class	Descriptor
I	Professional occupations
II	Managerial and technical occupations
III NM	Skilled non-manual occupations
III M	Skilled manual occupations
IV	Partly skilled occupations
V	Unskilled occupations

The Socio-Economic Group (SEG) was developed in the UK as an adaptation of the RGSC to classify occupations in relation to both social and economic dimensions. It goes beyond the parameters of the RGSC to take into account: employment status, nature of employment organisation, and nature of work (Office of Population Censuses and Surveys, 1990). There are three levels of SEG: the full version (using all 15 codes), the collapsed seven group version (Table 1.2), and the two group version (splitting the categories into manual and non-manual). The last of these versions remains a common analysis tool (Davy, 2007).

Table 1.2 Socio-Economic Group (SEG)

SEG numbers	Descriptor
3, 4	**Professional**
1, 2, 13	**Employers and managers**
5	**Intermediate non-manual**
6	**Junior non-manual**
8, 9, 12, 14	**Skilled manual (including foreman and supervisors) and own account non-professional**
7, 10, 15	**Semi-skilled manual and personal service**
11	**Unskilled manual**

While the SEG continues to be used for national statistics monitoring in the UK (Davy, 2007), the RGSC and the SEG have recently been replaced in official statistics with a new system – the National Statistics Socio-Economic Classification (NS-SEC). This new classification replaces skill and social standing with employment relations as the main determinant of social class. This has its basis in the international seven category occupational classification of Goldthorpe (Office for National Statistics 2005; National Statistics, 2007b).

There has been much criticism of the RGSC and SEG outlined by Rose and Pavlin (1994), including: that it had been almost unchanged from 1921 (which is also a strength of the index, particularly in terms of trends over time); that it lacks a theoretical basis; that it is outdated in terms of modern occupational structures and jobs; and that it has limited appreciation of differences between individuals in the same occupation group in terms of

both education and income. Nevertheless, its empirical usefulness has seldom been questioned – and its survival and perennial use are testimony to this, particularly in examining health inequalities. Further strengths include: its ability to capture social standing and income; and that while it has predominantly been used in the UK, it has been adapted extensively in many countries (Galobardes *et al.,* 2006b).

There are many other occupational social classification schemes from across the world and these are detailed by Kaplan and Lynch (2000). In measurement terms, most use the longest occupation to determine adult SES. It is also possible to infer SES from parental occupations to children and from head of household to the household unit or other dependents (Galobardes *et al.*, 2006a). Rose and Harrison of the University of Essex are leading a collaborative to develop a pan-European occupational social classification. This European Socio-economic Classification (ESeC) is currently going through a series of validation exercises (ESeC, 2007).

In general, the advantages of occupational social class include: it is widely available in routine data (such as census and death certificates); it provides the major link between education and income – such that education determines occupation which in turn determines income; occupation is not only a major way in which society is stratified, but it is a major influence on the structure of individual's lives (Lynch and Kaplan, 2000; Galobardes *et al.,* 2006a).

The disadvantages of using occupational social class according to Berkman and Macintyre (1997) and Galobardes *et al.* (2006a, 2006b) are: the method of coding occupations to different social classes is arbitrary and somewhat subjective; each strata can be heterogenous in terms of education and incomes; a significant proportion of the population – those not in employment – are not assigned SES (including unemployed people, retired people, students, people who's work is in the home (mainly women); occupational classifications also struggle to keep up with continually evolving and more complex jobs (such as those in information and technology, or management).

Uses and effects: Occupational social class can be used to measure adult SES and is strongly associated with both income and standing which can make it particularly useful for investigating the direct effect on health of this measure. It can be used to indicate broad 'styles of life' (Berkman and Macintyre, 1997). It can also be linked to other aspects of work such as: working conditions, type and nature of work, occupational (toxic) exposures, social networks, and the relationship between work demands and control or empowerment

(Lynch and Kaplan, 2000; Galobardes *et al.*, 2006a). Further, much of the earlier evidence in terms of health inequalities comes from mortality data from death certificates which also record occupation.

Unemployment is a particular occupational classification. It has many definitions and meanings which vary in different countries, but is broadly categorised by exclusion from work, and, in the UK, attempts are made to exclude those not working on grounds of illhealth or childcare (Bartley and Ferrie, 2001). Bartley (1994) indicated that unemployement can be measured by number and or length of unemployment spell. She also proposed four potential mechanisms through which unemployment can affect health (i) relative poverty; (ii) social isolation and loss of self esteem; (iii) health related behaviour; and (iv) the effect of unemployment on future employment patterns.

1.3.3.4 Income

The third key indicator of socioeconomic status is income. It is defined in terms of material or economic resources. Its use is more common across the Americas; and according to Liberatos *et al.* (1988) it captures Weber's 'economic' and 'class' dimensions, which in turn relate to 'prestige' and 'power'. However, it is not necessarily consistent with occupations.

Measurement is usually through direct reporting of monthly or yearly income or by reporting via the selection of a predefined range of income. Further, income can either be for the individual, or more usually the household (this latter option more readily captures the income of dependents in a household including children and in particular women who may not be the main household earner) (Liberatos *et al.*, 1988; Galobardes *et al.*, 2006a).

The advantages are centred on the direct nature of income as an indicator of SES, in that it provides a measure of economic and material resources. It is also the only measure that is continuous and can fully capture the range of socioeconomic circumstances from the extremes of poverty to wealth, in addition to explicitly measuring the potential access to material products and to services (Berkman and Macintyre, 1997).

The main disadvantage is that it is a controversial indicator of SES (this was highlighted in a personal communication from Professor Graham Hart (2002), formerly of the Centre for Sexual Health Research, University of Glasgow, when he confirmed that 'people in the UK were more likely to tell you the most intimate detail of their sex lives, than tell you how

much they earned'). However, Dorling (1999) argues that this may in fact be more anecdote than evidence-based in that income data are readily obtainable. It is also the most likely measure to change over a relatively short time period, although this dynamic aspect of income is rarely considered in epidemiology (Galobardes *et al.,* 2006a). Berkman and Macintyre (1997) and Galobardes *et al.* (2006a) also point out that income only partially captures economic status since income measures do not include assets, inherited wealth, savings, or benefits. Further, income from the 'informal' or 'parallel' economy ('black market') is also not included; nor usually are the number of people supported by the income.

The uses and effects of income as an indicator of SES in epidemiological studies are that it captures information on the direct health impact of: material resources in relation to access to health enhancing experiences, commodities, food, and housing; as well as to services such as health, leisure, and possibly education. It also can be related to self esteem, social standing, and participation in society (Berkman and Macintyre, 1997; Galobardes *et al.,* 2006a).

1.3.3.5 Other individual measures

There are a vast number of other measures of individual SES which exist, in summary, they include: a wide-range of occupational indices, often country specific (Galobardes *et al.,* 2006a); indicators of wealth (Lynch and Kaplan, 2000); housing tenure, housing conditions, household amenities (Galobardes *et al.,* 2006a); material possessions, such as car ownership (Berkman and Macintyre, 1997); and proxy indicators, such as numbers of siblings, health measures (Galobardes *et al.,* 2006a).

There have also been a number of composite or hybrid measures described which include different combinations and weightings of education, occupation, and income. The two common examples referred to are the Hollingshead Index and the Nam-Power Index which are described in detail by Liberatos *et al.* (1988) and Berkman and Macintyre (1997). They describe how they may be of use in particular settings e.g. developing countries. However, Galobardes *et al.* (2006b) argue that such indices are only of historical interest as they have not been updated in recent years.

Other 'proxy' measures of individual socioeconomic status have been described by Galobardes *et al.* (2006a), these include: number of siblings (although interpretation of this

can vary in different populations and cultures), some health measures (e.g. infant or maternal mortality), or other characteristics (e.g. marital status, race/ethnicity).

1.3.3.6 Area-based measures: socioeconomic circumstances

Area-based measures, also known as ecological measures or indices of deprivation, are measures of socioeconomic circumstance for geographic areas. They have received much attention in recent years and have been reviewed in general terms by Berkman and Macintyre (1997) and Galobardes *et al.* (2006b); and in more detail with particular emphasis on the UK and Scotland, by Morris and Carstairs (1991) and Carstairs (1995). However, there is limited peer-reviewed critique in the literature of the newly developed 'indices of multiple deprivation', now in widespread use across the UK.

Following a general overview of the principles and concepts behind area-based measures, the new indices of multiple deprivation, together with the other area-based measures, will be reviewed in turn, by discussing the: definition, measurement, advantages, disadvantages and uses of each.

Area-based measures, according to Berkman and Macintryre (1997) and Galobardes *et al.* (2006b), utilise data from individuals from census or other administrative databases and aggregate the data at a usually small area level. The geographical 'areas' in question are often based on local administrative boundaries – such as postcodes or census blocks, local authority areas, health administrative areas, political boundaries (such as parliamentary constituencies and council wards), or they can also be at the regional or country level. The data used include markers of poverty or deprivation such as education levels, occupational social class distribution, unemployment levels, and housing or other asset ownership (such as car ownership). These data are then combined to characterise the area in terms of level of deprivation on a continuous scale from deprived to affluent areas. Their utility is mainly in the allocation of resources and services.

Area-based measures of socioeconomic circumstance were initially used as proxy measures of individual socioeconomic status. Thus, individuals are characterised by the aggregate socioeconomic properties of the area in which they live (be that by: postcode, local government area or other geographical area). However, the focus of research is changing to investigate the issue of the different predictive value (and by implication, causal role) of individual levels (measures) of deprivation, as compared with living in a deprived area (area-based measures) – which began with Macintyre *et al.* (1993) when they

posed the question: ‘area, class and health: should we be focusing on places or people?’ In their analysis, they recognised that area-based measures have been found to broadly reflect individual based data – but they suggested the extent to which this was the case warranted further research. This observation is well corroborated in the literature, with area and individual measures being well correlated (Diez Roux *et al.*, 2001). However, Macintyre *et al.* (1993) caution on over-interpretation with the ‘ecological fallacy’ being described as the primary limitation – whereby individuals are assigned socioeconomic status based on an area’s socioeconomic level of deprivation.

In the follow-up review, Berkman and Macintyre (1997) concluded that a key purpose of using area-based measures of socioeconomic circumstance should be that, as a collective measure, it adds explanatory power by bringing an environmental dimension that is different but overlaps individual SES. This has been demonstrated by a number of studies where the area-effect has been shown to be independent or over and above that of the individual SES effect (e.g. Haan *et al.*, 1987; Stafford and Marmot, 2003). However, sometimes it is the other way round, with the individual SES effect being independent of the area effect (Sloggett and Joshi, 1994)

However, Berkman and Macintyre (1997) caution against trying too hard to disentangle the individual from the area, for there is a potential danger in missing important interactions. Further, Macintyre *et al.* (2002), more recently, note that the relationship between individual socioeconomic status and area socioeconomic level is also more complex than often assumed. Within ‘affluent’ or ‘deprived’ residential areas, there are wide differences in the socioeconomic status of the individuals living in them.

One of the key methodological issues in using an area measurement is the choice of the size of population unit or area on which to base the measurement. Small areas have been shown to provide a more precise level of socioeconomic circumstances (Krieger *et al.*, 2002). Another potential problem, with the interpretation of area deprivation indices, is the relationship with time. For example, there is a strong concentration on present rather than past socioeconomic status, i.e. the socioeconomic circumstances of the current residence and this may not reflect the past socioeconomic level of the area, or the individual may not have always lived there. Blakely *et al.* (2004) regard not considering such time-lags as an important source of bias in social epidemiology in general and area-based measures in particular. However, areas of relative deprivation have not changed for many years. For example, recent work has shown that the most deprived areas of east London (Tower Hamlets) at the beginning of the 21st century were the same as those identified in the late

19th century – despite the area being completely rebuilt following bombing and now having a much changed population profile (Prime Minister's Strategy Unit, 2005).

On the whole, the use of area-based measures of deprivation, as measured from census variables for small geographic areas in relation to a variety of health outcomes including cancer, has long been established (Carstairs and Morris, 1991; Carstairs, 1995). The main advantage is their ready and routine availability (Information and Statistics Division, 2007a). Area measures of deprivation have been used for various purposes in the context of health services and health research (Morris and Carstairs, 1991; McClaren and Bain, 1998). They have also been a key measure for investigating health inequalities, and have been frequently used to describe material deprivation inequalities in health. The gradients which emerge are generally stable and not sensitive to minor changes in their definition and construction.

There has been much written recently on the role of area-based socioeconomic measures in epidemiology, and there is broad agreement that it is important to be explicit about the distinction, but conscious of the codependency, between people and place effects, or as Macintyre *et al.* (2002) put it – the compositional and the context. They argue for the need for explicit hypotheses and research to test the 'chains of causation' between area of residence and health outcomes.

It is recognised that social epidemiologists in partnership with social geographers in the UK lead the way in this research, with many area-based measures being developed for different settings and geographies (Berkman and Macintyre, 1997). However, Lynch and Kaplan (2000) detail the ongoing development in this field in the US. There are occasional studies utilising adhoc area-based measures in parts of Europe (van Lenthe, 2006) – although there is as yet no standard European measure. Similar indicators do not seem to be well developed for other parts of world, particularly developing countries.

Following the taxonomy of Carr-Hill and Chalmers-Dixon (2002, 2005), there are two broad categories of deprivation index in the UK. The first is the 'traditional' measures which mainly utilise data from the decennial census, while the second is the newly developed indices which use census data together with information from other sources.

In the subsequent sections, the two main traditional deprivation indices used in epidemiological research in the UK will be reviewed – the Carstairs and Townsend indices. Thereafter, the newly developed indices of multiple deprivation will be discussed.

1.3.3.7 Carstairs index of deprivation

Definition and origin: Originally developed by Carstairs and Morris (1991) to measure deprivation in Scotland and known as the Carstairs Morris index of deprivation, it frequently became shortened to the Cartairs deprivation category, or 'DEPCAT', or Carstairs index. It followed the development of the Townsend Index for the north of England (Townsend *et al.*, 1988 – see below), but unlike Townsend, it avoided using the number of private households as the denominator and also did not use owner-occupied housing tenure as a variable (Carstairs and Morris, 1991; Elliot *et al.*, 2000).

Derivation: The Carstairs index is a small area-based measure of socioeconomic circumstances. The geographical areas are usually based on postcode sectors – that is areas with identical postcodes except from the last two characters (e.g. 'G84 9_ _' omitting the last two letters of the postcode) of which there are almost 1,000 in Scotland, with an average population of around 5,000 (McLoone, 2004). The main source of data about the socioeconomic characteristics of each area is the 10-yearly Census – which records information about the social and economic characteristics of the resident population. There are now indices for 1981, 1991, and 2001 census years. The Carstairs index is based on four variables from the Census: male unemployment rates; the proportion of households where the main earner is in social class IV and V; the proportion of people in private households with no car ownership; and a measure of overcrowding – the proportion of people living in private household with a density of more than one person per room (Carstairs and Morris, 1991). Each of these four indicators were equally weighted and the sum equals the Carstairs score (Carstairs and Morris, 1991). McLoone (2004) reports that these scores have been divided into seven categories by convention – which are arbitrarily based on the summed scores rather than on equal proportions of the population (with DEPCAT 1 representing the most affluent postcode sectors and DEPCAT 7 the most deprived). However, there is increasing recognition that standardising the scores to equal proportions of the population either into quintiles (20%) or deciles (10%) would provide a more intuitive method of stratification (McLoone, 2004).

McLoone (2004) also describes how the index has evolved with each census, to take into account minor changes in the census questions – particularly between 1991 and 2001 and the shift in occupational social classification from the RGSC to SEG. However, following analysis, he reports high correlation between the 1981-, 1991-, and 2001-census-based Carstairs scores.

Advantages and uses: The Carstairs index of deprivation has become widely used particularly in Scotland (McLaren and Bain, 1998; Information and Statistics Division, 2007a) and also in areas of the UK (particularly the north of England (e.g. Greenwood *et al.*, 2003) – where it has provided valuable insights on the distribution of health and disease in the population, and in examining and allocating health care resources.

The disadvantages of the index were reviewed in detail by the Scottish Executive Health Department Measuring Inequalities in Health Working Group (2003), and are common to all area-based measures. In summary, they are: (i) postcode sectors generally do not have populations which are socially and economically uniform; (ii) many postcode sectors will contain a mix of relatively deprived and relatively affluent households and individuals; (iii) they underestimates the extent of deprivation (due to convergence to the mean at the extremes), which if individual-level measures were available would be more apparent.

The census variables used within the Carstairs index vary somewhat from other area-based measures (e.g. Townsend), but the most contested variable is the use of car-ownership – on the grounds that while car ownership may be a relevant indicator of deprivation in urban areas, it is perhaps less suitable in rural area, where car ownership is essential given the limited availability of public transport. Moreover, there is no consideration given to the make or age of the car in this variable (Levin and Leyland, 2005).

Finally, while McLoone (2004) showed that the Carstairs index was stable when comparing the data at each 10-year census, it still has to be assumed that for an individual postcode sector, the relative socioeconomic level is stable between each census.

1.3.3.8 Townsend deprivation index

Definition and origin: The index developed by Townsend *et al.* (1988) precedes that of Carstairs, and built on the Department of the Environment (DoE) Index (Elliot *et al.*, 2000).

Derivation: Townsend *et al.* (1988) and Elliot *et al.* (2000) describe how the index is calculated from census data, including the variables: the proportion of economically active residents who are unemployed; the proportion of homes that are not owner-occupied; the percentage of households with no car; and the percentage of (overcrowded) households with more than one person per room. The important distinction of the Townsend index is that the denominator is all private households, so the index is not individual-based but

rather household-based. Each variable is given equal weight, standardised and summed in a statistical model to give a Townsend score. The scores are continuous, with areas with increasing positive scores considered relatively deprived and areas with decreasing negative scores considered relatively more affluent.

Townsend scores are usually calculated at the levels of enumeration district (about 450 people in 200 households) or ward level (about 5500 people in 2400 households), and can be determined from an individual's postcode (Adams *et al.*, 2005a). For the purposes of analysis, the Townsend scores are usually divided into quintiles (Aggarwal *et al.*, 2003).

Advantages and uses: Townsend set out to measure characteristics of areas of deprivation, rather than characteristics of individuals of low socioeconomic status (Townsend *et al.*, 1988). Thus, there was a concentration of area or household deprivation variables at the expense of individual criteria such as single parents, ethnic groups, and the older population (Elliot *et al.*, 2000). One of the main advantages of the Townsend index is that it has been widely used in health inequalities research across England and Wales, with its primary use being as a proxy measure for individual level deprivation (e.g. Aggarwal *et al.*, 2003; Feltbower *et al.*, 2003).

Disadvantages: Even although the Townsend index utilises small areas, such as enumeration districts and electoral wards, these areas are not necessarily homogenous with respect to socioeconomic levels. Carr-Hill and Chalmers-Dixon (2002) are also critical of the Townsend index on several grounds, including: its theoretical basis – particularly related to applying an area-based measure to individual socioeconomic status as it is often used; the time-lag due to relying on census data which can be up to 12-years old before new data are available; and the particular inaccuracies when applying the index to urban mobile populations. Martin *et al.* (2000) also criticise the Townsend index as misrepresenting deprivation in rural areas.

1.3.3.9 Other 'traditional' area-based measures

A large number of other 'traditional' deprivation indices have been developed in the UK, but they are more of historic interest. They have been reviewed by Elliot *et al.* (2000) and Carr-Hill and Chalmers-Dixon (2002), and in summary, they include: the Department of Environment (DoE) index; the Underprivileged Area (UPA) score – also known as the 'Jarman index'; and Gordon and Forrest's 'Matdep index' – a local authority housing stock index. An important aspect of these indices and the Carstairs and Townsend indices

described above is that they are all are census-based indices, in that they utilised variables and data from the census.

A number of indices which utilise non-census-based data or census data in combination with other information also exist, these include: the Breadline (Britain) index, the Health Poverty Index; the Arbuthnott resource allocation formula for allocation to Scottish Health Boards; and also the numerous recently developed indices of multiple deprivation. This latter group will now be discussed.

1.3.3.10 Indices of Multiple Deprivation

The UK Indices of Multiple Deprivation include: the Index of Multiple Deprivation (England), the Welsh Index of Multiple Deprivation, the Northern Ireland Multiple Deprivation Measure, and the Scottish Index of Multiple Deprivation (SIMD). Occasionally they are collectively referred to as the Oxford Indices, having been developed by the same research group, the Social Disadvantage Research Centre (SDRC) at Oxford University. These indices have much in common, with the main variation being the data used in each index, which varies by the data available in each area (Carr-Hill and Chalmers-Dixon, 2002). However, the one disadvantage is that they are not directly comparable and there is not one index available that can be used for the whole UK. The SIMD will be discussed in detail here.

1.3.3.11 The Scottish Index of Multiple Deprivation

Definition and origin: The prototype index for utilising non-census related information in an area-based measure of multiple deprivation was the Scottish Area Deprivation Index, developed by Kearns *et al.* (2000). It was based on postcodes, focused on urban deprivation, and contained six domains: housing, health, education, crime, labour market, and poverty. Despite not including any census data, Carr-Hill and Chalmers-Dixon (2005) found it correlated highly with the traditional census-based indices including Carstairs.

Shortly after this, the Department of the Environment, Transport and the Regions (DETR) in conjunction with University of Oxford's Social Disadvantage Research Centre (SDRC) developed indices for measuring multiple deprivation at the small area level in England (DETR, 2000). Following this, in 2002, the Scottish Executive commissioned the SDRC to develop a new index of deprivation for Scotland. The remit was to produce an index meaningful for the whole of Scotland and to address the concerns of the traditional

measures of deprivation, particularly around: the size of the geographic areas used; the lag-time of 10-years between censuses; the limited number and choice of variables which may not reflect the wider definition of deprivation; and the specific limitation of the traditional measures in terms of capturing rural deprivation (SDRC, 2003). Advances and developments in the concept and measurement of 'multiple deprivation' had made this development possible (Noble *et al.*, 2000). In addition, advances in the collection and use of non-census data, including health and local authority administrative data and social security information enabled this project to advance (SDRC, 2003).

The outcome of this commission was the 'Scottish Indices of Deprivation 2003' (SID-2003) which calculated an overall index available at the electoral ward level (SDRC, 2003). It was comprised of five separate domain indices: 'income deprivation', 'employment deprivation', 'health and deprivation and disability', 'education, skills and training deprivation', and 'geographical access to services deprivation' (SDRC, 2003).

The SID-2003 was the precursor to the Scottish Index of Multiple Deprivation 2004 (SIMD). SIMD-2004 was produced by the Scottish Executive. It was developed to the level of the 'data zone', the new small-area geography derived as part of the work for the Executive's Scottish Neighbourhood Statistics (2004) project. The SIMD-2004 was broadly similar to SID-2003, but used slightly different domains and indicators. As well as the new overall deprivation index, separate indices for the six different domains used in its calculation were made available, these included: income, employment, housing, health, education, geographic access and telecommunications (Scottish Executive, 2004c).

The overall SIMD-2004 is calculated for each data zone (n=6505, median population=769) by combining individual scores from the several indicators within each domain to produce a single deprivation score for that data zone. The score ranges from 0.54 (least) to 87.6 (most) deprived. Each data zone's score is then ranked, and in practice, these ranks are divided in quintiles, SIMD-1 (most affluent) to SIMD-5 (most deprived), or deciles of the whole Scottish population.

Postscript to the work undertaken within the time frame of this thesis, the SIMD-2006 has recently been produced which builds on the SIMD-2004 by updating the data in the six deprivation domains, and also adding a seventh new 'crime' domain (Scottish Executive, 2006b).

Uses: The SIMD is the official method of government planning and resource allocation in Scotland (Scottish Executive, 2004c). The SIMD-2004 is increasingly being utilised in the literature in examining health inequalities, access to health services (McConnachie *et al.*, 2003; Macintyre *et al.*, 2005; Leyland *et al.*, 2007; Woodward *et al.*, 2007), and by local authorities (Perring, 2006).

Advantages: The increasing wide-spread use and role of the SIMD in all layers of government will begin to unify the somewhat disparate and adhoc nature of the multiple deprivation indices previously used.

Disadvantages: There is only limited literature available which examines the effectiveness of the SIMD in terms of: assessing its comparability with the Carstairs traditional area-based measure in Scotland; exploring its effectiveness for rural and urban deprivation; or assessing the effects of the specific domains – particularly the health domain and the potential for 'mathematical coupling' of linking a deprivation index with a health domain to a health outcome.

Part of the reason for the limited research is due to the recency of the developments of the index, as highlighted by Leyland *et al.* (2007) who used Carstairs in their analysis of all cause mortality over the past two decades, and were only able to utilise the SIMD for similar data from 2000-2002. From the limited research available which examines the validity of the SIMD, Perring (2006) found that the SIMD was not suitable for fully gauging rural and remote deprivation; Macintyre *et al.* (2005) found no difference between SIMD and Carstairs in their study of access to out-of-home food outlets; and McConnachie *et al.* (2003) removed the health domain in their analysis of the distribution of GP practices in Glasgow, but did not test the effect of this.

One general review into the validity of the SIMD was undertaken by Bramley (2005). The main findings were that on the whole the SIMD is an appropriate and successful tool for identifying multiple deprivation at the small area level and has major potential for future resource allocation. The main issues he identified were related to its limited utility in remote areas and for comparisons over time (historically). He also highlighted the need for further research and validation to be undertaken.

There is more work exploring the strengths and limitations of the (English) Index of multiple Deprivation (IMD), from which inference can be drawn. Jordon *et al.* (2004) analysed the effects of the Index of Multiple Deprivation 2000 (for England) and found

that it was comparable with Townsend, overall, in terms of measuring premature mortality and performed better than Townsend for measuring inequalities in health in rural areas.

One of the key criticisms of the new indices of multiple deprivation, first identified (but not examined) by Jordan *et al.* (2004), is the inclusion of the health domain and the concern of 'mathematical coupling' – the phenomenon whereby two variables will inevitably correlate if they share elements of each other. Adams and White (2006) recently explored this in a detailed analysis of the effects of the health domain within the (English) IMD-2004. They found that for analysing inequalities in census-based self-reported health there was practically little effect on the inequalities gradient with removing the health domain from IMD, compared to the full IMD. They conclude that the health domain has a sound theoretical base – particularly when considering a full definition of deprivation. However, they urge caution in its utility when measuring and interpreting health inequalities.

1.3.3.12 Other (UK) Indices of Multiple Deprivation

Following the initial IMD for England (DETR, 2000), a new Index of Multiple Deprivation was developed for England in 2004 (IMD-2004). It is based on small geographic areas known as Super Output Areas (SOA) and is made up of seven domain indices: income deprivation, employment deprivation, health deprivation and disability; education, skills and training deprivation; barriers to housing and services; living environment deprivation; and crime. The overall IMD is conceptualised as a weighted area level aggregation of these specific dimensions of deprivation (Neighbourhood Renewal Unit, 2004). Separate indices have been developed in Wales, the Welsh Index of Mulitple Deprivation, WIMD-2005 (Welsh Assembly, 2005), and in Northern Ireland, the Northern Ireland Multiple Deprivation Measure, NIMDM-2005 (Northern Ireland Statistics & Research Agency, 2005).

1.3.3.13 Proxy area-based measures

Finally, consideration needs to be given to other geographic areas – which are proxy measures of the global level of socioeconomic circumstances. These include: global regional comparisons (e.g. 'developing and developed countries' – Leon and Walt, 2004) inter-country level comparisons (e.g. countries ranked by GDP or by level of income inequality – Wilkinson, 1992); intra-country comparisons based on region (e.g. the north-south divide in the UK – Doran *et al.*, 2004).

1.3.3.14 Choice of individual and area-based measures

Individual: There is wide-agreement that there is no one individual measure of SES which is the 'best' (Lynch and Kaplan, 2000). As has been shown above, each individual indicator measures different aspects of socioeconomic status, but there is a degree of overlap. Moreover, different indicators will be more suitable to different studies, depending on the study aims and design, and specifically to the health outcome of the study subjects. The life course or life-stage of the study subjects has received particular consideration in the review by Galobardes *et al.* (2006a). They concluded that different indicators are more suited to different stages of the life course, but ideally multiple indicators across the entire life course should be adopted for validation and to avoid residual confounding. The potential or hypothetical pathway between SES and the health outcome also needs to be considered *a priori*.

Area: Several studies have attempted to assess the differences in outcomes from different area-based measures. Morris and Carstairs (1991) found in correlation analysis with Scottish data that both the Carstairs and Townsend indices compared favourably to other (traditional) indices available at the time for identifying area levels of material deprivation. However, Carstairs performed better in terms of correlations with health data. Later Bradley (1999), found that for the mixed rural and urban areas of Northamptonshire, England, Carstairs and Townsend and other traditional indices were not as consistent at capturing deprivation as a simpler index of household income levels. The Townsend index was found to be robust at correlating with all cause health mortality in a UK wide of analysis by Davey Smith *et al.* (2001). However, they tested a newly developed index of 'social fragmentation' and found it to highly correlate with suicide. The only other study to actively have compared area-based socioeconomic measures was the systematic analysis undertaken in the US by Krieger *et al.* (2002), in which they analysed a wider range of measures (including US-versions of Carstairs and Townsend) in relation to disease specific mortality data. They found that measures were more robust when they had: a specific economic deprivation element; were based on smaller areas; and, rather than based on quintiles, had *a priori* cut-off points – e.g. proportion below the poverty line was consistently found to identify area-based socioeconomic inequalities.

From these studies, it seems that the choice of area-based measure depends on the research question. Macintyre and Ellaway (2000) point out that the interpretation of area-based measures is as important as the measure used.

Thus far, there has been limited comparative analysis using the newly developed indices of multiple deprivation, although it has been widely adopted in both practice and research. Comparisons with traditional indices would seem warranted.

Mulilevel: When both individual and area measures are used within the one study this is referred to as a multilevel analysis. Diez Roux *et al.* (2001) found in a pooled-secondary analysis of three cardio-vascular epidemiological studies in the USA that area and individual level measures of socioeconomic position were correlated, but far from perfectly correlated. Their research suggests that there are limitations of using measures at one level as proxies for measures at another level in causal epidemiological investigations and suggest that it may often be analytically possible to separate out the contributions of measures, at both levels, to outcomes. They go on to discuss that the variability of individual measures of social class within areas is the inherent limitation in using area-based measures as proxies for individual social class. However, conversely, they find that the variability of area socioeconomic measures within individual measures, suggests that area variables may provide information on socioeconomic circumstances not captured by individual measures (Diez Roux *et al.*, 2001).

There are two main factors that could be considered when using area-based measures at the individual level (Macintyre and Ellaway, 2000). Firstly, one could infer that an individual living in an ‘affluent’ area is ‘affluent’ and so commands a high income or has high socioeconomic status. Or, secondly, one could use an area-based measure directly as an ecological measure such that the inference from living in a ‘deprived’ area extends to the attributes of the physical and social environment such as difficulties accessing: health and social services.

Purely focusing on an individual’s social class is limiting. It masks the fact that people who live in the same area can share many of the socioeconomic circumstances not reflected by individual measures, in that the socioeconomic environment confers risk apart from or over and above that of their individual social class (Evans and Stoddart, 1990).

The hypothesis associated with an area-based measure of social class is that the individual’s living environment area affects health, such that the resources, services to which they have access, and the ‘stresses’ (e.g. insecurity of work, unemployment, fear of crime, debt, social capital / community cohesion) which individuals in an area are collectively exposed to, all interplay with health and wellbeing. Moreover, these area-based measures are based on more than an individual’s socioeconomic status. For example

'affluent' individuals living in 'deprived' areas may share more experiences, and circumstances than their affluent counterparts living in affluent areas.

It is this potential interplay between individual SES and area-based socioeconomic circumstances which may interact synergistically to increase individuals disadvantage and ultimately health risk. Taking diet as an example: healthy food may be relatively less accessible, less available and more expensive in deprived areas.

1.3.4 Socioeconomic status, socioeconomic circumstance and health

Using the measures described in Section 1.3.2, the association between health and socioeconomic status and socioeconomic circumstances will be considered briefly.

There are well established relationships between the individual measures of socioeconomic status: educational attainment, occupational social class, and income levels, and health and disease.

Berkman and Macintyre (1997) and Lynch and Kaplan (2000) outline how education can be related to health outcomes, in that it reflects early life circumstances, and can have influences on adult health, in addition to shaping occupation, income prospects, health knowledge, attitudes, and behaviours, and on social and psychological resources. They note that in life course terms, it can represent the transition acquired from parental socioeconomic status to that achieved as an adult.

Occupational social class can relate to health in several different ways. There is the potential for different levels to confer different: social and economic advantage (Berkman and Macintyre, 2007); work environments – including work related stress, work empowerment, and work relations (Marmot *et al.*, 1997; Marmot *et al.*, 2006); types of work – including manual and non-manual labour (Menvielle *et al.*, 2004), and occupational exposure to harmful toxins (IARC, 1972-1995).

The relationship between levels of income and health have consistently been demonstrated, such that with decreasing levels of income, comes increasing levels of illhealth and disease (Kawachi, 2000). Income can potentially influence health by providing access to material resources and to services, such as health care or leisure activities, in addition to influencing health behaviours (Lynch and Kaplan, 2000).

The circumstances in which people live, the places (or areas), and the organisation of society or the social environment around them also affects people's health (Krieger, 2001b; Macintyre *et al.*, 2002, 2003). The area effects which can impact on health include: standard of housing, employment opportunities, leasure and recreation opportunities, access to healthy commodoties particularly foods, level of crime in the area, and physical environmental pollution. Macintyre and Ellaway (2000) describe how the socioeconomic circumstances of an area can potentially impact on individual socioeconomic status, through opportunities for work in an area, and vice versa individual socioeconomic status may determine what kind of area one lives in. They describe the distinction between individual and area somewhat artificial and while supporting the efforts to unravel the relative importance of the area or the individual, they urge consideration of the interconnectedness of the two socioeconomic levels.

In terms of the area socioeconomic effects, attention is also turning to the wider area or country context. For example in the UK and Scotland, the differences between urban and rural socioeconomic area effects are being explored (Bradley, 1999; Levin and Leyland, 2005, 2006). Further, the international context is increasingly being considered, including, for example, country levels of inequality in Wilkinson's (1992, 2005) research, or the attention being given to the difference in cancer incidence and mortality between low and high income countries by IARC (Parkin *et al.*, 2003).

Regidor (2006) throws 'the social determinants of health' into the mix – bringing a further layer of complexity to the health- socioeconomic status / circumstances relationship. This is more a conceptual, and to a degree, a terminology problem. He notes that the social determinants of health have a number of definitions themselves (e.g. Evans and Stoddart, 1990; Marmot and Wilkinson, 2006), many of which overlap or relate to socioeconomic measures, but many are not fully or directly captured by these (e.g. social institutions, transport, housing conditions, pychosocial stress, poverty and inequalities).

1.3.5 Measurement of socioeconomic health inequalities

This section will expand on the issue of the measurement of health inequalities, and how this relates to the measurement of health outcomes in relation to the measures of socioeconomic status described above.

Over the past two decades there has been an explosion in the quantity of literature in the field of measuring health inequalities. Research in the field of health economics, began to

recognise the importance of the measurement of income-related inequalities in health. Sen (1983) was one of the pioneers of this, with his examination of relative poverty and inequalities. Wagstaff *et al.* (1991) then explored the measurement of inequalities in relation to health and reported that different measures could provide different outcomes. Mackenbach and Kunst (1997) took this further and reported 12 types of summary health inequality measure, concluding that different conditions and study aims will merit different approaches, and that in practice more than one measure may be selected not only to compare findings but to elucidate different potential explanations for the inequality.

By the turn of the century, Kawachi *et al.* (2002) and then Regidor (2004a) detailed the key outstanding debate in the area of measurement of inequalities as being whether it should: (i) focus on describing the distribution of health across individuals in the population, vs. (ii) measure the socioeconomic group differences in health. This debate is somewhat confusing, and not helped by the labels given to each approach: (i) inequality, vs. (ii) inequity (Kawachi *et al.*, 2002); and (i) inequality among individuals, vs. (ii) inequality among groups (Regidor, 2004a). This latter definition could be extended incorrectly to the belief that the measurement of health inequalities is different whether individual measures of socioeconomic status or area-based measures of socioeconomic circumstances are used. The approach to the statistical analysis of health inequalities is similar with both types of socioeconomic measure, however, different meanings can be extrapolated, and moreover multilevel analyses can be employed to assess both individual and aggregated or area-based measures within the one study. Both Kawachi *et al.* (2002) and Regidor (2004a) agree that both approaches, however defined, are complementary.

Regidor (2004a, 2004b) attempts to define a rather complex taxonomy to classifying the many statistical measurement techniques of health inequality. He divides measures into four broad categories: (i) measures of inequalities in health ‘in the strict sense’; (ii) measures of association; (iii) measures of potential impact; (iv) measures based on the ranking of socioeconomic variable. While this helps with the distinction of distribution of health variable and measures that examine the difference in health among various levels of a socioeconomic variable, it adds little to intuitively understanding and describing inequalities.

Thus, the more familiar categorisation of Mackenbach and Kunst (1997), used in the UK (Carr-Hill and Chalmers-Dixon, 2005) and widely employed in Scotland (Scottish Executive Health Department Measuring Inequalities in Health Working Group, 2003), will be adopted here, under the headings: (i) simple measurement techniques; and (ii) more

complicated measures. The areas where Regidor (2004a, 2004b) has expanded on these two categories will also be acknowledged.

1.3.5.1 Simple measures of health inequality

To understand health inequalities, basic descriptions and comparisons of health status across different socioeconomic groups are the important starting point (Carr-Hill and Chalmers-Dixon, 2005). Simple measurement techniques are defined by Mackenbach and Kunst (1997) as those which can be easily calculated and offer straightforward interpretation.

The socioeconomic groups can be either individually- or area-based, depending on the unit of observation in question and / or variables available, but there is usually a focus on the differences between the lowest and highest groups. Simple measures fit into the measures of association defined by Regidor (2004a, 2004b).

The differences between socioeconomic groups can be expressed in absolute or relative terms (Scottish Executive Health Department Measuring Inequalities in Health Working Group, 2003). Absolute measures focus on the absolute difference between these groups, while relative measures are most common and usually focus on the ratio between the lowest and highest socioeconomic groups. Both approaches can be used together, but can provide quite different information on inequalities.

The main simple measures of health inequality are: (i) the rate difference between the lowest and highest socioeconomic group; (ii) the rate ratio of lowest versus highest socioeconomic group; and, in addition (iii) the population attributable risk (associated with low SES) is considered a simple measure of inequality.

1.3.5.2 The rate difference in lowest and highest socioeconomic groups

The absolute difference in rates or frequencies between the lowest and highest socioeconomic groups can provide a measure of absolute inequality (which in someways is a contradiction in terms), which can gauge the extent of the range of inequality. According to Regidor (2004b), as with the relative ratios approach, it is a ‘measure of association’.

The Scottish Executive Health Department Measuring Inequalities in Health Working Group (2003) urge caution with this approach in that the absolute difference may vary over

time in the opposite direction to relative ratio or even when the relative ratio remains constant.

There is general agreement that when presenting the absolute difference, the relative ratios should be presented, although the converse does not hold – relative ratios do not always need the absolute difference presented.

1.3.5.3 The rate ratio of lowest versus highest socioeconomic group

Relative ratios between socioeconomic groups are the most common approach in epidemiology and were first defined by Mackenbach and Kunst (1997) who outline the flexibility in the choice of the two groups for this comparison. This choice can be the highest and lowest strata (also known as the range ratio), or can be more broad socioeconomic categories – involving collapsing individual socioeconomic groups or strata together. However, they urge caution with the latter approach in particular, in that it can mask the extent or range of the inequality.

Regidor (2004a) highlights the increased possibilities of the simple relative ratio approach to include: the ratio of the uppermost vs. the lowermost socioeconomic strata; the ratio of dichotomous socioeconomic variables (broad categories such as manual vs. non-manual occupational groupings); and the ratio of each socioeconomic group to a reference group. Carr-Hill and Chalmers-Dixon (2005) simplify this approach further, describing the possibility of measuring the comparison and calculating the ratio between any two socioeconomic groups. These additional perspectives and approaches offer increasing potential to observe a number of aspects within the range of inequalities. However, it is accepted that relative ratios do not fully capture all the potentially available information on inequalities.

The Scottish Executive Health Department Measuring Inequalities in Health Working Group (2003) describe an additional potential possibility, to compare (via a ratio) the lowest socioeconomic group to the national average or to a middle group in the population, as a ‘benchmark’ approach. However, they also note that there has been limited use of this approach.

Regidor (2004a) also describes the potential to express relative ratios as odds ratios, which are a proxy indicator of relative risk, being a measure of the odds of disease in those

exposed compared to those not exposed to a factor – which in this case is a level of socioeconomic experience.

1.3.5.4 The population attributable risk

The population attributable risk is a fraction or proportion described by Mackenbach and Kunst (1997) as a simple measurement technique, and by Regidor (2004b) as a measure of potential impact. Both papers detail how it is frequently used in analytical epidemiology, although it has had limited application to health inequalities research. They also note that it is basically a measure of the hypothetical reduction in disease outcomes, if the whole population were to have the (lowest) rate of those in the (usually) highest socioeconomic group (or reference group). The calculation is, therefore, the difference between the overall rate and the rate in the highest or reference socioeconomic group, and in addition it takes into account the population in each socioeconomic group.

Regidor (2004b) notes the advantage of this approach is in its implicit acknowledgement and inclusion of the whole range of inequalities in its computation. However, the main limitation is that it is not applicable to comparative studies where the reference socioeconomic group may not always represent the same proportion of individuals in different populations.

1.3.5.5 More complicated measures of health inequality

These measures employ more sophisticated techniques, usually including regression-based statistical analysis (Mackenbach and Kunst, 1997). They are more suitable where the socioeconomic variable is a continuous rather than a categorical variable, and they generally focus on the gradient of socioeconomic inequalities. In summary, the more complicated measures include: regression models of continuous socioeconomic variables, to assess: the relative ratios; absolute effects; and / or population attributable risk. In addition, the more complicated measures include the concentration index, the slope index of inequality and the relative index of inequality – all three fit in with Regidor's (2004b) definition of measures which are based on ranking socioeconomic variables.

The other group of complicated measures are those which Regidor (2004a) describes as measuring health inequalities in a strict sense. These measures aim to provide a measure of the distribution of a health variable across the population, and include the Gini coefficient, and the index of dissimilarity. Regidor (2004a) provides convincing evidence to show that

there is limited application of the Gini coefficient to assessing health inequalities, with previous definitions shown to be inaccurate, and the risk of obtaining similar values in situations where the socioeconomic gradient markedly differs (e.g. Wagstaff *et al.*, 1991). This final point is also the main limitation of the index of dissimilarity.

The general advantage of these approaches is that they provide valuable information on the extent of inequalities – particularly on the socioeconomic groups between the extremes (Carr-Hill and Chalmers-Dixon, 2005). However, the main disadvantage, in addition to their complexity is that they are not suitable for categorical variables (e.g. occupational socioeconomic status groups).

The Scottish Executive Health Department Measuring Inequalities in Health Working Group (2003) concluded that more sophisticated approaches were more difficult to present to a wide audience, which is essential for public health policy development. They, therefore, advised on the use of simple measures based on the extremes, but where appropriate, comparisons with more complex measures may be considered.

1.3.5.6 Choice of measure

It is apparent, but not explicitly described within any of the approaches (including the simple methods) of measuring inequalities, that before computing the absolute difference or the relative ratio, descriptive analysis and presentation of the rates in different socioeconomic groups could provide enlightening observations. These can then shape the analysis approach taken to ‘measure’ the inequalities.

The choice of measure depends primarily on: the nature of the data available (individual or area measures, categorical or continuous variables), the study question (absolute or relative inequalities), and the outcome required (policy development or research methodology study) (Regidor (2004a, 2004b).

1.3.6 Socioeconomic health inequalities

‘inequalities in health mirror wider injustices in society’ (Johnson, 2007)

The within country and between country picture of socioeconomic inequalities has been illustrated earlier (Sections 1.3.1.5, and 1.3.2). The question of how such inequality links to

or manifests as health inequalities has begun to be addressed both theoretically and empirically (Berkman and Kawachi, 2000).

It is also well acknowledged that the levels of individual socioeconomic status or level of area socioeconomic circumstances affect health, so that with every step down the socioeconomic hierarchy, rates of illhealth increase. This has been demonstrated for many health outcome measures and with all socioeconomic measures (Section 1.3.4). The question is to what degree the extent of socioeconomic inequality itself explains the health outcome.

Much of the between-country evidence of the effect of inequalities on health outcome comes from the work of Wilkinson (1992) in relation to income inequality and its relationship with life-expectancy. In this prominent work, he describes an inverse relationship between a country's equality (measured by the distribution of income in the population) and its life-expectancy, and demonstrated that this was independent of a country's per capita wealth. The main criticisms of such methods are related to the limitations of comparing measures of income distribution across countries (Judge, 1995). However, Wilkinson's findings are continually corroborated by different researchers using multiple methods (Kawachi, 2000). The data from income distribution from within countries is even more compelling. Lynch *et al.* (1998) found proportionally higher mortality rates in US cities with greatest income inequalities in their population.

In the UK, the 'inequality gap', measured by the inequality gradient in health by both socioeconomic levels of area-deprivation or occupational social class, is relentlessly demonstrated not only to exist but to be getting wider (Shaw *et al.*, 1999). Drilling down even further into the gradient, Marmot *et al.* (1991) have been studying health inequalities among British civil servants (none of whom could be described as being poor) since 1967. In a second similar cohort from 1985 to 1988, they found a health inequality gradient (for subjective health measures and health biomarkers) which mirrored that of both the income gradient and occupational social status gradients of civil servants.

Health inequalities are not, therefore, solely the results of the conditions associated with poverty or severe disadvantage (such as access to food, housing, transport, health care), but something to do with the relative nature of inequalities across its range. However, Kawachi *et al.* (2002) remind us not to lose sight that it is the inequalities that affect the low end of the socioeconomic scale which matter more than those at the higher.

1.4 Oral cancer

1.4.1 Cancer definitions

Cancer develops, as Weinberg (1998) simply puts it, from ‘one renegade cell’ and when ‘cells grow out of control’.

The origins of the term ‘cancer’ are in the writings of the early Ancient Greek physician and philosopher Hippocrates, who used the (Greek) word for crab ‘karkinoma’ to describe the radiating antennae-like growths extending from breast tumours (Weinberg, 1998). ‘Tumour’ is the non-specific term for a lump or swelling, and tumours are characterised as either ‘benign’ or ‘malignant’ (the characteristic of the latter being its invasiveness into surrounding normal tissue, while the former are considered ‘non-cancerous’ and do not spread (‘metastasise’) to distant parts of the body (National Cancer Institute, 2007a). The term ‘metastasis’ characterises the highest degree of tumour malignancy – and usually is the cause of death in cancer patients (National Cancer Institute, 2007a).

‘Histogenesis’ (or tissue origin) is the cancer descriptor and predictor of tumour behaviour most commonly used by pathologists. Simply, histogenesis is based on the concept that tumours behave differently depending on their tissue of origin (Barnes *et al.*, 2005). There are four further components to cancer: topography (anatomical site); morphology (cell type); differentiation; and tumour stage.

The term cancer is used to encompass a widely diverse range of diseases – almost all cells in the body can give rise to a particular form of cancer, but multiple forms of cancer can also develop from each cell type. Thus, cancer is considered primarily by its anatomical location or site, and secondly by its cell type (Percy *et al.*, 1990). The recognised standard system for coding cancer subsites and morphology, as with all diseases, is the World Health Organisation (WHO) International Classification of Diseases and Related Health Problems (ICD) – which provide a series of definition codes, now in its tenth revision (ICD-10) (WHO, 1992). There is also an International Classification of Diseases for Oncology (ICD-O) has been revised in second and third editions (Percy *et al.*, 1990; Friz *et al.*, 2000). These oncological classifications represent an extension of ‘Chapter II (neoplasms)’ of the ICD tenth revision, and offers more detailed coding for tumours both in terms of subsites and cellular morphology. These revisions followed the ninth revision of the ICD (ICD-9), and the first edition of the Oncology revision ICD-O (WHO, 1976) which was used from 1976 until 1992.

Pathologists grade tumours by grade of differentiation. Poorly differentiated tumours, where the tissues and cells do not have the same appearance as the tissue of origin, are generally highly malignant.

Tumour stage refers to the stage of tumour development at the time of presentation and clinical diagnosis: generally, the higher the stage, the worse the prognosis. Several factors contribute to tumour stage including: tumour size, extent of invasiveness, positive lymph node spread, distant metastasis (Barnes *et al.*, 2005).

Despite the diversity, all cancers have many key cellular hallmarks (Hanahan and Weinberg, 2000). However, the pathogenesis is well recognised as being a complex disease process and the aetiology as being not single causes (Doll and Peto, 1981). Epidemiologically, cancer is a significant cause of morbidity and death across the world. In developed countries, cancer is second only to cardiovascular disease as one of the leading causes of death; the picture is somewhat different in developing countries, where cancer is not a leading but an increasing cause of death (Murray and Lopez, 1996).

1.4.2 Oral cancer definition

Oral cancer itself has many definitions, based mainly on the debate around the coding of anatomical sites to include in the classification of the disease (Moore *et al.*, 2000). However, the debate perhaps lies deeper than with epidemiologists and pathologists coding of sites. Anatomists themselves seem unable to fully agree on a definition of the ‘oral cavity’, ‘the mouth’, and the ‘oropharynx’.

The oral cavity (or mouth) is generally considered to extend from the lips to the palatoglossal folds. Inferiorly, is the floor of the mouth and tongue, while superiorly is the hard palate. The buccal mucosa lines the cheeks from the commissure of the lips anteriorly to the palatoglossal fold posteriorly. The soft tissues bordering the teeth are the gingivae. The soft tissue mucosa is squamous cell epithelium, although the extent of keratinisation varies throughout the oral cavity (Bannister, 1995). The oropharynx lies behind the oral cavity – and is defined superiorly by the posterior aspect of the soft palate and inferiorly by the level of the superior border of the epiglottis (but not including the epiglottis itself). Anteriorly is the posterior third of the tongue and the isthmus of fauces and posteriorly is the oropharyngeal wall. Laterally are the palatopharyngeal arches and the tonsils (Bannister, 1995).

While these are broadly accepted definitions, they are not consistently defined in this way. The ‘major’ anatomical texts seem to be rather vague in their descriptions of the mouth or oral cavity in terms of its interface with the oropharyx. *Gray’s Anatomy* describes the boundary of the oral cavity and oropharynx as being the palatoglossal folds, and the ‘anterior two-thirds of the tongue’ being the inferior aspect of the oral cavity together with the floor of the mouth (Bannister, 1995). *Cunningham’s Textbook of Anatomy* describes the border between the oral cavity and oropharynx as being the ‘isthmus of fauces’ formed from the soft palate, platoglossal and palatopharyngeal arches and dorsum of the tongue (Johnson, 1981). Finally, *Hollinshead’s Textbook of Anatomy*, has limited mention of the posterior aspect of the mouth, describing the soft palate to be the posterior boundary, and the ‘major part of the tongue’ and mucosa of the floor of the mouth to be the inferior posterior aspects (Rosse and Gaddum-Rosse, 1997).

It seems the interface of the oral cavity and the oropharynx are not consistently defined. While, it may seem somewhat arbitrary, it also seems an overlooked fundamental anatomical issue, given the importance of coding sites. Further, histologically, the epitheilium shows no anatomical distinction between oral cavity and oropharyngeal tissue (Cawson *et al.*, 1995). Of course, it also needs to be borne in mind that cancers do not obey anatomical boundaries and often their site of origin overlaps multiple areas and are not specifiable.

It is evident that the oral cavity and oro-pharynx are also part of the continuum of the aerodigestive tract. This touches on the debate in anatomical circles of ‘structural’ vs ‘functional’. Functional or physiological definitions do not make a distinction between the oral cavity and oropharynx (Hiiemae and Palmer, 1999).

It follows that the definition of oral cancer is also variable. Oral cancer is often considered as malignant tumours (usually squamous cell carcinoma (SCC)) of the lip, mouth (oral cavity) and oral-pharynx (Slootweg and Eveson, 2005). This is usually defined by the following ICD cancer diagnostic groups: intra-oral sites (ICD-10 C00-C06), oro-pharynx (C09-10), and other ill-defined sites of the lip, oral cavity and pharynx (C14). But the parotid and other major salivary glands (C08-09), and the nasopharynx (C11), pyriform sinus (C12), and hypopharynx (C13) are usually exclude (Table 1.3) (WHO, 1992).

Table 1.3 ICD Codes for malignant neoplasms considered as oral cancer and/or oral and oropharyngeal cancer

ICD-10	ICD-9 equivalent	Site description
C00	140.0-140.9	lip
C01	141	Base of tongue
C02	141.1-141.9	Other & unspecified parts of tongue
C03	143.0-143.9	Gum
C04	144.0-144.9	Floor of mouth
C05	145.2-145.5	Palate
C06	145.0-145.1,145.6-145.9	Other & unspecified parts of mouth
C09	146.0-146.2	Tonsil
C10	146.3-146.9	Oropharynx
C14	149.0-149.9	Other & ill-defined sites of lip, OC& Pharynx

ICD – International Classification of Diseases

While the included sub-sites are anatomically diverse, cancers of the oral cavity and oropharynx are, for the most part, homogeneous with respect to descriptive epidemiology, clinical presentation and major risk factors known to be associated with their aetiology. Moreover, separate investigation of cancer of the oral cavity and oropharynx is complicated by the difficulties in assigning a site of origin to tumours that are often advanced and overlapping between the two locations (Johnson and Warnakalasuriya, 1993; Robinson and Macfarlane, 2003; Johnson *et al.*, 2005). Further, cancers at these sites are recognised as being uniquely accessible for direct visual inspection that allows a biopsy to be readily taken for definitive histopathological diagnosis (Macpherson *et al.*, 2003). In addition they are often clinically managed and treated together (Scottish Intercollegiate Guidelines Network, 2006).

1.4.3 Clinical review

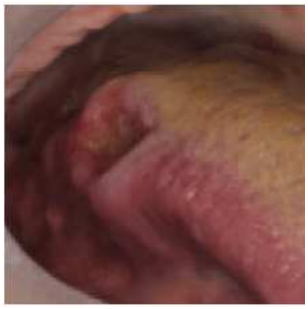
It is easy to overlook the clinical perspective when considering the epidemiology of a disease. Therefore, the clinical manifestations and the patients' experience will be summarised briefly.

1.4.3.1 Clinical presentation

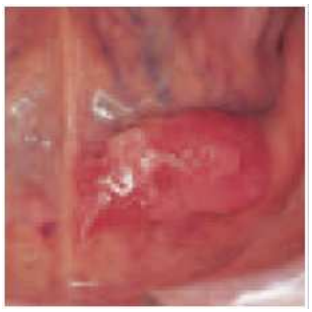
There are a highly variable number of signs or symptoms which oral cancer patients may complain of or present with, which to some extent depend on the stage of presentation. They have been reviewed for training health professionals by Neville and Day (2002) and Macpherson *et al.* (2003).

In summary, the common clinical presentation of oral carcinoma are: (i) a red patch; (ii) white and red ('speckled') patch; (iii) white patch; (iv) ulceration or erosion; (v) induration; (vi) fixation to surrounding tissues; (vii) lymphadenopathy; (viii) or a combination of these features (Figure 1.1) (Macpherson *et al.*, 2003).

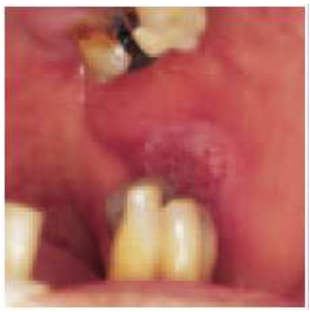
Figure 1.1 Clinical photographs of common presentations of oral cancer.



Ulcer with rolled edge - lateral border of tongue



Red patch - ventral surface of tongue and floor of mouth



Speckled patch - buccal mucosa

1.4.3.2 Potententially malignant lesions

The role of potentially malignant lesions has been reviewed by Barnes *et al.* (2005). In summary, it seems that while the majority of oral cancers may arise *de novo* (– from within normal healthy tissues), many of the potentially malignant lesions may already be squamous cell carcinomas, or carcinomas *in situ*, or show severe epithelial dysplasia as reviewed by Gale *et al.* (2005). However, some carcinomas are preceded by defined potentially malignant conditions (Neville and Day, 2002): (i) leukoplakia – an adherent white patch which cannot be diagnosed as any other disease; (ii) erythroplakia – a 'velvety' red patch which cannot be diagnosed as any other disease; (iii) speckled leukoplakia – white patches with a red component; (iv) oral submucous fibrosis – characterised by mucosal rigidity. The risk of malignant conversion of potentially malignant lesions will be considered within the review of risk factors for oral cancer (Section 1.4.5.13).

1.4.3.3 Oral cancer screening

Oral cancer screening is not the focus of this research, however, given the debate around its role in a public health response, brief consideration of the recent position of the literature on this topic is worthwhile. Screening for oral cancer is basically early detection for early intervention, and it is an instinctively attractive idea. Criteria have been developed to aid decisions about whether a screening programme is worthwhile (UK National Screening Committee, 2007). A recent report by Speight and colleagues (2006) set out to address some of these criteria particularly from a cost-effectiveness point of view. In their 'Health Technology Assessment', a range of options for oral cancer screening programmes were reviewed (including no screening, invitational screening, opportunistic screening and targeted screening), in a range of primary care settings. As part of this process, a series of three systematic reviews were undertaken.

The first systematic review investigated the sensitivity and specificity of oral cancer screening and found generally high test performance, but no additional benefit of the use of toludine blue dye. A second systematic review, pooled the evidence on the potential health benefits associated with and the effectiveness for oral cancer and pre-cancer screening and had equivocal findings (Downer *et al.*, 2006). This was in broad agreement with an earlier Cochrane review (Kujan *et al.*, 2005). The final systematic review assessed the literature on the cost-effectiveness of screening for oral cancer and diasappointingly yielded only one study where a full economic evaluation was undertaken. Additional evidence on resources and costs for management of oral cancer and pre-cancer in primary and secondary care was then gathered via questionnaires, expert opinion, and case-studies. The authors then created a cost-effective analytical decision model populated with the evidence they had compiled. The main findings were presented with a degree of caution arising from the uncertainty of the data in the model parameters. They found that opportunistic targeted screening to high risk groups particularly in General Dental Practice may be cost-effective. However, more questions remain than were possible to answer with current knowledge. These uncertainties were described as including: malignant transformation rate, disease progression, patterns of service access and referral and the full costs involved.

Thus, the jury remains out on the core issue of cost-effectiveness of oral cancer screening. Further, a crucial issue, not addressed in the report by Speight *et al.* (2006), but important when considering a screening programme, is the broader economic issue of finite resources. This necessitates consideration of the cost-effectiveness of oral cancer screening relative to other health interventions which could be offered instead (Baum, 1995).

Nevertheless, this report is a comprehensive gauge of the current research on oral cancer screening. Recommendations for further research are detailed and researchers in the field could employ this as the new baseline on the subject of oral cancer screening.

1.4.3.4 Histopathology

The histology of oral cancer is almost always squamous cell carcinoma (SCC) – accounting for over 90% of all invasive tumours at this site (Mayne *et al.*, 2006). The characteristic histopathological features of SCC include: invasion of underlying deeper tissues, varying degrees of squamous cell differentiation and cellular pleomorphism, increased nuclear staining, and tendancy to metastasise to regional lymph nodes (Johnson *et al.*, 2005).

Oral squamous cell cancer is graded histologically as: well; moderately; or poorly differentiated carcinoma (Johnson *et al.* 2005). Well differentiated tumours contain orderly stratification and heavy keratinization in a 'pear formation'; moderately differentiated tumours have prickle cells, some stratification, and less keratinisation; and poorly differentiated tumours are still recognisable as squamous cell carcinomas but manifest prominent nuclear pleomorphisms and atypical mitosis (Johnson *et al.*, 2005). This information is an important part of pathological reporting of oral cancer, although there is limited evidence of an association between differentiation status and clinical outcome or treatment response (Mao *et al.*, 2004). In addition, Cawson and colleagues (1995) argue that the severity of dysplasia related to malignant potential cannot be objectively quantified and a significant proportion of dysplastic lesions either remain static or even regress. There remains a lack of studies which follow-up large series of dysplastic lesions and attempt to assess the association between histological features and whether malignant change is observed.

The patterns of lymphatic spread – one of the primary routes of oral cancer spread – were reviewed by Johnson *et al.* (2005). As oral cancers spread through the lymphatic system, lymph nodes in the submandibular region and deep cervical chain may be palpable. Cancers of the tongue and floor of the mouth show a higher tendency to regional metastasis than cancers of the lower lip. It should be noted that cancers may show ipsilateral, contralateral or bilateral lymphatic spread (Johnson *et al.*, 2005).

The presence of a lymphocytic response may have prognostic value, as does the manner of invasion (pushing or spreading) (Johnson *et al.*, 2005). Spread can occur by local

infiltration, lymphatic drainage (to cervical nodes in the first instance) and late spread via the blood stream. A recent review by Woolgar (2006) of the prognostic value of histopathological features related to the primary tumour and the cervical lymph nodes picked out tumour thickness and extracapsular nodal spread as the most important 'prognosticators'.

The molecular biology of oral cancer is also increasingly beginning to be understood as comprehensively reviewed by Hunter and colleagues from the University of Glasgow (Hunter *et al.*, 2005; Hunter *et al.*, 2006).

1.4.3.5 Diagnosis

Diagnosis of early lesions, according to Cawson *et al.* (1995), depends on a high index of clinical acuity and a readiness to biopsy lesions on suspicion. Tissue biopsy is the 'gold-standard' required to diagnose oral cancer. The tissue specimen taken then undergoes histopathological processing and examination to determine the pathological diagnosis.

Until recently, histological examination of biopsies and 'invasive' imaging techniques (e.g. radiology) have been the only methods of diagnosis and assessment of tumour characteristics. Latterly, there has been increasing interest in optical spectrospcopy systems to provide real-time, non-invasive and *in situ* tissue diagnosis according to Swinson *et al.* (2006).

Clinical assessment, staging, and treatment are topics out with the scope of the thesis.

1.4.3.6 Prognosis

Literature on prognosis for patients with oral cancer will be considered in detail in the review of the epidemiological data on survival (below). However, in general, the prognosis following oral cancer diagnosis is widely recognised as being poor (Soutar and Robertson, 2001). The literature on quality of life related to oral cancer is beyond the scope of this thesis.

1.4.4 Descriptive epidemiology of oral cancer

1.4.4.1 Definitions

Methodologically, descriptive epidemiological research into oral cancer is complicated by the previously described multiple anatomical subsites and definitions which have led to diversity in reporting in this field (Moore *et al.*, 2000) (see Section 1.4.2). The possibility of some degree of misclassification of the site of cancer origin should always be considered. Separation of oral cancer from pharyngeal cancer is virtually impossible and has rarely been attempted (Franceschi *et al.*, 2000). Moreover, the difficulty in assigning a precise site of origin for many tumours of the head and neck, or upper aerodigestive tract is well recognised (Franceschi *et al.*, 2000; Slootweg and Eveson, 2005). This is compounded by many of these tumours overlapping multiple sites, and is increased for larger tumours. Therefore, detailed descriptive epidemiological subsite analyses for subsites such as the tongue, and floor of the mouth are particularly inhibited. Oropharyngeal separation from the rest of the pharynx is also difficult and is resultantly less common. However, it also well recognised that more precise separation and subsite analysis would be undoubtedly of additional interest (Boyle *et al.*, 1990; Franceschi *et al.*, 2000).

Correspondingly, there have been limited descriptive epidemiological investigations of oral cancer by a combined or separate oral cavity and oropharyngeal definition, with some notable exceptions (Møller, 1989; Macfarlane *et al.*, 1994a; Boyle *et al.*, 1990; Hindle *et al.*, 1996).

The vast majority of the descriptive literature describes oral and pharyngeal cancers together – with no distinction of oropharyngeal from the rest of the pharynx (La Vecchia *et al.*, 1992a; Macfarlane *et al.*, 1994b; Cox *et al.*, 1995; La Vecchia *et al.*, 1997; Franceschi *et al.*, 2000; Mucci and Adami, 2002; Mayne *et al.*, 2006; Møller and Brewster, 2005). Alternatively, definitions such as head and neck cancer, or cancers of the upper-aerodigestive tract are also commonly used which encompass cancers of both the oral cavity and oropharynx but rarely separate them from other head and neck tumours – which can include a vast array of tumours, e.g.: the larynx, naso- and hypo-pharynx, and occasionally the salivary glands, and the oesophagus (Jayant and Yeole, 1987; Macfarlane *et al.*, 1996b; Notani, 2000).

In terms of the morphology (histology) within descriptive epidemiology studies, the vast majority of cancers of the oral cavity and oropharynx are squamous cell carcinoma

(Johnson *et al.*, 2005). Most descriptive epidemiology studies include all malignant or 'invasive' tumours in the sites under investigation, which approximate for squamous cell carcinomas, although, relatively rarely, malignant neoplasms do arise in the minor salivary glands and other adjacent soft tissues (Johnson *et al.*, 2005). Mostly, however, these non-epithelial tumours including those originating in the major salivary glands, jaw bones, neural, connective, or other adjacent tissues can readily be excluded from epidemiological analyses by utilising the ICD classification and limiting data examined in terms of their anatomical site (Percy *et al.*, 1990; Johnson *et al.*, 2005).

Given such a range of definitions employed, for the purposes of reporting the descriptive epidemiological literature, the definition of 'oral cancer' as described in the study will be quoted. All studies reviewed will have at least included oral and / or oro-pharyngeal cancers within their definition.

1.4.4.2 Global: incidence

1.4.4.2.1 Geographic

A detailed contemporary study of the descriptive epidemiology of the incidence of oral and oropharyngeal cancer around the world which compares country and regional variation has yet to be published. From the published data available, the incidence of oral combined with pharyngeal cancer varies markedly world-wide. Overall, it is the eighth most common malignancy, with over 400,000 newly diagnosed cases of oral cancer estimated worldwide in 2002 (Ferlay *et al.*, 2004; Parkin *et al.*, 2005). The highest rates are generally registered in a few developing countries particularly those of South East Asia and the Indian subcontinent, with the disease accounting for up to 40% of all malignancies in these areas. However, there are pockets of high incidence in western countries – in the Bas-Rhin region of France, some of the highest rates in the world are experienced: with an age-standardised incidence greater than 52 per 100,000 (Ferlay *et al.*, 2001). Across Europe, from the 1980s through to the 1990s, there was wide between-country variation in incidence reported, with some of the highest rates recorded in Southern and Central Europe, and generally lower in Eastern, then Northern European countries (Franceschi *et al.*, 2000). In the United States, between 1996 and 2000 there was an overall incidence rate of 10.2 per 100,000 for oral and pharyngeal cancer (Mayne *et al.*, 2006).

1.4.4.2.2 Sex

There are wide variations in the incidence of oral and pharyngeal cancer in men and women, with the highest male rate in the Somme and Bas-Rhin regions of France (over 40

/100,000). For females, the highest rate reported has been in South Karachi, Pakistan and in Bangalore, India (over 10 / 100,000) (Parkin *et al.*, 2005). Globally, oral and pharyngeal cancer accounts for just over 5% of all cancers in men, and 2.5% of cancers in women (Ferlay *et al.*, 2001; 2004). In developing countries, oral and pharyngeal cancer ranks the third most common cancer in males, and fourth most common in females (Parkin *et al.*, 2005), while in some countries of South East Asia it is the single most common cancer registered (Notani, 2000). In the United States, oral and pharyngeal cancer accounts for nearly 3% of all cancers in men and 1.5% in women (Ries, 2003). In Europe, in addition to the high rates in men from Bas Rhin (above), a few areas in southern and central Europe also have high rates (close to or greater than 15 per 100,000); while rates for women have been shown to be much lower than those for men, substantial variation has been reported (ranging from 0.7 in Spain to 4.6 / 100,000 in Switzerland) (Franceschi *et al.*, 2000). In all countries with oral and pharyngeal cancer data available, incidence rates are higher in men than in women. While there is variation in the ratio, in general, men have about a two-fold higher rate.

1.4.4.2.3 Age

In most countries, oral and pharyngeal cancer is rare in both men and women below the age of 45 (Ferlay *et al.*, 2001; 2004). The age-specific rates for oral cancer, as with most cancer (particularly those of epithelial tissue origin), demonstrate the marked increased incidence with increasing age. While this pattern is consistent across all countries globally, there is marked variation in absolute incidence rates at every age (Ferlay *et al.*, 2001; 2004; Ries, 2003).

Over the last few decades there have been descriptive epidemiology reports noting increases in incidence in younger adults (generally defined as under 45 years). Davis and Severson (1987) were among the first who pointed out an increasing incidence of tongue cancer in young adults in the United States – with data from the 1970s to 1980s. They reported a 13-fold increase in those aged 10-29 years (although very small numbers and no significant trend), a 1.8-fold increase in those aged 30-39 years, no change in the 40-49 age-group and a 1.2-fold increase in those aged 50 and over. These increases were all accounted for by rises in male incidence. Coleman *et al.* (1993) also picked this up in a global review publication although the age-range was a bit higher (35-70 years) – where rates had almost doubled to the end of the 1980s in males (35-70 years) in Germany, Denmark and Scotland, and parts of Spain; and in females (35-70 years) in Denmark, France, Germany, and Scotland. Similar findings have also come out of India – with Gupta predicted a ‘new epidemic’ of oral cancer in younger adults, based on projections of the

age-profile of those presenting with submucous fibrosis being greater in those under 50 years (Gupta, 1999). In Switzerland a detailed study of all cancers in those aged 20-44 years between 1974 and 1992 found that oral and pharyngeal cancers were one of the few cancers to be increasing in incidence with an almost doubling in incidence over the period (Levi *et al.*, 1995).

More recent data from the US exploring the period 1973-1997, show an almost 7% annual increase in tongue cancer incidence from 1973 to 1984 in those under 40 years, which then remains stable through to the 1990s, while in those over 40 years the incidence increased only marginally (Schantz and Yu, 2002).

Despite these increases in younger adults, the incidence rates for older adults remain significantly higher in all of these studies. The explanations for the increases in younger populations are generally unclear, with various hypotheses around behavioural risk factors proposed. Much of the descriptive epidemiology related to young adults is related to mortality data or comes from the UK and Scotand – which will be discussed below.

1.4.4.2.4 Race / ethnicity

The topic of race and ethnicity in relation to health and epidemiology was recently the subject of a considered review by Bhopal (2007). He describes the terms ‘race’ and ‘ethnicity’ as increasingly interchangeable and synonomous, and the hybrid term ‘race/ethnicity’ more frequently being adopted. In health research, the use of ‘race’ is more common in the United States, and ‘ethnicity’ in the UK. The concept of ‘race’ and its utilisation in research in general has been highly criticised (Bohpal, 2007) – particularly in terms of its underlying ‘biological determinism’ and its ‘racist potential’. Race and ethnicity will be reported as recorded in the original literature. However, caution will be employed given the controversy around some of the teminology.

The global incidence data on this topic were comprehensively reviewed by Scully and Bedi (2000) where they note that most of the data on race / ethnicity come from the USA. There, Black people have been reported to have the highest overall incidence rates of oral and pharyngeal cancer (11 / 100,000), followed by White people (8 / 100,000). Asian, Pacific Islander men and those of Hispanic Origin have broadly similar rates (5 / 100,000), lower than the rates of Black and White people, and American Indians the lowest rates (4 / 100,000) (Mayne *et al.*, 2006). The most recent available data from the US National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) report finds that before the age of 55, oral and pharyngeal cancer is the sixth most common cancer in White

men, but is the fourth most common in Black men (SEER, 2007). In states of America which are part of the SEER programme, of the estimated 30,000 newly diagnosed cases in 2004, incidence rates in Black Americans approached 25 per 100,000, compared to an average of 11 per 100,000 in the White American population (SEER, 2007). Significant inequalities in the racial distribution have been noted in the US, although teasing out how much of this is socioeconomically related does not seem to be generally considered (Morse and Kerr, 2006).

Oral cancer incidence data related to ethnic groups from the rest of the world is broadly limited to comparisons by geographical region, inter-country, or to level of global development (Scully and Bedi, 2000). Intra-country comparisons by ethnic groups will be considered under migrant studies.

1.4.4.2.5 Migrant studies

Migrant studies are few and far between in the literature related to oral cancer. Those undertaken have demonstrated that those who migrate tend to retain the risk of oral cancer from their country of origin. McCredie and colleagues (1994) found migrants from the Middle East to Australia have lower rates than native Australians. Migrants from Asia and China to London, UK have also been shown in several descriptive case-series studies to bring with them a higher risk of oral cancer compared to others in the area (Swerdlow *et al.*, 1995; Warnakulasuriya *et al.*, 1999). This risk was shown to be passed down generations, such that second and subsequent generations born in the UK of minority ethnic origin maintained an increased risk and this was considered to be a result of cultural behaviours including tobacco and betel quid use (Swerdlow *et al.*, 1995; Warnakulasuriya *et al.*, 1999; Warnakulasuriya, 2002). One such survey reported that 80% of the Bangledeshi community living in London reported using betel quid chewing while also adopting the cigarette behaviours of the native Londoners (Ahmed *et al.*, 1997).

1.4.4.2.6 Socioeconomic status

At the global level, there are substantial inequalities in the burden of oral and pharyngeal cancer in developing compared to developed countries – almost three-quarter of the global burden of cases occur in developing countries (Boyle *et al.*, 1990; Ferlay *et al.*, 2004; Parkin *et al.*, 2005). In developing countries, oral and pharyngeal cancer has been ranked fourth in frequency overall, while in developed countries it ranks eleventh overall (Ferlay *et al.*, 2004; Parkin *et al.*, 2005).

The descriptive epidemiological studies which explore the relationship of oral cancer incidence with socioeconomic status were comprehensively reviewed (up to 1997) by Faggiano *et al* (1997). Eight individual studies in the review provided ecological data, mainly in the form of record linkage of cancer registry to various sources of socioeconomic data, including: area of residence, census occupational social class, family income, or educational data. They noted no general trend in the relationship of incidence of cancer to SES with only: one study, from Colombia (Cuello *et al.*, 1982), showing a lower incidence in mouth cancer among men from lower social classes; and two studies demonstrating increasing incidence in lower social classes – among men from Denmark (Lynge and Thygessen, 1990) and women from Sweden (Vågerö and Persson, 1986). The majority of studies (Finland, Italy (2 studies), UK, and USA) demonstrated no clear relationship (Faggiano *et al.*, 1997). Since this review, there seems to have been no further descriptive epidemiology studies from around the world. Detailed recent reports from the US investigating cancer incidence related to socioeconomic status overlook head and neck or oral cancer as a site of interest (Kawachi and Kroenke, 2006). However, there have been some such studies undertaken in the UK (see below).

1.4.4.2.7 Time-trends

Overall, there continues to be an increase in the number of newly diagnosed cases of oral and pharyngeal cancer estimated globally: from 390,000 in 2000 to over 400,000 by 2002 (Ferlay *et al.*, 2001; Parkin *et al.*, 2001; Ferlay *et al.*, 2004; Parkin *et al.*, 2005). However, there is much global variation as to whether trends in the incidence of oral and pharyngeal cancer have increased, decreased, or remained unchanged over time as noted by Franceschi *et al.* (2000) and Mucci and Adami (2002). They noted substantial increases in incidence over time across Europe – particularly in Southern and Eastern European countries. Similar trends were observed in Australia between the 1970s and 1980s (Macfarlane *et al.*, 1994b) – while in Japan, dramatic increases from the 1970s (less than 1 / 100,000) to the present (approaching 6 / 100,000) have been noted (Franceschi *et al.*, 2000). In developing countries, over the same time period, oral and pharyngeal cancer remained stable, but at higher levels, particularly in India and much of South East Asia, with limited improvements observed over recent years (Franceschi *et al.*, 2000).

By sex: Marked differences in the incidence of oral and pharyngeal cancer between the sexes have been observed over time. Until the 1980s, increasing rates for males, and increasing or relatively unchanged rates for females were generally reported in Denmark (Møller, 1989), Australia (Macfarlane *et al.*, 1994b), Slovakia (Plesko *et al.*, 1994), Sweden (Östman *et al.*, 1995), and New Zealand (Cox *et al.*, 1995). However, more

recently, over the past few decades, these trends have been seen to be converging – with this largely being explained by increases in oral cancer rates for women in all age-groups (Franceschi *et al.*, 2000; Shiboski *et al.*, 2000; Mucci and Adami, 2002).

By age: Similarly, with regard to trends in age-specific incidence over time (as reviewed above), increasing incidence rates of oral and pharyngeal cancer in younger adults has been more frequently noted over the past few decades. There is some evidence to suggest that age-related changes over time are birth cohort based rather than age per-se although they are inextricably linked. Much of this evidence comes from the UK (see below). However, Morse *et al.* (1999) showed a cohort effect in the United States, perhaps related to secular changes in exposure to environmental risk factors, and Ho and colleagues (2002) attributed an oral cancer cohort observed increase effect in Taiwan to a rise in betel quid use together with a rise in alcohol consumption. In Europe, similar cohort effects have been found in Denmark (Møller, 1989), and in Slovakia (Plesko *et al.*, 1994) – where the trends highly correlated with per capita alcohol consumption and smoking patterns.

By ethnicity: In the United States, Shiboski and colleagues (2000) showed that incidence rates in White people had decreased from 1973 to 1996, while there was a corresponding increase in their Black contempories.

1.4.4.3 Global: mortality

Global mortality from oral cancer is relatively high in both developed and developing countries with approximately 207,000 deaths (compared to the 390,000 newly diagnosed cases) estimated in 2000 (Ferlay *et al.*, 2001) and approximately 211,000 deaths (compared to the 400,000 newly diagnosed cases) estimated in 2002 (Ferlay *et al.*, 2005). In Europe, La Vecchia *et al.* (1997) reviewed the mortality rates of oral and pharyngeal cancer in 32 European countries over time and found that the rates in the 1990s were two- to eight-times higher than in the 1950s.

Some studies seem to suggest that mortality is also increasing at a more rapid rate in younger adults. Depue (1986) was among the first to report a 2-fold rise in mortality from cancer of the tongue in the US during the period 1950-82 for those aged 10-29 years, with slightly lower increases among those aged 30-39, but no increase reported in older age-groups. Franceschi *et al.* (1994) in their comprehensive review of trends in cancer mortality from 24 European countries in young people (aged 20-44 years) for the multiple cancer sites, showed that increased trends in oral and pharyngeal cancer were more

common than for other cancers. Comparing oral and pharyngeal cancer mortality data from 1955-59 to 1985-89 showed that a greater than 2-fold increase was observed for males in nine countries (Austria, Belgium, Bulgaria, Czechoslovakia, Hungary, Poland, Spain, West Germany, Yugoslavia) and for females in three countries (Hungary, Spain, West Germany). Three countries had greater than 7-fold increased male mortality rates (Denmark, Hungary, West Germany). UK and Scotland data did not demonstrate any significant increase, and no countries demonstrated a significant reduction in these mortality trends. As with the increased incidence trend in younger groups, the explanation is unclear.

While there do not seem to be any formal ecological relationship studies utilising incidence data, there are a number of studies utilising mortality data. These ecological studies have compared trends in oral and pharyngeal cancer mortality with trends in known risk factors and have mainly focused on tobacco use and alcohol consumption. Macfarlane *et al.* (1996b) compared male upper aerodigestive tract cancer mortality trends with per capita alcohol consumption and trends in lung cancer as a proxy measure for smoking levels. Using data from 25 countries between 1950 and 1989, per capita alcohol consumption was found to be a strong predictor of UADT cancer deaths in men.

More recemtly, Petti and Scully (2005) undertook a similar international country-level ecological comparative analysis of oral cancer mortality using data from 20 countries (not including UK). Incorporating alcohol (per capital consumption, by drink category), a measure of population prevalence of tobacco smoking amongst adults, and life-expectancy data, they found high correlations between high alcohol consuming countries and oral cancer mortality. This was evident when adult smoking prevalence was controlled for and was more significant in high spirit drinking nations. While no countries are singled out, it seems the trend is particularly apparent in eastern European countries.

In terms of the relationship between oral cancer mortality and SES, the descriptive epidemiological literature was comprehensively reviewed (up to 1997) by Faggiano *et al* (1997). Thirteen studies provided data on mortality and SES for the review from record linkage of cancer registry with various sources of socioeconomic data, including: area of residence, census occupational social class, family income, or educational data. Excess mortality from oral cancer was found in men from low socioeconomic groups in most of the populations investigated, with the exception of Japan, and in the United States the trend was not so obvious. The trend for oral cancer mortality in women was less obvious, except

in the United Kingdom where an increased risk in low socioeconomic groups was observed (see below).

1.4.4.4 Global: survival

Despite the purported advancements in surgical techniques and adjuvant therapy, the prognosis for patients with oral and pharyngeal cancer remains poor with global 5-year survival rates of 40-50% which have not changed significantly in the last three decades (Jemal *et al.*, 2002). Five-year survival in the Indian sub-continent has been estimated even lower, at 30-40% (Ton Van *et al.*, 2000).

Survival rates in the US and Europe are similar. In the US, the most recently available data from SEER show that overall 5-year survival for those with oral cancer is 56% in men and 60% in women (Ries *et al.*, 2003). In Europe, similar data from EUROCARE-3 show wide variation across Europe with an overall 5-year relative survival for oral cavity cancer of 45%, and for oropharyngeal cancer of 32% – with survival consistently shown to be poorer in men than in women (Sant *et al.*, 2003). Most of the Europe-wide inter-country variation can generally be explained following adjustment for case-mix (mainly due to anatomical site-specific differences). However, more research is required to determine the extent to which residual differences, particularly between eastern and western European countries, are due to health service provision (i.e. access to care, early detection and treatment) which may have a socioeconomic dimension (Sant *et al.*, 2003).

There were no international studies which directly investigated the relationship between SES and oral cancer survival.

1.4.4.5 UK / Scotland: incidence

Most of the UK and Scotland studies investigating incidence have done so from the perspective of examining trends over time. This is as expected as time is a necessary component on the computation of incidence. Consequently, there are limited data which looks at overall incidence (independent of some degree of time-trend analysis). Therefore, the literature will be reviewed bearing this in mind, but within this examination differences by geographic area, age, sex, and socioeconomic circumstances will be discussed.

1.4.4.5.1 Availability of incidence data

The most recent studies available at the time of commencing this research reported incidence data for England and Wales from: 1962 to 1986 (Hindle *et al.*, 1996), and 1971 to 1996 (Quinn *et al.*, 2001); and for Scotland from: 1960 to 1989 (Macfarlane *et al.*, 1992), 1986 to 1995 (Harris *et al.*, 1998), and 1965 to 1997 (Robinson and Macfarlane, 2003). In addition, Boyle *et al.* (1990) analysed the historic (to 1980) descriptive epidemiology of oral cancer in the UK and Scotland in the context of a global review of all head and neck cancer. They report that incidence data were available from 1959 in Scotland. The picture of these trends is also complicated by the lack of consistency in definitions of oral cancer employed.

1.4.4.5.2 Historic incidence trends

Hindle *et al.* (1996) analysed the trends in oral cancer incidence in England and Wales, between 1962 and 1986. They report a significant downward trend overall across the period, but pick up a potential cohort effect of increased incidence in younger adults. Incidence rates per 100,000 in males fell from 3.1 in 1962-66 to 2.8 in 1967-81 followed by a slight increase to 2.9 in 1982-86. In females, the rate increased from 1.2 per 100,000 in 1962-66 to 1.3 in 1982-86. Incidence rates were analysed by birth cohorts and revealed varying trends. While the trend for increasing incidence with increasing age held in both males and females, in males over 60 years there had been a general reduction in incidence, while in those under 60 years there had been an increase. A similar, but not so marked, pattern was observed for females.

Boyle *et al.* (1990) analysed the UK oral (cavity) cancer mortality trends in detail (Section 1.4.4.6), unfortunately, only reported the age-standardised incidence rates for oral cancer at one point in time, in 1980. At this time, the incidence rates were low (relative to those in other countries) being in England and Wales: 1.2 per 100,000 in males, and 0.5 per 100,000 in females, and in Scotland: 2.0 per 100,000 and 1.2 per 100,000 for males and females respectively.

Macfarlane *et al.* (1992) did, however, explore the historic incidence data for oral (cavity) cancer in Scotland. They noted that the age-standardised incidence rates had increased in men from 1.6 per 100 000 in 1960-64 to 5.1 per 100 000 in 1985-89 and in women from 1.3 to 1.9 per 100 000 over the same period.

1.4.4.5.3 Recent incidence trends

For both males and females, in England and Wales, the overall age-standardised incidence rate of (the broader defined) oral and pharyngeal cancer declined slightly during the 1970s from around 9 per 100,000 in males and over 4 per 100, 000 in females to 8 and 4 per 100,000 in males and females respectively. These rates remained stable during the 1980s before rising gradually into the early part of the 1990s – returning to the levels seen in the 1970s of 9 and over 4 per 100,000 in males and females by 1996 (Quinn *et al.*, 2001). The broader definition employed by Quinn *et al.* (2001) complicates the data presented, as cancers of the nasopharynx and salivary glands are also included – both of which are usually considered distinct entities. Further, these incidence data to some degree mask the numbers of cases of oral and pharynx cases in England and Wales which increased for males by 24% from 1,900 in 1971 to almost 2,400 in 1997, and for females by 21% to over 1,400.

In Scotland, increased incidence has continued to be observed through to the 1990s (Robinson and Macfarlane, 2003). During the time period 1989-96, standardised incidence rates for oral and pharyngeal cancer at all ages rose by 31% in males from 9.5 to 11.5 per 100,000, and by 16% in females from 3.8 to 4.8 per 100,000. More recent analysis of oral and oropharyngeal cancer trends by the Scottish Cancer Registry showed that by the mid-1990s, between 400 and 500 new cases were reportedly diagnosed each year. Oral cancer was twice as common amongst males as females, with incidence rates of approximately 12 per 100,000 in males and 5 per 100,000 in females (Macpherson *et al.*, 2000).

1.4.4.5.4 By age

Younger patients, defined arbitrarily here and elsewhere, as being aged less than 45 years, have been estimated from case-series studies to account for approximately 6% of all oral cancers (Mackenzie *et al.*, 2000; Llewellyn *et al.*, 2001).

Quinn *et al.* (2001) reported that oral and pharyngeal cancer in England and Wales was rare in patients under 45 years, occurring mainly in males in their 6th and 7th decade of life. In their analysis for the period 1971-96, incidence rates in both sexes increased with age, and incidence in males was consistently around twice that in females in all age-groups. Over the whole period, incidence in elderly men was seen to fall dramatically, from a high of 100 per 100,000 to 38 (a drop of over 60%). However, they did observe increases in rates in the 55-64 age-group of over 40% in men and 25% in women.

In Scotland for the period 1989-96, Macfarlane and Robinson (2003) report that the standardised incidence rates truncated for the age-group 35–64 years increased from 18.0 to 23.6 per 100,000 in men, and from 7.3 to 8.5 per 100,000 in females. Macfarlane and Robinson (2003) also analysed incidence trends via an age-period-cohort model and demonstrated a consistent increase (for the period 1989-96) in incidence in males aged 40-64 years in cohorts born after 1905. These increases ranged from an increase of around 5 to 10 per 100,000 for the 40-44 year cohort, to an increase of 30 to 60 per 100,000 for the 60-64 year cohort. These compare to the constant level of incidence observed in those aged 30-39 years born after 1930 (with incidence rates under 3 per 100,000). In females, variable rates were observed for the younger cohort, with a general increase in the older age-group, although both the level and extent of the increases were far lower than for males. While the Robinson and Macfarlane (2003) paper demonstrates a most comprehensive analysis – the data are only presented in graph form, so it is difficult to see the detail of the incidence rates and how they change over time.

1.4.4.5.5 By socioeconomic factors

There has been some, limited, descriptive epidemiological research on oral cancer incidence by socioeconomic status or deprivation status.

Kogevinas (1990) was one of the first to look at ‘socio-demographic’ factors related to oral cancer incidence and survival through a record linkage study between the 1971 census and a 1% sample of 1971-81 cancer incidence data from the UK. Using data for males only, and utilising housing tenure as the socio-demographic indicator, a mixed picture emerged. There was a slightly reduced risk (around 20%) in owner occupiers, an increased risk (around 30%) in those who were in private rented accommodation, and a slight increased risk (around 10%) in those in council tenancies. The main limitation of this study was in the small numbers of cases (n=169) which would have given wide confidence intervals on the data – but they were not reported.

The first descriptive epidemiological study of the relationship between head and neck cancer and socioeconomic circumstances was undertaken in the south west of England by Thorne and colleagues (1997). Data on all head and neck cancers registered between 1985 and 1991 were linked to the Carstairs index. Subsite analysis of the oral cancer data showed that males from the most deprived areas had significantly higher incidence (around 15 per 100,000) than all other groups, reducing with increasing levels of affluence (down to around 5 per 100,000 in the most affluent quintile). The relationship was similar but not

so clear and at a lower level in females, ranging from around 2.5 per 100,000 in the most deprived area to 1.5 per 100,000 in the most affluent area.

In the north east of England, O'Hanlon *et al.* (1997) investigated the incidence or oral cancer from 1971-74 to 1983-86. Linking age-standardised incidence rates of oral cancer to the Townsend deprivation index, a significant 2-fold higher incidence in the most compared to the least deprived areas was observed for males, while there were no significant equivalent differences for females.

Edwards and Jones (1999) examined upper aerodigestive tract cancer (UADT) data from the Thames, West Midlands, West of Scotland and Yorkshire cancer registries in the UK between 1984 and 1993. Their definition of cancer definition was broad and included cancers of the mouth, pharynx, larynx and salivary glands, and they linked the data to the Carstairs deprivation index. They found significantly higher UADT cancer in those from deprived areas compared to affluent areas, while not presenting the incidence data (they focus on survival in their paper), they report the age-standardised incidence rate of UADT cancers (for the combined years 1984–1993) for each health authority area was strongly correlated with the mean Carstairs score for that area. They also note that both deprivation and incidence were highest in the West of Scotland and lowest in South East England.

A recent case-series study of 100 consecutive patients diagnosed with oral cancer between 1998 and 2000 in Newcastle looked at the effects of high alcohol consumption, smoking and long-term unemployment on the incidence of oral cancer. All three factors were highly correlated in the subjects, but when considered in combination, the effect of long-term unemployment became non-significant, suggesting some confounding with the effect of low SES (measured here by unemployment) being mediated through behaviours (Greenwood *et al.*, 2003).

For England and Wales, Quinn *et al.* (2001) presented data for the period 1989-93. They demonstrated for males a greater than 3-fold higher incidence of oral and pharyngeal cancer in the most deprived compared to the most affluent groups. They found similar, but less pronounced, patterns for females.

There have not been many descriptive epidemiology studies in Scotland examining oral cancer incidence data in relation to socioeconomic factors, and none have looked at this in detail. Harris *et al.* (1998), for the period 1986-1995, demonstrated a clear almost linear relationship between age-standardised incidence rates for oral cavity cancer and Carstairs

deprivation. In males there was a greater than 4-fold increase between those in the least deprived deprivation category (DEPCAT) 1 and those in DEPCAT 7 – the most deprived. The relationship was not as strong for females but was still present, with an increase of 25% for the equivalent comparison.

1.4.4.6 UK / Scotland: mortality

1.4.4.6.1 Historic mortality data

In the UK, mortality data are available further back in time than incidence data. Hindle *et al.* (1996) analysed data on oral cancer mortality rates for England and Wales from 1901 to 1990, while Boyle *et al*. (1990) investigated oral cancer mortality data for Scotland from 1911 to 1983.

Hindle *et al.* (1996) report significant overall reductions in oral cancer mortality rates over the century in England and Wales. From a peak in 1916-20, for men at over 10 per 100,000 and women at 1 per 100,000 there were subsequent decreases in both sexes until 1971-75, to 1.5 in males and around 0.5 in females. Quinn *et al.* (2001) note that the dramatic reduction in mortality rates of oral and pharyngeal cancer (including a wider range of sites) in males occurred during the 1950s and 1960s.

Boyle *et al.* (1990) present the historic data from 1911 on oral cancer mortality rates available for Scotland. However, they separate the tongue from the mouth and only present male data in their analysis. Thus, tongue cancer mortality shows a dramatic fall from nearly 6.0 per 100,000 to around 1.0 per 100,000 in the 1960s with only a slight decline to just less than 1.0 per 100,000 in 1983. Equivalent mouth cancer mortality data begin at just less than 2.0 per 100,000 in 1911 rising to 2.5 per 100,000 by the 1930s where it remained until the 1950s before steadily returning to just less than 2.0 per 100,000 by 1983. Robinson and Macfarlane (2003) also examined the trends in oral and pharyngeal cancer mortality in Scotland in considerable detail. They also demonstrated a dramatic fall in male mortality rates between 1950 and the mid-1970s (around 7 to 3 per 100,000) and a similar fall in females but at lower levels (around 2 to 1 per 100,000). Between the 1970s and mid-1980s a gradual increase was then seen in males (3 to 4 per 100,000) with female rates plateauing over this period at just over 1 per 100,000.

Ecological comparative analyses are somewhat limited. Hindle *et al.* (1996), in an interesting analysis, compared oral cancer mortality trends (from 1911 to 1990 in England and Wales) with those of lung cancer and liver cirrhosis, which are closely related to

smoking and alcohol consumption respectively. They found a negative correlation with patterns of lung cancer, however, a strong positive correlation with rates of liver cirrhosis, particularly in males aged 35-64 years.

1.4.4.6.2 Recent mortality trends

La Vecchia *et al.* (2004) compared mortality data from 1980 and 1992 in England and Wales (combined), Scotland, Northern Ireland, and the UK as a whole were included as part of a comprehensive analysis of oral and pharyngeal cancer mortality trends in Europe. These data demonstrated that mortality rates in men and women in England and Wales were almost half those in Scotland, and there has been limited change in mortality rates between 1955 and 1992 (La Vecchia *et al.*, 2004). Northern Ireland rates were slightly less than those for Scotland which were 5.2 and 2.0 per 100,000 for men and women respectively for 1955-59; reducing to 4.2 and 1.4 per 100,000 respectively by 1990-92.

In the analysis of oral and oropharyngeal cancer mortality rates in England and Wales by Hindle *et al.* (1996), the rates remained relatively stable from the mid-1970s to 1990, at around 1.5 per 100,000 in males and around 0.5 per 100,000 in females. Quinn *et al.* (2001) demonstrated that mortality rates in men in the 1990s (around 4 per 100,000) were under half that of the early 1950s (over 9 per 100,000), although the 1990s rate had been achieved by the mid-1970s. They also showed that in females the rate fell more gradually, and by about 40% over the whole period, from over 2.5 per 100,000 in the 1950s to 1.5 per 100,000 in the 1990s.

Robinson and Macfarlane (2003) examined the age-standardised mortality rates in oral cancer in Scotland between 1989 and 1997 noting they were more variable than for the incidence rates, although there had been little change between 1989 and 1997 overall (males: 4.2 to 4.3 per 100,000; females 1.4 to 1.6 per 100,000), there was a peak at around 1995 (males: 4.8 per 100,000; females 1.9 per 100,000).

1.4.4.6.3 By age

Hindle *et al.* (1996) found that mortality rates in England and Wales were beginning to increase in younger cohorts since the 1970s. Their detailed analysis of historic age-standardised mortality data over time revealed that oral cancer mortality rose in both the under and over 65 year-old men in the early part of the century, peaking in the younger men at nearly 19 per 100,000 in 1916-20 and the older group 10 years later (but at a significantly higher level: nearly 74 per 100,000). Thereafter, they report there were progressive declines in mortality rates of older males to just over 10 per 100,000 in 1986-

90. However, in younger males, the decrease progressed to under 2 per 100,000 by 1966-70 but then increased again to nearly 3 per 100,000 in 1986-90. A remarkably similar pattern was observed in their analysis of female mortality rates, but at substantially lower levels. Oral cancer mortality rose slightly in both age-groups of women early in the century, peaking in younger (under 65 years) women at nearly 2 per 100,000 in 1916-20 and in 1926-30 at nearly 7 per 100,000 for the older age-group (over 65 years). Thereafter, they showed a decrease in the older group to just under 5 per 100,000 in 1986-90, and in the younger group a decrease occurred until 1971-75 to under 1 per 100,000 – rising only slightly (but remaining under 1 per 100,000) to 1986-90. Quinn *et al.* (2001) looked at these and more recent trends which corroborated with their findings for head and neck data. They showed that to the mid 1990s mortality rates in younger groups in both sexes seem to be flattening at the levels of the late 1980s, but older men and women seem to be experiencing a slight increase in mortality rates. They also noted that the birth cohort patterns in mortality were similar to those in incidence for England and Wales described above.

Age-standardised mortality rates from the 1980s to early 1990s in Scotland seem to have remained relatively stable in both sexes and all age-groups, with males 35-64 years rising only slightly around 8 per 100,000 and females 35-64 years remaining at just over 2 per 100,000 (Robinson and Macfarlane, 2003). In their detailed cohort modelling analyses Robinson and Macfarlane (2003) also showed a general increase in male cohorts born in 1944 and later, but due to the small numbers of females dying from oral and pharyngeal cancers in Scotland this limited the possibility of detecting cohort effects in this group, although in general terms, they noted that mortality rates have risen in older cohorts (born in 1914 or later).

The most recent mortality rate data from the Scottish Cancer Registry show that, as with the increased oral cancer incidence over the past decade, there has been a corresponding increase in the number of deaths per year. The average number of deaths in Scotland per year from oral cancer is 121 and 63 for males and females respectively, for the period 1990-1999. This represents an overall death to registration ratio of 0.4, which is higher than that seen for many other cancers (Macpherson *et al.*, 2000).

1.4.4.6.4 By socioeconomic factors

There are limited studies which explicitly have looked at UK / Scotland oral cancer mortality data in relation to deprivation.

Between 1979-80 and 1982-83 for men and women aged 20-64 years oral and pharyngeal cancer mortality data related to the UK census occupational social classification were presented by Faggiano *et al.* (1997). They found an increase in the relative risk of death from oral and pharyngeal cancer with 'ever' working in manual occupational classes, from protective effects of 40% and 30% for those in social class I and II to increased risk effects of over 2-fold in social class V.

Quinn *et al.* (2001) found that variations in mortality of oral and pharyngeal cancer by deprivation category for England and Wales very closely resembled those for incidence – with greater mortality in more deprived groups (as detailed above).

Mortality rates are particularly important when considering the influence of treatment and are also reflective of treatment outcome and survival.

1.4.4.7 UK / Scotland: survival

It has often been reported that despite the remarkable advances in medicine in general and cancer treatment in particular, the five-year survival rate for oral cancer has improved only marginally (Jones *et al.*, 1998), if not at all, over the past 20 years, with survival currently lingering at just under 50% in the UK and Scotland (Soutar and Robertson, 2001). However, improved survival rates may yet become apparent if the general trends (observed above) for increased incidence are greater than that of mortality.

The apparent static survival data may be due to a number of factors, but potentially important among these is the continued late presentation and detection of lesions. While the prognosis depends on the site and the stage of the lesion, the relative five-year survival rates are 44% (males) and 49% (females). Worryingly, there is some evidence that survival has actually declined recently in persons under 65 years of age (Soutar and Robertson, 2001). This may be related to an increase in incidence among persons in low socioeconomic groups, who tend to have a generally poorer prognosis – although this is an under-researched area.

A study of survival in head and neck cancer patients conducted in the north west of England indicates that these survival trends are not consistent across the UK (Jones *et al.*, 1998). They noted several factors were important in their improved survival rates, including: an improved cure rate, better physical condition of patients and reduced recurrence of tumours at the primary site.

Survival data from England and Wales have also been shown to exhibit a strong socioeconomic gradient with those from the most deprived areas having the poorest survival. This gap in survival between the most and least deprived has been quantified as a 15% difference in 5-year survival and noted as being greater than for any other type of cancer (Coleman *et al.,* 1999). Macfarlane and colleagues (1996a) also reported that potential trends for decreased survival in Scotland may reflect the increase in the proportion of cases coming from socioeconomically deprived communities.

1.4.4.8 Key points from descriptive epidemiology of oral cancer in UK / Scotland

From the published descriptive data on oral cancer available, it is apparent that incidence in Scotland seems to be higher than in the rest of Britain. However, no detailed comparative analyses of oral cancer incidence data have been undertaken covering the whole of the UK (to also include Northern Ireland), and there has been limited investigation of regional variations by age, sex, and over time. Particularly, there is not a clear picture of recent trends, especially in young people; and there are also no time-trends analyses of oral cancer incidence related to socioeconomic factors. Further, detailed analyses of how the UK oral cancer incidence data compare with those from other countries have not yet been undertaken.

1.4.5 Analytical epidemiology – Risk factors for oral cancer

1.4.5.1 Risk factors for oral cancer

Recent epidemiology studies have begun to reveal several important risk factors for oral cancer and there are a number of narrative reviews published which attempt to harness the burgeoning literature in the field (Boyle *et al.,* 1990; Mucci and Adami, 2002; Mayne *et al.*, 2006). In summary, these reviews record the epidemiological studies over the past few decades which describe the pathogenic risk factors and salutogenic protective factors for oral cancer. The main established risk factors include tobacco use, alcohol consumption, and the combination of these behaviours. Other possible risk factors include human papillomavirus (HPV) infection while, at present, there is insufficient evidence for herpes simplex virus (HSV) and for fat intake. The established protective factor for oral cancer is dietary intake of fresh fruit and vegetables. Possible other protective behaviours include vitamin C, vitamin E and beta-carotene, while there is insufficient evidence for the protective effect of fibre intake.

These major oral cancer reviews, which reflect the aetiological analytical epidemiology literature, have a heavy focus on lifestyle behaviours and genetic risk factors. There is limited mention or review of socioeconomic factors in any of these otherwise substantial and thorough reviews (Boyle *et al.*, 1990; Mucci and Adami, 2002; Mayne *et al.*, 2006). Furthermore, the term lifestyle can have connotations of 'victim blaming' and overly emphasises behaviour as simply a voluntary matter of 'choice', neglecting the wider circumstances in which people live and in which such behavioural choices are made as Blaxter (1990), in her thesis on the issue, concluded. Thus, the term 'behaviour' will be used in place of 'lifestyle' with regard to considering risk factors.

The evidence for and against behavioural and social factors will be updated, discussed, and reviewed in detail, while the literature pertaining to genetic factors, which is beyond the scope of the present body of work, will be briefly summarised.

A brief search on the Medline database using keywords for oral cancer and linking items related to specific risk factor-related topics revealed the tip of the enormous extent of the literature in the field (Table 1.4). These crude results demonstrate the extensive amount of research and accumulated knowledge in the area and the mamouth task of distilling such knowledge. Where possible, systematic reviews and then narrative review articles were saught in the first instance, and through search and review were updated where necessary.

Table 1.4 The results of a Medline search for publications on various oral cancer topics

SEARCH TERMS	CITATIONS
Oral cancer AND Epidemiology	5,018
Oral cancer AND Tobacco	3,808
Oral cancer AND Alcohol	1,019
Oral cancer AND Diet	772
Oral cancer AND Genetics	4,784
Oral cancer AND Socioeconomic factors	668

Search performed in August 2007, results back to 1950.

1.4.5.2 Tobacco

Tobacco use is widely considered the most important and dominant risk factor for oral cancer (Boyle *et al.*, 1990; Mucci and Adami, 2002; Mayne *et al.*, 2006). Rothman's

estimate – that approximately 75% of all oral cancer is attributed to the use of tobacco, is widely quoted. However, the data from which this estimate is calculated relate to the joint effect of alcohol and tobacco use (Rothman and Keller, 1972; Rothman, 1978).

Tobacco can be smoked or taken in unsmoked forms and its use varies across the world. In 'Western' countries: in Europe, USA, Australia and Japan, cigarettes, cigars, and pipes are the main types of smoked tobacco, while chewing tobacco and snuff are not uncommon particularly in the US and Sweden (Scandinavia). In Asian countries, while cigarette consumption is high and increasing, traditional smoked forms, including bidi smoking is also prevalent; and smokeless forms include: betel quids (pan), and gutka (Gupta, 1996). Each of these behaviours has many dimensions and aspects to them which are potentially important in influencing the tobacco risk factor effect on oral cancer. These include: type of tobacco, pattern, frequency and duration of use, and combination with other ingredients. For smoked forms, other considerations include: the type of filter used; the effect of environmental tobacco smoke or 'passive smoke'; the consequences of quitting; and the combination with marijuana. For smokeless forms, the main additional considerations are the combination and formulation with other ingredients, including: betel leaf, slaked lime, spices and the areca nut (Gupta, 1996).

Smoking tobacco exposes the oral cavity to over 60 carcinogens including polycyclic aromatic hydrocarbons (PAHs), aldehydes, and nitrosamines which have been evaluated by the International Agency for Research on Cancer, and for which there is 'sufficient evidence for carcinogenicity' in either laboratory animals or humans (IARC, 1986). A recent IARC monograph which attempted to quantify the effect of tobacco smoke from 16 case-control and three cohort studies on oral cancer found a higher risk (OR 4.0-5.0) for tobacco smoking (all forms) (IARC, 2004a). A number of the ingredients commonly taken in combination with smokeless tobacco (including betel-quid and areca-nut) have been classified as carcinogens, both in combination and in their own right, by the International Agency for Research on Cancer (IARC, 1985; IARC, 2004b). Chewing tobacco and snuff contain tobacco-specific N-nitrosamines that have been shown to be oral carcinogenic; while betel quid and areca-nut contain 3-(methylnitrosamino)-proprionitrile considered 'probably' carcinogenic (IARC, 2004b).

The evidence for each tobacco behaviour will be considered in turn.

1.4.5.2.1 Cigarette smoking

A positive association between cigarette smoking and oral cancer has consistently been reported around the world (Boyle *et al.*, 1990; Mucci and Adami, 2002; Mayne *et al.*, 2006). The evidence for causation comes from many case-control studies and a small number of cohort studies. However, no systematic review and meta-analysis of these observational studies has been undertaken.

The cohort studies come from the US and were reported together as a National Cancer Institute monograph (National Cancer Institute, 1997). There were two cohort studies with separate data for oral and pharyngeal cancer. The first, a cohort of almost 300,000 US Veterans followed between 1954 and 1980, reported an increased mortality rate in the range of 1.5 to 2.6 for oral and pharyngeal cancer in former cigarette smokers compared to never smokers (Hrubec and McLaughlin, 1997). The second cohort was 121,700 female registered nurses enrolled in the 'Nurses' Health Study' in 1976 and followed up to 1990 (Kawachi *et al.*, 1997). Current smokers were found to have a significant 5-fold increased risk for oral and pharyngeal cancer mortality. However, this related to only six cases and highlights both the difficulty in undertaking cohort studies for relatively low incidence conditions, and the power of such studies in elucidating causality (Kawachi *et al.*, 1997). A further two US cohort studies: Cancer Prevention Study (CPS) I (1959 to 1965) and CPS II (1982 to 1988), with over one million participants each, had their findings compared by Thun and colleagues (1997). They reported an increased relative mortality risk in current cigarette smokers compared to never smokers for non-lung smoking related cancers (including oral and pharyngeal cancer) of 1.8 for women and 2.7 for men in CPS I, increasing to 2.6 for women and 3.5 for men in CPS II.

There is an abundance of evidence from many case-control studies from across the world covering all aspects of cigarette smoking behaviour. These studies have been thoroughly reviewed recently by Mayne and colleagues (2006) and more historically by Boyle *et al.* (1990). Cigarette smoking status has an effect on risk, with current smokers found to have approximately a 3- to 12-fold increased risk over never smokers and ex-cigarette smokers having around a 1- to 5-fold increased risk (Mayne *et al.*, 2006). This latter point reflects the evidence, also corroborated by Mucci and Adami's review (2002), that cigarette cessation confers a risk approaching the risk of never smokers after 10 years. A dose-response relationship is evident from the case-control literature, with heavy smoking increasing the risk up to 3-fold (Mayne *et al.*, 2006). In addition to quantity smoked, duration is also important, with a clear increased risk associated with cumulative exposure (pack-years) being described (Mucci and Adami, 2002; Mayne *et al.*, 2006). These reviews

also demonstrate an increased risk associated with inhaling, compared to not-inhaling cigarettes, and with filtered compared to non-filtered cigarettes – although handmade cigarettes generally confer increased risk. Mayne *et al.* (2006) also reviewed the literature detailing the effects on specific anatomical subsites, and found cigarette smoking to have the greatest effect on the oral cavity (and the floor of the mouth in particular) compared with pharyngeal sites. However, there were many inconsistencies in the literature reviewed.

Assessing the risk of cigarette smoking is further complicated by the close relationship with other risk behaviours, particularly alcohol consumption. The synergistic effect on magnifying the risk for oral cancer is well-recognised (see below). The International Head and Neck Cancer Epidemiology (INHANCE) consortium pulled together individual patient data (IPD) from 15 case-control studies to provide sufficient numbers of case (n=1598) and control subjects (n=4051) who smoked cigarettes but who never consumed alcohol (and vice versa). They found that among those who never drank alcohol, cigarette smoking was associated with just over a 2-fold increased risk of head and neck cancer, compared to never smokers and there were clear dose–response relationships for the frequency, duration, and number of pack-years of cigarette smoking (Hashibe *et al.*, 2007).

1.4.5.2.2 Cigar and pipe smoking

There have been few studies which have looked at the effect on oral cancer risk from cigar or pipe smoking. Data from several cohort studies, all from the US, reveal the increased risk of oral and pharyngeal cancer associated with cigar smoking to be within the range 3- to 8-fold (Shapiro *et al.*, 2000). Recent data from over 500,000 men in the Cancer Prevention Study II (CPS-II) study found a 4-fold increase in oral cancer mortality associated with cigar smoking (with six deaths recorded). This followed a reported 8-fold increased risk from the earlier CPS-I cohort (Shapiro *et al.*, 2000). Additionally, data from around 1500 men who smoked cigars and over 16,000 who did not followed from 1971 to 1996, found an almost 3-fold increased oral pharyngeal cancer mortality associated with cigar smoking (with eight deaths recorded) (Iribarren *et al.*, 1999). These findings come in the context of dramatic increases in cigar use in the 1990s, which were all the more surprising for they had followed similar dramatic declines from the 1960s until 1990 (Shapiro *et al.*, 2000).

Case-control study evidence, reviewed by Mucci and Adami (2002), and Mayne *et al.*, (2006), confirm the association, with a range of 2- to 9-fold increased risk of oral cancer

associated with exclusive cigar smoking and with increases dependent on frequency, duration, and cumulative exposure.

Pipe smoking has received less attention, due to the very low prevalence of the behaviour. However, case-control studies have demonstrated around a 2-fold increased risk with exclusive pipe smoking or after adjusting for other behaviours (Mucci and Adami, 2002; Mayne *et al.*, 2006).

Mayne *et al.* (2006) also reviewed the literature with regard to the effects of both cigar and pipe smoking on anatomical subsites of the oral cavity. They demonstrated that different case-control studies indicated that the floor of the mouth, buccal musosa, and soft palate were at the greatest risk for cancer development as a result of cigar or pipe smoking.

1.4.5.2.3 Bidi smoking

Rahman and co-workers (2003) undertook a meta-analysis of 12 case-control studies investigating bidi smoking, the South Asian traditional tobacco habit, which consist of a small amount of tobacco wrapped in the leaf of another plant. A 3-fold increased estimated risk of oral cancer incidence for bidi smokers was calculated compared to never smokers, but there was an insignificant increased risk compared to cigarette smokers. However, other tobacco behaviours and alcohol consumption were not adjusted for in the analyses (Rahman *et al.*, 2003).

1.4.5.2.4 Passive smoke

To date, passive exposure to environmental tobacco smoke (ETS) has been reported in only one very small case control study (with only 10 cases and 27 controls who had no ETS exposure) from the US (Zhang *et al.*, 2000). After controlling for potential confounders, including active smoking and alcohol consumption, ETS either from the home or workplace, was found to give a dose-response in the region of a 2- to 4-fold increased risk for oral cancer from moderate to heavy exposure.

1.4.5.2.5 Marijuana smoking

The epidemiological evidence for the association of Marijuana (cannabis) – one of the most widely used illegal drugs – in relation to oral cancer risk was recently and comprehensively reviewed by Hashibe and colleagues (2005). They found four case-control studies which provided equivocal findings. However, they reported extraordinary difficulties in disentangling the effects of marijuana from tobacco use (primarily because they are often smoked together).

1.4.5.2.6 Western smokeless tobacco use

Literature on the risks of smokeless tobacco use in Western societies associated with oral cancer is mainly from Sweden and the US – reflecting the countries where such practices are relatively common. There are many forms of smokeless tobacco available. Generally, in the US, both chewing tobacco and moist snuff are used, while in Sweden moist snuff (known as Swedish 'snus') is almost exclusively used. Chewing tobacco basically consists of dried tobacco leaves with sweeteners or flavourings added. Moist snuff is tobacco cut into strips or powdered, mixed with flavourings, and usually contained in a small pouch – there are a range of varieties and combinations.

Rodu and Cole (2002) undertook a limited meta-analysis of studies which investigated the risk of oral cavity cancer associated with using a range of Western smokeless tobacco products. Summary estimates for oral cancer risk associated with the following types of smokeless tobacco use were calculated: for chewing tobacco from two studies, meta-analysis almost halved the risk estimate (although it is unclear what the reference category is in this comparison – i.e. other smokeless tobacco habits or tobacco smoking); for dry snuff use from three studies a 4-fold increased risk was yielded; and finally for non-specified smokeless tobacco use, an almost 3-fold increase increased risk from four studies was summarised (Rodu and Cole, 2002). The primary limitation of such meta-analysis was the lack of consideration given to potential confounding factors, including smoking. More recent detailed narrative reviews undertaken by Mayne *et al.* (2006), and Rodu with Jansson (2004) also found increased risks in studies from both the US (for chewing tobacco) and Sweden (for snus), where the analyses were restricted to non-smokers.

However, in contrast, a number of Swedish studies have failed to find an increased oral cancer risk associated with Swedish snus (Lewin *et al.*, 1998) and, in particular, a recent large cohort study from 1969 to 1992, involving 125,576 non-smoking Swedish male construction workers, found no excess risk of oral cancer either in current or former users, although a 2-fold increased risk for pancreatic cancer was observed (Luo *et al.*, 2007).

1.4.5.2.7 Asian smokeless tobacco use

The experience in Sweden contrasts with that in Asia. In particular, the Indian subcontinent (India, Pakistan and Southeast Asia), where smokeless tobacco in its various combinations of betel-leaf, areca nut, lime and tobacco has been established as a risk factor for oral cancer following several major reviews (IARC, 1985; Gupta *et al.*, 1996; Cogliano *et al.*, 2004; IARC, 2004b).

Asian smokeless tobacco products include: betel quid, paan, naswar, nass, and gutka, and their use is widely considered to be related to the high rates of oral cancer in the region (Gupta *et al.*, 1996). The evidence for the use of smokeless tobacco in Asian countries was recently re-reviewed in some detail by Mayne *et al.* (2006). The case-control studies largely originate in the Indian subcontinent and report widely varied findings. Merchant *et al.* (2000) found the risk of developing oral cancer in users to be 2- to 4- fold higher than in non-users, while Balaram and colleagues (2002) report a 5- and 42-fold higher risk for users of paan (containing tobacco) in men and women respectively (although the confidence intervals for the female risk were wide: 24-76). A further large case control study with over 1,500 cases of oral cancer, reported the association with betel chewing to be nearly 3-fold without tobacco included in the quid, compared to a nearly 7-fold increase when tobacco was included (Znoar *et al.*, 2003). Tobacco appears to be the key aetiological factor, but its combination with other components may enhance the risk (Gupta, 1996). Subsite analysis of the literature revealed that the buccal mucosa (usually adjacent to where the tobacco is placed in the oral cavity) is the site oral cancer most commonly develops when associated with these forms of tobacco use (Mayne *et al.*, 2006).

1.4.5.3 Alcohol

Epidemiological evidence of the association between alcohol and oral cancer has been reviewed extensively. Detailed narrative reviews include those carried out historically by: IARC (1988), Boyle *et al.* (1990), and more recently by: Mucci and Adami (2002), Mayne *et al.* (2006) and Boffetta and Hashibe (2006). Systematic reviews and meta-analyses have also been attempted on the topic, first by the World Cancer Research Fund in association with the American Institute for Cancer Research (WCRF / AICR, 1997), and more recently in a series of studies by researchers from the Istituto di Ricerche Farmacologiche ‘Mario Negri’ in Milan (Corrao *et al.*, 1999; Bagnardi *et al.*, 2001a; Bagnardi *et al.*, 2001b; Corrao *et al.*, 2004).

The narrative reviews paint a very convincing picture associating alcohol consumption with oral cancer risk. In examining epidemiological studies from across the world since as early as the 1960s, alcohol has been shown to be consistently associated with increased risk of oral cancer – both independently and synergistically with tobacco (IARC, 1988; Boyle *et al.*, 1990; Mucci and Adami, 2002; Mayne *et al.*, 2006). In summary, from these reviews, several aspects and patterns of alcohol consumption were consistently found to be important. An increased oral cancer risk was associated with increased frequency of drinking, but no relationship was found with duration (years) of consumption, and no risk

associated with ‘light’ consumption (usually defined as 0-4 drinks per week). A decreased risk with alcohol cessation was also found, although the evidence was not strong. Differential effects between the sexes were presented, with men generally having a 3-fold increased risk with heavy drinking, compared to a 2-fold in women; and certain types of alcoholic beverage seem to confer differential risk. The type of alcohol most commonly consumed in a particular country or culture usually was found to confer the greatest risk at equivalent consumption levels – thus, beer and spirits in the United States, wine in Italy, Sake in Japan, and Calvados in the Bas-Rhin, France conferred greatest risks. In addition, consumption of alcohol out with meals was found to be associated with increased risk. There was no consistency in the anatomical subsite at highest risk from alcohol consumption. Most of the studies reviewed were of case-control design, with one of the earliest and largest (753 case and 832 control subjects) by Blot *et al.* (1988) being amongst the most widely quoted on the topic – where they found an increased risk in heavy drinkers who were not smokers, but no risk with light alcohol consumption.

The systematic reviews took a more focused approach to the question of the risk associated with alcohol consumption. The World Cancer Research Fund in association with the American Institute for Cancer Research (WCRF / AICR, 1997) undertook a systematic review of evidence linking alcohol consumption to cancers of the upper aerodigestive tract. They concluded that data from 11 (6 retrospective and 5 prospective) cohort studies, and from 19 case-control studies showed an increased risk for oral and pharyngeal cancer with higher alcohol consumption, irrespective of the type of alcohol consumption. While they did not undertake a meta-analysis of the data, they did qualitatively assess the strength of the relationship as providing ‘convincing’ evidence (assessment based on pre-set criteria, on a four-point categorical scale as being: ‘insufficient’, ‘possible’, ‘probable’, and ‘convincing’).

The series of systematic reviews and meta-analyses from Italy attempted to quantify this relationship (Corrao *et al.*, 1999; Bagnardi *et al.*, 2001a; Bagnardi *et al.*, 2001b; Corrao *et al.*, 2004). All reviews provide an estimate demonstrating an increased risk of oral cancer associated with alcohol consumption. Each review built on the previous one and added the most recent studies in the area. Corrao *et al.* (2004) provided the most comprehensive estimate with relation to oral and pharyngeal cancer. In assessing the alcohol associated risk, 14 case–control studies and one cohort study provided 4,507 cases of oral and pharyngeal cancer. Meta-analysis found a strong direct trend of increasing risk with increased alcohol consumption for oral and pharyngeal cancer, a stronger risk than that for both oesophageal and laryngeal cancer across all levels of alcohol drinking. Significant

increased risks were found, starting from the lowest dose of alcohol considered (25 g/day, corresponding to about two drinks per day), where there was nearly a 2-fold increase, rising to a 6.5-fold increase in people drinking the highest amounts (100 g/day). Thus, there was no threshold limit to the amount of alcohol associated with increased risk, that is, there was a significant risk associated with even modest amounts of alcohol consumption. The nature of the design of these meta-analyses meant that it could not necessarily fully control for the effects of tobacco use, and could not assess the impact of patterns of drinking behaviour.

The difficulty in elucidating evidence of the risk of alcohol consumption, independent of other factors, particularly smoking, was a strong recurring theme in both the narrative and systematic reviews. A recent International Head and Neck Cancer Epidemiology (INHANCE) consortium pooled analysis of individual patient data (IPD) from 15 case-control studies and had sufficient cases and controls to disentangle the effects of smoking / tobacco use from alcohol consumption (and vice versa). They found that among the never users of tobacco (cases n=1072; controls n=5775), alcohol consumption was associated with an increased risk of head and neck cancer only when alcohol was consumed at high frequency (2-fold increase for three or more drinks per day, compared to never drinkers) (Hashibe *et al.*, 2007).

The most recent significant data related to alcohol and oral cancer, which were not considered in either the systematic reviews nor the INHANCE pooled analysis, were those from the National Institute of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study in the US (Freedman *et al.*, 2007). This large prospective cohort study of 611 men and 183 women (over 50 years of age) contributed 2,203,500 person-years of follow-up between 1995/96 and 2000. For heavy drinkers (>3 drinks per day) the increased risk was just over 2.5-fold for women, significantly higher than for men who had an approximately 1.5-fold increased risk, while moderate consumption of up to one drink per day may be associated with reduced risk relative to non-drinking in both males and females.

Several reviews on the potential caricinogenic mechanism for alcohol in relation to oral cancer have been undertaken over the past decade, mainly led by Ogden at the University of Dundee (Wight and Ogden, 1998; Ogden and Wight, 1998; Ogden, 2005). These reviews have focused on histological and exfoliative cytological studies of the oral epithelia which have examined the effect of alcohol on cellular structure and function. In summary, the pathways are not fully understood, but alcohol may influence the

proliferative cells by both intracellular and intercellular (permeability) pathways. The carcinogenic exposure of the proliferating stem cells in the basal layer may also be regulated through these pathways. Thus, alcohol may enhance the vulnerability of epithelial cells to carcinogens such as those from tobacco smoke, or itself cause mucosal atrophy, or inhibit DNA repair. Debate ensues about whether alcohol is carcinogenic in itself. However, there is broad agreement that particular alcoholic beverages may contain specific carcinogens which act directly on oral tissues and that the metabolism of alcohol into the carcinogenic acetaldehyde may also take place in oral tissues. The explanation of why oral cancer arises in some, but not most people, who consume excess alcohol and smoke is generally left unsatisfactorily to 'individual variation' and genetic factors.

1.4.5.4 Combination of tobacco and alcohol

The many studies which have examined the interaction between alcohol and tobacco on oral cancer risk have been extensively reviewed by Boyle *et al.* (1990), Mucci and Adami (2002), and Mayne *et al.* (2006). A strong synergistic relationship between these two major risk factors is well recognised. First observed in a case-control study by Rothman and Keller (1972), and repeated in many studies since, the combined risk of smoking and alcohol consumption is greater than additive, with the heaviest users of tobacco and alcohol being found to have up to a 30-fold increased risk (Blot *et al.*, 1988). A recent meta-regression analysis of two case-control studies (containing 1,022 case and 1,216 control subjects) with data on oral and pharyngeal cancer found a greater than 20-fold increased risk with the combined behaviours of more than 30 cigarettes per day and four or more alcoholic drinks per day (Zeka *et al.*, 2003).

Asian smokeless tobacco products have also been reported to have a greater than additive effect on oral cancer risk when combined with alcohol consumption (Ko *et al.*, 1995).

1.4.5.5 Diet and nutrition

The importance of diet and nutrition in the aetiology of oral cancer is increasingly being accepted. Historically, interest initially stemmed from the observation that women with Plummer-Vinson syndrome, an iron-deficiency condition, were at increased risk of oral cancer (Boyle *et al.*, 1990). This previously quite common condition, was described as contributing to a very high female to male ratio of oral cancer in Sweden through the 1970s (Larsson *et al.*, 1975).

Several detailed narrative reviews have attempted to capture the full extent of the association between nutrition and oral cancer, including those by Boyle *et al.* (1990), Chainani-Wu (2002), IARC (2002), Mucci and Adami (2002), and Mayne *et al.*, (2006). However, the diversity of definitions and the multiple components of the diet make such reviews seem cumbersome and ad-hoc.

The relationship between diet and oral cancer risk is best considered via the two systematic reviews that exist in the area. The first was undertaken by the World Cancer Research Fund in association with the American Institute for Cancer Research (WCRF / AICR, 1997), while the second was undertaken more recently by Pavia and colleagues (2006).

The WCRF / AICR (1997) undertook a comprehensive systematic review of evidence linking food and nutrition to all cancers, and included a chapter on oral and pharyngeal cancer. Fifteen case-control studies (from 1977 to 1993) contained data on fruit and vegetable consumption. Eight of the ten studies reporting data on fruit and five of the seven studies reporting data on vegetables, demonstrated a protective association. One cohort study (Hirayama, 1985) included in the review found a decreased risk of oral and pharyngeal cancer with higher intake of green and yellow vegetables. These findings were consistent when comparing the studies which adjusted for tobacco use and alcohol consumption. While they did not undertake to quantify the effect, they did qualitatively assess the strength of the relationship as providing ‘convincing’ evidence (assessment based on pre-set criteria, on a four-point categorical scale as being: ‘insufficient’, ‘possible’, ‘probable’, and ‘convincing’) for diets high in fruits and vegetables to decrease the risk of oral and pharyngeal cancer.

In the same review, data from five case-control studies found that vitamin C also ‘possibly’ decreased the risk of oral and pharyngeal cancers. There was inconsistent or limited evidence and therefore no judgement could be made on the association between any other vitamins or minerals. In terms of other foods or drinks, there was either no or limited evidence available to assess the effect of: cereals (grains); pulses; meat, poultry, fish, and eggs; milk and dairy products; herbs, spices, and condiments; coffee or tea; or on food processing methods including: salting and refrigeration; curing or smoking; or cooking methods. However, there was, in the view of the expert review panel, ‘possible’ evidence from four case-control studies suggesting that drinking maté (a tea-like drink made from infusion of dried Yerba maté leaves, common in South America) was associated with increased oral and pharyngeal cancer.

A second report from the WCRF / AICR, due for publication in November 2007, plans to update the evidence and use more analytical methods for assessing the relationship between nutrition and cancer (WCRF / AICR, 2002).

Pavia *et al.* (2006) updated this systematic research and took the analysis a step further by attempting to quantify the effects of fruit and vegetable consumption (reviewed by Conway, 2007). Sixteen observational studies (15 case-control and one cohort) from the worldwide literature met the inclusion criteria and provided diet data from over 5,000 study subjects. A thorough review and analysis methodology included utilisation of: quality assessment of included studies; robust data extraction; and comprehensive meta-analyses techniques. The main findings from the meta-analysis were that each portion of fruit or vegetable consumed per day reduced the risk of oral cancer by around 50%. Interpretation of individual studies on diet risk factors are extraordinarily difficult due to the various methods and forms of collecting information on diet as well as the general dietary differences between populations. This was reflected in the high level of heterogeneity when the studies were pooled. Nevertheless, the results held in a systematic series of meta-analyses, including sub-group and sensitivity analyses including limiting the analyses to those adjusting for smoking and alcohol – although residual confounding could still have been present.

Fully assessing dietary behaviour independent of smoking and alcohol consumption is not straightforward. In particular, cigarette smokers have been shown in a meta-analysis of fifty-one published nutritional surveys from 15 different countries with 47,250 non-smokers and 35,870 smokers to consume less essential nutrients from fruit and vegetables (Dallongeville *et al.*, 1998). Therefore, fully disentangling smoking and diet is not only difficult, but may be less relevant, than an approach which builds a ‘multiple risk factor’ aetiological model to assess the risks associated with oral cancer.

Nevertheless, the data linking fruit and vegetable intake to oral cancer are increasingly being recognised. The Joint Expert Committee of the WHO and the UN Food and Agriculture Organisation (FAO) concluded that there was a ‘probable’ association between fruit and vegetable intake and oral cancer – the highest grading of evidence given for any cancer site (Joint WHO/FAO Expert Consultation, 2003).

As a ‘pseudo-biomarker’ for nutritional status, anthropometric measures are also receiving some interest, particularly with regard to body mass index (BMI) – i.e. the relationship between weight and height. The literature is not conclusive on this matter. Two case-

control studies reviewed by Mucci and Adami (2002) and a further two more recently undertaken case-control studies (Nieto *et al.*, 2003) suggest that low BMI, indicating poor overall nutritional status, is associated with increased oral cancer risk. There are many difficulties involved in interpreting these data, not least the effect oral cancer itself has on body mass, but also the difficulty in separating the BMI effects from dietary and other behavioural risk factors. Finally, on a somewhat related theme, no relationship has been noted associating oral cancer risk to physical activity (or to the lack of) (Mucci and Adami, 2002).

1.4.5.6 Human papillomavirus

There have been several narrative reviews which assess the evidence of the relationship between human papillomaviruses (HPV) and oral cancer (Scully, 2002; and Mayne *et al.*, 2006), and the evidence is increasing.

More than 100 different strains of HPV have been identified to date. HPV can potentially be transmitted through sexual contact including oral sex (see below). Infection with HPV most commonly is associated with genital warts or papillomas which are benign epithelial lesions. However, the causal association of mucosal human papillomaviruses (HPV) with cervical cancer in particular, but also with cancers of the male and female genitals, and the anus, is becoming well established – with up to 10 strains of HPV being implicated (Walboomers *et al.*, 1999; Bosch and De Sanjose, 2003). There is also strong molecular evidence supporting the role of HPV (particularly HPV-16) in the pathogenesis of oral cancer. Kreimer *et al.* (2005) undertook a systematic review and pooled analyses from over 5,000 head and neck cancer specimens from 60 studies. They found an overall HPV prevalence of around 25%, which was higher in oropharyngeal cancers (36%) than in oral cavity cancer (24%). HPV-16 accounted for the majority of oropharyngeal cases (87%), compared to oral cavity cases (68%); while HPV-18 was rare in oropharyngeal cases (3%), but higher in oral cavity cases (34%). Gillison and co-workers (2000) from the Johns Hopkins School, Baltimore, in the first of a series of studies in this area, found an HPV prevalence of 25% in over 250 cases of oropharyngeal tumours (90% HPV-16).

In the very recent Johns Hopkins follow-up study investigating behavioural risk factors, oral HPV infection was found to be strongly associated with oropharyngeal cancer among subjects, independent of tobacco and alcohol use (D'Souza *et al.*, 2007). Additionally, in 2005, in the largest case-control study to date, an international multi-centre IARC coordinated study examined data on 1,670 cases and 1,732 control subjects and found an

almost 3-fold increased risk for oral cavity cancer and an over 9-fold increased risk for oropharyngeal cancer (Herrero *et al.*, 2003).

The interest in HPV in the aetiology of oral cancer is also associated with the finding that those tumours which are HPV positive are associated with a better prognosis. This was also shown in the Johns Hopkins series, with oropharyngeal cancer patients with HPV-positive tumours having an almost 60% reduced mortality rate compared to those with HPV-negative tumours (Gillison and Shah, 2001; Gillison, 2004). Such findings have also led to growing interest in the possibility of HPV-vaccinations for oral cancer (D'Souza *et al.*, 2007), following the success of HPV-vaccinations for preventing cervical cancer (Harper *et al.*, 2006). However, as yet no clinical trials have been undertaken or are currently registered with the WHO International Clinical Trials Registry Platform (ICTRP) (ICTRP, 2007).

1.4.5.7 Other infections

A multitude of other viral, fungal (candidal), and bacterial infections have been reported in the literature as being associated with oral cancer. The limited evidence available has been reviewed thoroughly by Scully (2002) and Mucci and Adami (2002).

Other viral infections potentially associated with oral cancer, include the Herpes Simplex Virus (HSV). Both HSV-1 and HSV-2 strains have been found in a small US case-control study to show up-to a 3-fold increased risk (Maden *et al.*, 1992). However, the evidence is weak and inconsistent. In a more recent US case-control study of similar size, Parker *et al.* (2006) found no association when adequately adjusting for tobacco and alcohol use. They also compared their results to all other recent studies which had investigated the HSV-oral cancer association and found the evidence was equivocal.

While the human immunodeficiency virus (HIV) and the associated acquired immunodeficiency syndrome are related to a number of different malignancies, including non-hodgkins lymphoma and skin cancers among others, there is only limited evidence in the form of case-series studies which associate it with (squamous cell) oral cancer (Flaitz *et al.*, 1995). A large record-linkage cohort study found HIV, via subsequent opportunistic infection with Herpes virus (HHV-8), to be strongly associated with Kaposi's sarcoma (Biggar *et al.*, 1996). Employment of similar methodologies has shown that HIV increased the risk of HPV-associated cancers, including oropharyngeal cancer (Frisch *et al.*, 2000).

Other viruses have also been shown to be associated with cancer. Evidence from small Japanese pathology case-series studies, one a small case-series study (Shimkage *et al.*, 2002) and one a descriptive epidemiology study, found that the Epstein-Barr virus (HHV-EBV) is a common virus association with infectious mononucleosis and oral hairy leukoplakia. It is also associated with Burkitt's lymphoma, Hodgkins and Non-Hodgkins lymphoma and nasopharyngeal carcinoma.

The suspected role of fungal infection, in particular chronic candidal infections, in the aetiology of oral cancer does not come from the epidemiological literature, but rather the pathology case-series literature – where they have been shown to be present in potentially malignant and dysplastic oral lesions (McCullough *et al.*, 2002).

In terms of bacterial infections, the only epidemiological study to focus on the association of syphilitic (*Treponema pallidum* bacterium) infection with oral cancer was a large US cohort study, following over 15,000 people between 1972 and 1987 (Michalek *et al.*, 1994). They noted an increased risk in oral cancer incidence (although non-significant), but failed to satisfactorily control for tobacco and alcohol behaviours. Further, it was untreated late stage (tertiary) syphilis which has previously been implicated. This is now a relatively rare condition, due to early diagnosis and treatment, and its role in oral cancer aetiology is not considered significant (Johnson, 1991). Other pathology studies have attempted to associate the oral microbial flora with oral cancer. Although the evidence for aetiology is rather unconvincing, increased numbers of anaerobic bacteria were found in the biofilms of pathological samples taken from a series of 21 patients with oral cancer (Nagy *et al.*, 1998).

1.4.5.8 Occupational exposures

The role of occupational exposures has been explored in both historic (Boyle *et al.*, 1990) and recent reviews (Mucci and Adami, 2002; Mayne *et al.*, 2006). All reviews note limited consistency in findings from individual studies and the inherent difficulty in isolating specific occupational toxic exposures, in addition to the complication of adjusting for the highly variable tobacco and alcohol behaviours across and within occupations.

Boyle and colleagues (1990) report the early findings of increased oral cancer mortality among those involved in the manufacture and trade of alcohol, although these were not repeated in more recent studies. Textile workers were the next group to receive attention, with several case-control studies and cross-sectional surveys pointing to an increased risk,

especially among women. Inconclusive findings on the increased risk associated with working in the printing industry were also distilled.

Mucci and Adami (2002) detail the evidence from three cohort and two case-control occupational studies from across Europe and the United States. While noting the interpretational and confounding difficulties, these studies have highlighted increased risk associated with particular industry and occupational workers, including those in the rubber industry with three cohort studies experiencing a 3- to 4- fold increased oral cancer mortality risk. The finding was confirmed in a detailed review of cancer risk in general related specifically to the rubber industry (Kogevinas *et al.*, 1998). Cooks are the other group highlighted in this review, with data from three European case-control studies demonstrating up to a 7-fold increased oral cancer risk (particularly in younger cooks).

Finally, in Mayne and colleagues' (2006) review, from data in a series of case-control studies, the finger is pointed at a wide-range of specific occupations and industries including: butchers, carpet fitters, machinists, leather-workers, textile workers, electronics industry workers, and sugarcane farmers. One large cancer registry to census occupation record-linkage cohort study from Finland seems to suggest occupational factors are not significantly associated with increasing oral and pharyngeal cancer. However, a cohort study of similar design in Sweden finds increased risk in a range of occupations including dentists, hairdressers, launderers, and dry cleaners – which they propose may be partly explained by their work related exposures (Ji and Hemminki, 2005).

The interconnectedness of industries, occupations, and occupational exposures with socioeconomic circumstances – even with occupational social class – is not considered in any of the major oral cancer aetiological reviews. Individual studies are also sparse, although Menvielle *et al.* (2004) in a case-control study found that the socioeconomic risk associated with increased laryngeal cancer risk could be explained by a combination of adjustments for alcohol consumption, tobacco use, and occupational exposures. The literature relating to occupational exposures on the whole is far more advanced with regard to investigations of lung and laryngeal cancers. Here, job-exposure matrices have been employed in large studies to elucidate risk associated with specific occupational chemical toxins and hazards (Berrino *et al.*, 2003).

1.4.5.9 Sexual behaviour

Sexual behaviour has thus far escaped significant attention in the major oral cancer aetiological reviews. Scully (2002) reviewed the evidence for oral cancer risk in relation to the sexual transmission of HPV – noting that an oro-genital transmission for HPV was becoming an accepted hypothesis, although he noted the evidence was not yet conclusive, and many studies were underway.

Schwartz and colleagues (1998) were the first to investigate sexual history and behaviours (including oral sex) in relation to oral cancer risk. In a reasonably sized US case-control study (almost 300 cases, and nearly 500 controls) they found no increased risk for any sexual behaviours in estimates either unadjusted or adjusted (for tobacco and alcohol use). These findings were echoed in a further three case-control studies from across the world in: Italy (Talamini *et al.*, 2000), Cuba (Garrote *et al.*, 2001), and Poland (Lissowska *et al.*, 2003). However, four case-control studies – one from India (Rajkumar *et al.*, 2003); two from the US (Smith *et al.*, 2004b; D'Souza *et al.*, 2007), and one from Sweden (Rosenquist *et al.*, 2005) – have begun to see an association with (mainly oral) sexual behaviours, although the estimates were highly variable. Strong conclusions are cautioned against due to the possibility of transmission through direct mouth-to-mouth transmission. However, these studies do find strong correlations with HPV infection (often with biomarker evidence), and demonstrate a greater risk for oropharyngeal cancer over oral cavity cancer.

Thus, there seems to be some equivocacy in the literature regarding sexual history, but perhaps some convergence recently on the associations of oral sex and HPV with regard to increased association with oropharyngeal risk.

1.4.5.10 Dental conditions, oral hygiene, and mouthwash

Mayne *et al.* (2006) have reviewed most of the dental factors in relation to increased oral cancer risk. General poor oral health, measured by the number of missing teeth, from five case-control studies, seems to show an association with increased oral cancer. However, this finding does not hold up consistently to adjustment for tobacco and alcohol, and rarely are socioeconomic factors, which are strongly correlated with poor oral health (Treasure *et al.*, 2001), taken into consideration. Data from eight case-control studies did not demonstrate an association with denture wearing and oral cancer risk.

Periodontal health has recently, for the first time, been assessed in relation to oral cancer. A small retrospective case-control study from the US, in which 51 White male patients with tongue cancer had their records and radiographs compared to a similar number of hospital clinic controls (Tezal *et al.*, 2007), suggests an association between chronic periodontitis and tongue cancer in men. However, the study was very small and there was inadequate adjustment for tobacco exposure as life-time smoking histories were not available. Poor oral hygiene seems to be inconsistently associated with oral cancer risk, with as many as six case-control studies presenting varied, equivocal and rarely significant evidence of a relationship between infrequent toothbrushing and increased risk. There has been considerable interest in the association between mouthwash (particularly, but not exclusively, alcohol containing ones) and oral cancer. As many as eight case-control studies have attempted to evaluate this association. However, no clear or consistent findings or trends were demonstrated, in relation to oral cancer, with regard to type used, or frequency or duration of use (Mayne *et al.*, 2006).

Other potential oral factors, identified by Mayne *et al.*, (2006), include broken, rough or jagged teeth, with data from four case-control studies not suggesting any increased oral cancer risk. There is also no evidence in the literature to suggest any dental treatments are associated with increased oral cancer risk. Three case-control studies have attempted to investigate the relationship with dental radiographs, but found no evidence for an excess oral cancer risk in those exposed (Mayne *et al.*, 2006).

1.4.5.11 Medical factors

There seems to be no evidence to support the role of ionizing radiation or medical treatments in oral cancer. There was some recent interest in the role of non-steroidal anti-inflammatory drugs, but this work has been discredited due to research fabrication (Horton, 2006). In terms of medical conditions, Boffetta and co-workers (2001) found an increased risk in head and neck cancer, particularly oral cancer, of the order of a 5-fold excess risk (along with lung cancer) in alcoholics in a large Swedish hospital-based cohort study. This followed nearly 200,000 patients for over 10 years, on average, between 1965-1994. This finding correlates with the data presented previously in relation to the excess risk associated with heavy and prolonged alcohol drinking. Other medical conditions, highlighted in the review by Mayne *et al.*, (2006), potentially associated with increased oral cancer risk include Fanconi anaemia and psoriasis, although disentangling the common risk factors of smoking and alcohol behaviours between psoriasis and oral cancer makes strong conclusions rather suspect.

1.4.5.12 Hormonal factors

Mucci and Adami (2002) reviewed the literature with regard to the potential association of reproductive factors, hormones, and hormone receptors with oral cancer risk. While there were no studies which find these factors associated with oral cancer (squamous cell carcinoma), there were a number of studies which had begun to suggest that salivary gland tumours may, at least in part, be mediated by hormonal factors. Salivary gland tumours are beyond the scope of this thesis.

1.4.5.13 Potentially malignant lesions

The literature on potentially malignant lesions as a risk factor for oral cancer comes mainly from the pathology literature, rather than from an epidemiological perspective, and was reviewed recently by Scully *et al.* (2003). Zhang *et al.* (2005) more recently concluded that there is little understanding of the factors that affect the transformation or progression rates of potentially malignant lesions to oral cancer. Conversion rates for potentially malignant lesions to oral cancer are very low. In one recent Canadian study involving a series of 116 potentially malignant lesion cases, a range from 11 months to 8 years was observed, even in those with a high risk histology and verified with molecular biomarkers present (Rosin *et al.*, 2000). In the UK, clinical opinion considers only 2-3% of white patches and 3-5% of red patches to progress to oral cancer (Lewis, 2003). However, the data to support this statement are not so obvious, mainly due to the difficulties in determining which of a range of potentially malignant lesions will progress to a malignancy. It is out of this uncertainty, therefore, that all patients with potentially malignant lesions should be kept under some form of clinical observation.

From 10 studies with pathology case-series data, in a review by Scully and colleagues (2003), oral leukoplakia is reported as having low malignant transformation (although is the most commonly present oral potentially malignant lesion). The level of malignant transformation has been found in case-series studies to range from around 4-35% over 10 years. This is likely to reflect the range of types of leukoplakia lesions that exist, particularly with regards to levels of dysplasia present. The most recent study in this area, undertaken in the Netherlands by Schepman *et al.* (1998) where they followed up 166 hospital-bound patients with histologically confirmed leukoplakia, recorded a 3% annual malignant transformation rate. In an earlier case-series study by Hogewind *et al.* (1989) (not included in the review by Scully *et al.*, 2003) of over 200 patients, also from the Netherlands, diagnosed with oral cancer, there were co-existing white lesions present in

48% (Hogewind *et al.*, 1989). An additional long-term case-series study (also not included in the review by Scully *et al.*, 2003), found that the longer the lesion is present, the greater the risk of malignant transformation (Silverman *et al.*, 1984). Homogenous white leukoplakias are generally not reported to be malignant or potentially malignant, while verrucous or speckled leukoplakias are much more likely to be premalignant. This was reported by Scully and colleagues in a further review, which focused mainly on prevention and diagnosis of oral cancer (Abdel-Salem *et al.* 1990; Scully *et al.*, 2005).

Scully *et al.* (2003) also reviewed three pathological case series studies on erythroplakias (erythroplasia) and reported that they have the highest malignant potential – up to 17 times more than leukoplakia. They reported that this high malignant potential was related to the finding that these lesions contain areas of dysplasia, carcinoma *in situ*, or invasive carcinoma in virtually every case.

Oral submucous fibrosis was considered as a risk factor for oral cancer in a recent review by Tilakaratne *et al.* (2006). They noted that it is a relatively common potentially malignant condition in the Indian subcontinent and that chewing the areca nut is associated with increased risk. They also found from summarising the findings of three case-series follow-up studies that the malignant transformation rate varied by study population, between 7 and 26% and that it exhibits a moderate malignant potential – in between that of leukoplakia and erythroplakia. In the one long-term follow-up Indian study, the transformation rate was 8% in 17 years (Murti *et al.*, 1985).

There are further aspects of potentially malignant lesions which may help explain the malignant transformation story. These are largely beyond the scope of review of the risk factors for oral cancer. However, in summary, they include: the presence and degree of dysplasia exhibited by a potentially malignant lesion, although the criteria for the histological assessment of dysplasia severity does not always predict malignant transformation with certainty, and further genetic / molecular biomarkers are being searched for to aid prediction (Rosin *et al.*, 2000).

Risk factors for potentially malignant oral lesions themselves needs mention, although they are by and large the same as for oral cancer. Tobacco chewing has been reported as an important risk factor for leukoplakia, erythroplakia, and oral submucous fibrosis; while tobacco smoking was described as a potential risk factor for only oral leukoplakia in a series of reports from a study in India of risk factors for potentially malignant lesions (Hashibe *et al.*, 2000a; Hashibe *et al.*, 2000b; Hashibe *et al.*, 2002; Hashibe *et al.*, 2003).

From the same series, alcohol drinking appears to increase the risk of oral leukoplakia by 50% (Hashibe *et al.*, 2000a), the risk of oral submucous fibrosis by 100% (Hashibe *et al.*, 2002), and the risk of erythroplakia by 200% (Hashibe *et al.*, 2000b). High socioeconomic status was found to be protective and reduced the risk for all oral potentially malignant lesions by 30-40% (after adjustment for age, sex, BMI, tobacco chewing, smoking, drinking, and fruit / vegetable intake) (Hashibe *et al.*, 2003).

1.4.5.14 Second (or multiple) primary tumours

Having an exisiting primary oral cancerous lesion is considered a risk for getting another (Johnson *et al.*, 2005; Mayne *et al.*, 2006). The WHO, IARC definitions for second primary tumours are: synchronous – within six months of primary tumour diagnosis at a different oral site; and metachronous – after six months of primary tumour diagnosis at a different site or at the same site after three years (Johnson *et al.*, 2005). Two theories exist regarding the process of developing a second tumour or multiple primary tumours: the independent development of cancerous cells; or the spread of such cells to other areas of the oral mucosa. Both of these processes have been demonstrated as co-existing, and described as ‘field cancerisation’ by van Oijen and Slootweg (2000) in their recent review. In the same paper, a review of three pathology case-series studies found that in 10-35% of cases a synchronous or metachronous tumour developed, and that this depended on the location of the first primary tumour and the age of the patient.

The epidemiological literature is generally limited in this area. However three case-control studies between them, have demonstrated an association between smoking, and low fruit / vegetable intake, and increased risk of a second primary tumour. Quiting smoking was only found to be protective, with regard to the risk of developing a second tumour, if it began before diagnosis of the first (Day *et al.*, 1994; Mayne *et al.*, 2006). The descriptive epidemiology of data from cancer registries is also underexplored with regard to investigating second primary tumours. However, IARC are currently coordinating an international multicenter study of second malignant neoplasms, pooling 25 years of data from 13 population-based cancer registries from across the world (including Scotland). They have recently undertaken work on childhood, testicular, and nasopharyngeal cancers and are planning to undertake work on head and neck and oral cancer in due course (Richiardi *et al.*, 2007; Brewster *et al.*, 2007).

1.4.5.15 Family history of oral cancer

A very recent and widely publicised, but rather unscientific, online survey utilising opinion poll methodologies was undertaken by the UK national charity Cancerbackup (2007). They report that there was widely held but incorrect views on the role of family history in the aetiology of cancer, with: 91% of people questioned believing that if someone in their family has had cancer, they had a greater than average chance of getting cancer themselves; one fifth of those responding also thought around half of cancers were hereditary; and the majority of people canvassed believed family history was the biggest risk factor for cancer. However, the best estimates available on the inherited risk associated with cancer in general are around 5% where a familial association has been demonstrated (International Commission on Radiological Protection, 1998). How these, rather incorrect, opinions are formed is perhaps another matter, but it is an interesting context to investigate family history as a risk factor for oral cancer.

Mayne *et al.* (2006) reviewed the literature on familial aggregation rather comprehensively. From 12 studies (of a combination of case-control, case-series and record-linkage design) patients with oral cancer were found to have an increased likelihood of the order of 2-3-fold of having a first degree family relation also with oral cancer. It is unclear whether these patterns are due to shared alcohol and tobacco use behaviours (perhaps even environmental tobacco smoke in the family home) as such information from family history probands are limited. A re-analysis of one of the case-control studies reviewed found both: an inherited component of the risk for oral cancer over and above that of environmental factors observed when satisfactory adjustments had been made; and in addition a greater than additive synergistic relationship was seen when considering both environmental and inheritable factors together (De Andrade *et al.*, 1998). Inherited susceptibility is best considered as part of the broader genetic epidemiological picture.

1.4.5.16 Genetic epidemiology review

The genetic and molecular epidemiology is beyond the focus of this current body of research. However, no review of the risk factors associated with oral cancer would be complete without considering this topic – particularly, given the ever increasing research focus in this area. Comprehensive epidemiology reviews of the genetic and molecular risks and determinants for oral cancer have recently been published (Mucci and Adami, 2002; Mayne *et al.*, 2006). The main areas of research in this area include: high-penetrance gene

mutations and low-penetrance polymorphisms and somatic mutations – which occur as a result of both the interaction between environmental factors and genetic susceptibility.

High-penetrance genetic mutations are very rare, more often considered as familial or inherited risks (e.g. patients with Fanconi anaemia). The oral cancer risk associated with inherited cancer syndromes, which are an expression of high-penetrance gene mutations, was comprehensively reviewed by Prime and colleagues (2001) in Bristol where a number of genetic syndromes were found to increase the risk of oral cancer.

Low-penetrance polymorphisms are more often considered as gene-environment interactions and have been thoroughly reviewed by Mucci and Adami (2002) and Mayne *et al.* (2006). Genes that may affect the occurrence of oral cancer include those involved in: (i) metabolism of nutrients / carcinogens; (ii) DNA repair; and (iii) cell cycle control. However, most studies which investigate these associations encompass an aggregation of all head and neck cancers (usually including oral cavity, pharynx and larynx; and occasionally including oesophagus). All studies are of case-control study design which to some degree lowers the level of evidence and conclusiveness that can be drawn from the studies. This is often overlooked when considering genetic-associated investigations because of the subject matter and high-level technological analyses employed. Small sample size in such studies can add to the potential for bias (Garcia-Closas *et al.*, 1999). Only the gene-environment interactions will be considered in more depth here.

The main gene-environment interactions emerging in the aetiology of oral cancer have been previously documented (Mucci and Adami, 2002; Mayne *et al.*, 2006) and are summarised here: (i) Glutathione S-transferase enzymes (GST) are a family of genes that have a role in the detoxification of carcinogens such as benzo(a)pyrene found in tobacco smoke and also ethanol and its metabolites; (ii) Cytochrome P450 (CYP) are genes which code for enzymes also responsible for metabolising benzo(a)pyrene as well as other aromatic hydrocarbons in tobacco smoke – although within the CYP family of genes there are inconsistent findings reported about their role in oral cancer; (iii) N-Acetyltransferases (NAT) genes are involved in the detoxification of aromatic amines found in tobacco smoke and in some workplaces. However, there is limited evidence of their role in increasing oral cancer risk with only one case-control providing such evidence; (iv) Alcohol dehydrogenase (ADH) genes are involved in the metabolism of alcohol to acetaldehyde or acetic acid. Contradictory evidence is available in this area, but preliminary pooled analyses of over 4000 cases and over 5000 controls from the INHANCE consortium studies, where a full range of ADH genes have been profiled, suggest protective effects of

particular ADH variants (ADH1B and ADH7), with the effect increasing with increasing alcohol consumption (Hashibe *et al.*, 2007).

Hanahan and Weinberg (2000) describe the six hallmarks of cancer – these refer to the acquired capabilities of: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evading apoptosis (programmed cell death), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. The pathway of particular interest at present, in terms of the socio-biological interface, is the role of telemeres and telomerase related to the limitless replicative potential of tumour cells.

Over-expression or neo-expression of the intra nuclear enzyme telomorase has also been found to be associated with oral cancer development, albeit in small case-series studies of oral lesions (Curran *et al.*, 1998; Fujita *et al.*, 2004). The role of telomeres and telomerase in relation to oral cancer was recently reviewed by Sebastian and colleagues (2005). Briefly, telomorase is generally absent in normal cells but present in cancer cells. It seems to confer longevity on tumour cells by allowing the life-span controlling telomere to retain their length at the ends of the chromosomes. Telomeres are located on the ends of chromosomes and maintain the structure of the genome. Telemeres naturally shorten after mitotic division, but the rate of shortening may be increased by oxidative stress (von Zglinicki, 2002).

Shortened telomeres are a defining characteristic of most cancers including oral cancer (Sebastian *et al.*, 2005), while telomerase reactivation restores telomere function, albeit at a shorter set length (DePinho, 2000). Recently, there has been focus on telomere shortening as a potential aetiological risk factor itself for various diseases including coronary heart disease (Brouilette *et al.*, 2007) and some cancers (McGrath *et al.*, 2007). However, there is debate about whether telomere shortening is a true risk factor for these diseases or a biomarker for processes such as ‘biological ageing’(Cawthon *et al.*, 2003; Adams and White, 2004). This theory is complicated by the confounding effect that behaviours (associated with cancer) such as smoking (McGrath *et al.*, 2007) which increase oxidative stress, and the potential life ‘stresses’ associated with poor socioeconomic circumstances (Adams and White, 2004; Epel *et al.*, 2004) have also been found to shorten telomeres.

The interaction between genes and the environment have not been fully explored from a socioeconomic point of view. Mackenbach (2005) found no empirical evidence in the area but set out hypotheses on the subject. A direct genetic link to socioeconomic circumstances or ‘poverty gene’ was all but rejected; however, genetics could still potentially play a role.

He did propose that genetic determinants of personal attributes (e.g. cognitive abililty, personality, physical, and mental illness) could influence education, occupation, and social mobility, either directly or through a behavioural pathway. However, he warned that both this kind of research and the potential findings could have worrying ethical implications. A concern echoed recently by Professor Alyson Pollock of Edinburgh University: 'Poverty is not a genetic issue, it is an economic issue. If you go down that route you may end up with eugenics, and that is extremely worrying' (Gray, 2006).

Genetic epidemiology has been limited to date by trying to explore individual genes or variations in the building blocks of the genetic code. Single nucleotide polymorphisms (SNPs) represent the single DNA building block (National Cancer Institute, 2007a). With the coding of the full human gene recently completed by the International Human Genome Sequencing Consortium (2004) and the full gene code having begun to be assessed for certain conditions and cancers (National Cancer Institute, 2007b) – there is potential in the future for a full gene approach to be considered for oral cancer research.

Davey Smith *et al.* (2005) describe further developments including the establishment of population-based 'biobanks' – which are the storage of biological material from large numbers of individuals within a population. In effect they become a large cohort-study resource with the potential to enhance the understanding of the interaction between social, demographic, behavioural, genetic, and health factors related to multiple disease aetiologies. The relatively small number of cases of oral or even head and neck cancer may be out of reach of individual biobanks, however, international pooling of such resources may offer a solution.

1.4.5.17 Race / ethnicity

The main data available on race / ethnicity are from descriptive epidemiological studies, (reviewed in Section 1.4.4.2). However, it is important to consider race / ethnicity as a determinant and potential factor when considering the risk of oral cancer. The paucity of analytical epidemiological studies on this topic was noted by Scully and Bedi (2000). There seems to be only two notable exceptions in the literature, with both papers reporting findings pertaining to the same large US population-based case-control study (Gridley *et al.*, 1990; Day *et al.*, 1993). They found that differences in oral cancer risk between Black and White people could primarily be related to differences in alcohol consumption and tobacco use amongst the Black subjects, but could also be potentially explained by nutrition and socioeconomic factors.

1.4.5.18 Age

Peto and Doll (1997) urged caution in over interpreting the influence of age in cancer aetiology, arguing that there is no common biological process which could be defined as aging. However, DePinho (2000) described advancing age as the 'most potent risk factor' for many cancers – describing emerging concensus around the age-related combined physiological, genetic, and molecular effects contributing to the induction of cancers primarily within epithelial tissue.

Rather than being the focus of epidemiological research, however, age is usually simply adjusted for in the analysis of other effects. However, age may be considered a component of oral cancer risk from two perspectives. Firstly, with increasing age, time or biological ageing may affect the biology and function of cells which perhaps affects the immune system competence and paves the way for malignant transformation. The other age-related time factor is the potential for cummulative exposure to other risk factors such as tobacco use, and alcohol consumption. It may take prolonged exposure to these factors over several decades to precipitate cancer development. This latter perspective, arising from descriptive epidemiology (reviewed earlier), in addition to being a factor of the time exposed, may be related to a cohort effect – whereby those in a specific population who were born around the same time were potentially exposed communally to risk factors.

From the descriptive epidmemiology data (reviewed earlier) the incidence of oral cancer is highly correlated with age. Older adults are at greatest risk, but potentially the risk is increasing more rapidly in younger adults. However, this has not been adequately explored in the analytical epidemiology literature.

One small case-series of 40 oral cancer cases in Scotland found that most were exposed to the traditional behavioural risk of smoking, high alcohol consumption, and low fruit and vegetable intake (Mackenzie *et al.*, 2000). Two, rather small, case-control studies have investigated risk factors in young adults in the UK (Llewellyn 2004a, 2004b). Both studies were undertaken in the South East of England, one between 1990 and 1997, and the second between 1999 and 2001, with 53 and 116 cases respectively. Again, tobacco use and alcohol consumption were the dominant risk factors, although both studies concluded that due to the short duration of exposure other factors (yet unascertained) may be involved. Data from two larger case-control studies from Italy and Swtizerland were pooled together by Rodriguez and colleagues (2004). From the 137 cases under 46 years, similar findings

were shown, with tobacco and alcohol behaviours exhibiting a dominant role in elevating risk.

Despite the evidence, a number of commentaries (Soutar and Robertson, 2001; Scully, 2005) still suggest that oral cancer in younger adults is a different disease, with different aetiological factors. However, further and larger studies are required to investigate this further. Due to the practical problem of ensuring sufficient numbers of younger people are included, a pragmatic approach would be to pool individual patient data (IPD) from multiple studies – a stated aim of the INHANCE consortium (INHANCE, 2007).

1.4.5.19 Sex

From the descriptive epidemiology data (reviewed earlier) men are more likely to develop oral cancer than women, although the differences seem to be narrowing over time.

Most case-control studies control or adjust for sex routinely, rather than report separate data for men and women. Many case-control studies focus only on men (as could be observed in the detailed descriptions of the studies in the analytical epidemiology review), but few studies could be located that focus only on women. A series of small case-control studies focusing on women were undertaken in the US in the 1980s (Kabat *et al.*, 1989). One case-control study (reported in two articles) of over 250 women with oral cancer and over 500 controls in the Southern United States revealed that the exceptionally high mortality from this cancer among White women in the South is primarily related to chronic use of chewing tobacco ‘snuff’ or to tobacco and alcohol use (Winn *et al.*, 1981). They also found no occupational associated risk with the textile industry – the main female occupation in the region (Winn *et al.*, 1982).

A second case-control study of 125 female cases and 107 controls started out with the hypothesis that mouthwash was a particular risk factor in women. However, it discovered the risk associated with its use was confounded by smoking and alcohol use – where mouthwash was being used to ‘disguise the smell of tobacco or alcohol’ – and that the main risk factors were smoking and alchol drinking.

While there has been no more recent case-control studies focusing on women, one case-series in the Netherlands of 314 female patients diagnosed with oral cancer, reported high alcohol and tobacco use in many (although the data collection was limited to medical records), with those with late stage disease having the heaviest use (de Boer *et al.*, 1997).

Further, age at presentation was also affected by the amount of alcohol and tobacco consumed, with non-users presenting with tumours approximately 15 years later.

While these studies have mainly focused on risk factors in females, there are limited analyses that have tried to investigate the role of sex as a risk factor. Future pooled analysis of IPD from existing case-control studies, may provide sufficient numbers to explore in detail whether risk factors are different by sex, or whether aspects of gender other than behaviours may influence risk.

1.4.5.20 Socioeconomic circumstances and inequalities

Whether socioeconomic circumstances are considered as a risk determinant or a risk factor as defined here is an interesting debate. Factors are considered to some degree amenable to change, and are more often related to behaviours, while determinants are by and large fixed and set (Greenland, 2005). However, by these criteria, it has also been argued that socioeconomic circumstances should be considered risk factors in the same way as genetic factors and other factors (Susser and Schwarz, 2005). As there is a potential prospect of influencing the expression of genes and there interaction with the environment, so to it may be possible to influence the upstream socioeconomic factors. Further, from an analytical perspective, Susser and Schwartz (2005) provide a convincing case outlining that there is no theoretical basis to treat socioeconomic factors differently.

The literature on socioeconomic status, socioeconomic circumstances, and inequalities in relation to the risk of oral cancer is rather limited. A recent prominent review of both the descriptive and analytical epidemiology of oral and oropharyngeal cancer failed to even mention the socioeconomic perspective (Mucci and Adami, 2002).

The descriptive epidemiology has been reviewed in Sections 1.4.4.2 and 1.4.4.5 in relation to global and UK incidence data respectively. With regard to analytical epidemiological studies, there are not many which have the questions of the relationship between oral cancer and socioeconomic status as their aim.

Following a detailed literature search in the Ovid suit of databases (which included Ovid Medline 1950-2007, and Embase 1980-2007), and the ISI Web of Science databases, only six oral cancer analytical epidemiological studies were identified that set out to examine socioeconomic factors. As these studies often covered more than one socioeconomic

measure, rather than separate out the individual measures in this review, each study will be reviewed in turn.

Elwood *et al.* (1984) undertook the first case-control study which investigated social factors in relation to head and neck cancer. In a robust analysis, they compared data in 374 matched case-control pairs in total (133 oral and 87 pharyngeal cases) in Vancouver, Canada. For low compared to high occupational social class, they found a 1.5-fold significantly increased risk for mouth cancer, and just over 2-fold elevated risk for pharyngeal cancer (they also had made efforts to control for alcohol and cigarette consumption).

In northern Italy, Ferraroni *et al.* (1989) (data also presented in La Vecchia *et al.*, 1992b) looked at occupational social class and educational attainment in 50 cases of mouth and pharynx cancer (among other tumours of the digestive tract) and in 1944 controls. They found a significant protective effect, in the order of 80%, with high education attainment (>12 years) compared to low education levels (<7years) which was maintained following adjustment for smoking and alcohol behaviours. High occupational social class (social class I or II) provided a nearly 0.5-fold reduced risk, compared to those in low social class groups (IV or V). However, these effects were not significant when adjusting for smoking and alcohol consumption.

Greenberg *et al.* (1991) undertook a large comprehensive case-control study to focus on education, and also looked at occupational social class in relation to oral and pharyngeal cancer risk. From across the US, in 762 male cases and 837 male controls they found no significant elevated risk for low education or occupational social class in unadjusted analyses and also when they adjusted for use of tobacco products, alcohol consumption, and poor dentition. However, they also adjusted for percentage of years worked in these analyses, which itself was independently associated such that low percentage (<80%) of years worked gave an over 2-fold significantly increased risk compared to high percentage (>90%) of years worked. This adjustment may have confounded the education and occupational social class – it could be considered a potential measure of socioeconomic status, perhaps being related to unemployment experience or retirement (however, it could not be determined if these were self-determined or involuntary events).

Using the data from the series of case-control studies in northern Italy and also from studies in Switzerland, Bosetti *et al.* (2001) compared education and occupation socioeconomic factors over the periods 1984-1992 and 1992-1997. In total there were

1,126 cases of oral and pharyngeal cancer, and 4,642 controls. The main findings were that the socioeconomic correlates had changed between the two periods. In analysis adjusted for alcohol and smoking, data from 1984 to1992, showed that compared to higher socioeconomic groups: low levels of education (<7 years) conferred over a 2-fold increased risk, and low occupational social class (IV and V) gave nearly a 5-fold increased risk. Data from 1992 to 1997 showed that there were no significant differences in socioeconomic groups using both education and occupation measures. Unfortunately, the paper only seems to report these data without any detailed exploration of the explanations, or further analysis of the behavioural data in these periods.

More recently, Guneri *et al.* (2005), in a small case-control study of 79 oral cancer cases and 61 controls in Turkey, noted that low education levels (i.e. 'illiterate') conferred over a 3-fold significant increased risk of oral cancer when compared to high education levels ('high school or university'). However, there were no differences observed within either occupational social classes or between income groups. It also must be noted that there were no adjustments for alcohol and tobacco behaviours in these analyses.

Andreotti *et al.* (2006) in a case-control study of 325 cases and 468 controls from São Paulo, Brazil found no significant differences between low (illiterate) and high (high school and university) education groups, while the occupational analysis was related to occupational related hazardous exposures rather than to socioeconomic status.

Therefore, there is a somewhat equivocal picture of the socioeconomic effects associated with oral cancer risk – although this has been obtained from only six studies which had clearly set out to examine socioeconomic factors in relation to oral cancer. However, it is also evident that there are an enormous number of studies which have included socioeconomic analyses as part of a comprehensive analysis of behaviour risk factors, primarily with a view to adjust for socioeconomic status in the analysis of lifestyle factors.

It was felt that a narrative review of the socioeconomic data in all studies could only provide a 'scattergun' approach to reporting the literature, and it was decided that the best way to deal with the potentially enormous quantity and variation of literature related to socioeconomic factors was to conduct a systematic review, with a meta-analysis where possible to quantify the effects. Within this approach, the importance of the various different socioeconomic measures could be assessed, and also differences by age-group, sex, geographic location, and adjustment factors could be comprehensively analysed.

1.5 Hypotheses

The overall aim of this body of work is to test the following hypotheses:

1. The incidence of oral cancer in the UK is increasing, and there are large differences in the incidence and trends of oral cancer between Scotland and the rest of the UK. The increases are greater amongst younger age-groups.

2. Inequalities in the socioeconomic distribution of oral cancer in Scotland are widening.

3. Globally, oral cancer risk is associated with low individual socioeconomic status.

4. Within a case-control study for head and neck cancer socioeconomic bias effects the selection and participation of cases and controls.

5. Local individual socioeconomic status and area-based socioeconomic circumstances are associated with increased risk of oral cancer, over and above that of known behavioural risk factors particularly: alcohol, tobacco, and diet.

1.6 Objectives

These hypotheses will be tested through the following objectives, each of which will comprise a chapter:

1. To undertake a descriptive epidemiology study to investigate the recent incidence trends in oral cancer in Scotland and the UK. This will focus on assessing the influence of age, sex and geographic region on incidence (Chapter 2).

2. To undertake a descriptive epidemiological study to assess the distribution of oral cancer in Scotland – focusing on the level of area-based socioeconomic deprivation and whether this pattern has changed over time (Chapter 3).

3. To systematically review and meta-analyse the case-control study literature from around the world to determine the risk of oral cancer associated with low socioeconomic status (Chapter 4).

4. The Alcohol Related Cancers and Genetic susceptibility in Europe (acronym ARCAGE) case-control study will be utilised to explore the socioeconomic factors associated with participation and selection in a case-control study (Chapter 5);

5. ARCAGE will also be utilised to investigate the risk associated with components of individual socioeconomic status and area-based socioeconomic circumstances (Chapter 6).

2 Descriptive epidemiology (I): Incidence of oral cancer in the United Kingdom (1990-1999) – recent trends and regional variations

2.1 Introduction

As outlined in Chapter 1, epidemiological research into oral cancer is complicated by the variety of anatomical subsites which has led to diversity of reporting in this field (Moore *et al.*, 2000). While these sites are anatomically diverse, cancers of the oral cavity and oropharynx are for the most part homogeneous with respect to the descriptive epidemiology, and major risk factors associated with their causation (Robinson and Macfarlane, 2003). Moreover, from a clinical point of view, all sites can be examined by a routine oral health assessment (Macpherson *et al.*, 2000). Hence, in this chapter, the term 'oral cancer' will be used to encompass both oral and oropharyngeal cancer.

Oral cancer in the UK is rare in patients under 45 years, occurring mainly in males in their 6th and 7th decade of life from socioeconomically deprived backgrounds (Quinn *et al.*, 2001; Scottish Cancer Registry, 2003). Younger patients, defined arbitrarily here and elsewhere, as being aged less than 45 years, have previously been estimated to account for approximately 6% of all oral cancers (Llewellyn *et al.*, 2001). Concern that mortality rates for tongue cancer are increasing in young males was raised from analysis of Scottish data over 15 years ago (Macfarlane *et al.*, 1987). Later evidence confirmed that this may be a problem experienced worldwide (Macfarlane *et al.*, 1994a). From a risk factor point of view, it has been suggested that oral cancer in the young may be a distinct entity which acts in an aggressive manner (Mackenzie *et al.*, 2000; Llewellyn *et al.*, 2001).

Rising trends in oral cancer incidence have been observed internationally (Ferlay *et al.*, 2004) and also within the UK (Johnson and Warnakulasuriya, 1993; Quinn *et al.* 2001; Macpherson *et al.*, 2000) and a dramatic increase in incidence has been reported in Scotland from the 1980s to the mid-1990s (Robinson and Macfarlane, 2003). However, a detailed comparative analysis across the UK has not been undertaken.

2.2 Aims

This chapter describes the recent time trends of oral cancer incidence in the UK by age and sex, and also investigates regional variations using data from the population-based UK cancer registries.

2.3 Patients and methods

Initially, the Scottish Cancer Registry, hosted within the Information and Statistics Division (ISD) of the NHS National Services Scotland (NHS NSS), was contacted regarding accessing data on oral cancer. In accordance with the guidelines of the Scottish Cancer Registry – acting on behalf of all UK cancer registries, access was approved by the Caldicott Guardian for NHS NSS, and a Confidentiality Statement was signed by the author and Professor Jeremy Bagg, Head of the Dental School as study Sponsor.

UK cancer registries were then contacted directly through links provided by the United Kingdom Association of Cancer Registries (UKARC). Data were requested electronically, utilising a pre-formed data collection sheet based on the information available in the Scottish Cancer Registry (Appendix 1). Follow-up requests were made via the Scottish Cancer Registry. Data were first requested in May 2003 and finally received from all 12 UK regional cancer registries by September 2003 (Figure 2.1).

The study population included all individuals registered with histologically confirmed carcinoma of the lip (International Classification of Diseases, ICD-10 C00), mouth or oral cavity (C01-06), and oropharynx (C09-10) as detailed in Table 1.3 (Chapter 1), diagnosed between January 1st 1990 and 31st December 1999, from the 12 regional registries – which have 100% coverage of the UK population. Where case diagnoses were provided coded to ICD-9, they were re-coded to ICD 10 (WHO, 1992).

For each of the cancer registry areas, annual mid-term population estimates for the period by age and sex were supplied for England and Wales by the Office for National Statistics (Office for National Statistics, 2003); for Northern Ireland by the Northern Ireland Statistics and Research Agency (General Register Office Northern Ireland, 2003); and for Scotland by the General Registrar Office for Scotland (General Registrar Office for Scotland, 2003).

Figure 2.1 12 UK Regional Cancer Registries

Scotland

N. Ireland

Northern & Yorkshire

North Western

Merseyside & Cheshire

Wales

West Midlands

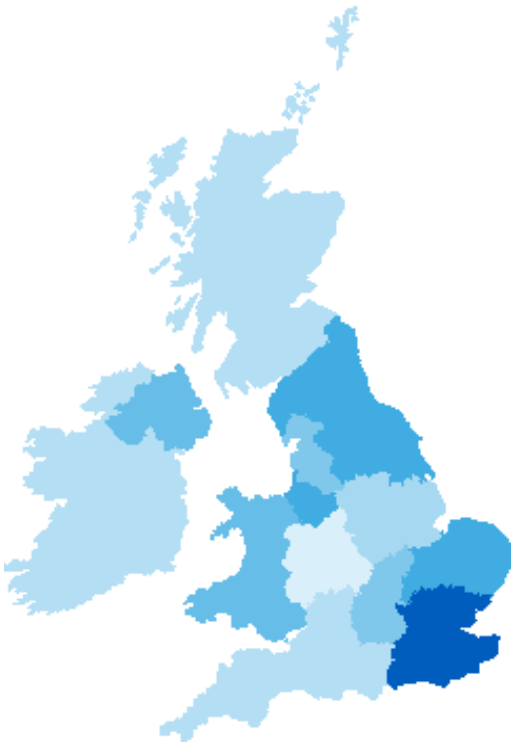
Oxford

Trent

South & West

East Anglia

Thames



All incidence rates are reported as age-standardised per 100,000 person-years at risk. To account for changes over time in the age composition of the population, incidence rates were age-standardised using the direct method to the 'European standard population' (Waterhouse *et al.*, 1976), giving European age-standardised rates (EASRs). It is recognised that age-standardised incidence rates give greater insight into trends over time and are more useful for comparison between areas, age-groups and sexes (Harris *et al.*, 1998).

Overall (all age) incidence rates were ranked separately for males and females by cancer registry and by UK country. The 'rank statistic' is an intuitive way of representing the relative burden in different geographical areas (Harris *et al.*, 1998). In addition, the lifetime risk of oral cancer was calculated using the revised method of calculation, known as the 'lifetime risk' method (see Section 1.2.2.8) (Harris *et al.*, 1998).

Poisson regression models were used to assess the significance of trends in incidence after adjusting for age (5-year age-groups) and sex. Variations in trends between cancer

registries were assessed using Poisson regression – examining interactions between time and cancer registries. Poisson regression was also used to model the incidence trends, adjusting for any changes in the age profile of the population (using registry specific populations adjusted for age profile, not EASR). Estimates of the percentage change from the first to the last year (and average annually) in incidence over time were extracted from the models. The nine regional cancer registries of England were combined to provide data for England which were used in UK intra-country comparisons. Due to the shortened time-period of available data from Northern Ireland (NI), UK estimates for changes over time, excluded NI data.

Statistical analyses were performed on SPSS for Windows 7.5 (SPSS Inc.) and Poisson regression analyses were performed using STATA9.0 (STATA Corp.) statistical package.

2.4 Results

2.4.1 UK

Anonymised individual records by, 5-year age-groups and sex, were received from all 12 cancer registries in the UK. A total of 32,852 cases of oral cancer were reported: 21,230 (65%) males and 11,622 (35%) females. This gave a UK age-standardised incidence rate of 5.2 / 100,000 person-years: with oral cancer being more than twice as common in males (7.3 / 100,000) than females (3.1 / 100,000) (Table 2.1). The lifetime risk of developing oral cancer was considerably higher in Scotland (1.84% in males; 0.74% in females) than the rest of the UK (0.97% in males; and 0.48% in females); and consistently higher in males than in females (Table 2.1).

2.4.2 Registry area

Table 2.1 shows the overall incidence of oral cancer per 100,000 person-years at risk for each of the UK cancer registries, the four UK countries and for the UK as a whole. There were large variations in the incidence rates when computed by registry areas. The highest rates were found for Scotland which were significantly ($p<0.001$) higher than all the other registries, being nearly double the rates found for some registries (for both males and females). Rates were significantly ($p<0.001$) lower in the South of England (East Anglia, Oxford, South & West, and Thames) compared to the North of England (Merseyside & Cheshire, Northern & Yorkshire, North Western, Trent, and West Midlands) and the other

countries (Northern Ireland, Scotland, and Wales). The rates for males were significantly higher ($p<0.001$) than for females in all registry areas.

Table 2.1 **UK cancer registry comparisons of oral cancer incidence rates and cumulative percentage lifetime risks – period 1990-1999. Ranked by age-standardised incidence rates per 100,000 person-years at risk (European standardised population) for UK cancer registries, countries of the UK, and UK combined; by sex.**

Males			Females		
	EASR	**Lifetime risk (%)**		**EASR**	**Lifetime risk (%)**
By Cancer Registry:					
Scotland	12.6	1.84	Scotland	5.0	0.74
Merseyside & Cheshire	8.8	1.19	North Western	3.3	0.48
North Western	8.8	1.21	Wales	3.3	0.54
Wales	8.8	1.29	Merseyside & Cheshire	3.2	0.49
Northern & Yorkshire	8.3	1.21	Oxford	3.1	0.52
N. Ireland (1993-1999)	7.7	1.29	Northern & Yorkshire	3.0	0.48
East Anglia	6.5	1.03	East Anglia	2.9	0.47
Oxford	6.1	0.94	South and West	2.9	0.46
Trent	6.1	0.89	Thames	2.8	0.43
West Midlands	6.0	0.86	N. Ireland (1993-1999)	2.7	0.45
South and West	5.8	0.89	West Midlands	2.7	0.41
Thames	5.9	0.84	Trent	2.6	0.39
By Country:					
Scotland	12.6	1.84	Scotland	5.0	0.74
England	6.6	0.97	England	2.8	0.48
Wales	8.8	1.29	Wales	3.3	0.54
Northern Ireland	7.7	1.29	Northern Ireland	2.7	0.48
United Kingdom	7.3	0.97	United Kingdom	3.1	0.48

Table 2.2 UK cancer registry comparisons of oral cancer incidence rates for younger (<45 years) and older age-groups (+45 years) – period 1990-1999. Numbers of registrations with % change in incidence between 1990 and 1999 and significance of this change; by sex and age-group.

Registry	Aged < 45					
	Males			Females		
	EASR (1990-99)	%change[2] incidence	p value for trend	EASR (1990-99)	%change[2] incidence	p value for trend
East Anglia	0.7	72.9	0.11	0.6	-42.3	0.43
Merseyside & Cheshire	1.1	12.6	0.72	0.4	51.3	0.39
North Western	0.9	-18.9	0.50	0.5	-12.6	0.74
N. Ireland (1993-1999)	0.5	-41.4	0.63	0.4	-94.2	0.16
Northern & Yorkshire	0.8	-35.1	0.14	0.4	61.2	0.08
Oxford	0.9	-4.5	0.89	0.5	90.9	0.07
South & West	0.7	67.5	**0.01**	0.6	38.7	0.21
Scotland	1.1	22.5	0.34	0.4	50.4	0.22
Thames	0.7	57.2	**< 0.01**	0.4	58.5	**0.02**
Trent	0.7	7.2	0.81	0.5	9.0	0.81
Wales	0.7	-1.8	0.96	0.6	-7.2	0.87
West Midlands	0.7	62.9	**0.03**	0.4	132.3	**< 0.01**
England	0.8	26.1	**< 0.01**	0.5	46.8	**< 0.001**
UK[1]	0.8	24.7	**< 0.01**	0.4	43.2	**< 0.001**

Registry	Aged 45 +					
	Males			Females		
	EASR (1990-99)	%change[2] incidence	p value for trend	EASR (1990-99)	%change[2] incidence	p value for trend
East Anglia	16.8	1.4	0.91	7.1	5.5	0.73
Merseyside & Cheshire	22.4	4.5	0.66	8.3	18.9	0.20
North Western	22.9	10.8	0.16	8.2	41	**< 0.001**
N. Ireland (1993-1999)	20.4	-36.0	**< 0.01**	6.8	4.2	0.83
Northern & Yorkshire	21.5	6.6	0.29	7.6	23.9	**< 0.01**
Oxford	15.5	26.1	**0.03**	7.7	31.5	**0.04**
South & West	14.9	23.0	**< 0.01**	7.0	32.4	**< 0.001**
Scotland	32.2	27.9	**< 0.001**	12.4	32.9	**< 0.001**
Thames	15.1	31.1	**< 0.001**	7.1	26	**< 0.001**
Trent	15.7	14.4	0.09	6.5	38.6	**0.01**
Wales	23.1	14.4	0.10	8.2	46.8	**< 0.001**
West Midlands	15.3	1.4	0.86	6.7	29	**< 0.01**
England	16.5	15.3	**< 0.001**	6.9	27.9	**< 0.001**
UK[1]	18.9	17.1	**< 0.001**	7.7	29.4	**< 0.001**

[1] NI excluded from UK estimates;
[2] %change calculated between 1990 and 1999;
significant values (p<0.05) in bold

2.4.3 Age

Table 2.2 presents the overall incidence rates for the period 1990 to 1999 by age (45+: "older" and <45: "younger" groups) and by sex (the trends over time presented in this table will be discussed in detail below). Oral cancer incidence for the whole period (1990-1999) was significantly ($p<0.001$) higher in older compared to younger adults across the UK. This was true for all the cancer registry areas and was seen for both sexes.

For males, in the younger groups, those in Scotland and in Merseyside & Cheshire had incidence rates significantly ($p<0.01$) higher than the UK average. In the older age-group, those in Merseyside & Cheshire, the North West, Northern Ireland, Northern & Yorkshire, Scotland, and Wales all had incidence rates significantly ($p<0.01$) higher than the UK average. Males in the South of England had significantly lower incidence rates than the UK average for the older age-group ($p<0.001$) but not the younger age-group (Table 2.2).

For females, incidence rates for the younger age-group were fairly similar across the cancer registries. In the older age-group, females in Merseyside & Cheshire, the North West, and Scotland had incidence rates significantly ($p<0.01$) higher than the UK average (Table 2.2).

2.4.4 Time-trends

2.4.4.1 Overall

For both sexes and all ages, between 1990 and 1999, there was an almost universal significant ($p<0.05$) increase in incidence across all registries of the UK, with the exception of Merseyside & Cheshire and East Anglia cancer registry areas (Table 2.3).

2.4.4.2 By sex

A summary of the incidence trends over time by country for all ages are highlighted for males and females in Figures 2.2 and 2.3 respectively. Between 1990 and 1999, the UK incidence rates for oral cancers rose in males of all ages from 6.5 to 8.3 per 100,000 (percentage increase in EASR 18%); and in females from 2.6 to 3.6 per 100,000 (percentage increase in EASR 30%). These increases in both males and females were seen across the UK with the exception of Northern Ireland, where there has been a steady reduction in the incidence since 1993 (the year from which data are available). However,

caution must be given to interpreting the Northern Ireland data, with the incidence only being accounted for by a small number of cases. In males, the increase was most marked for Scotland, but this increase was not significantly different from the rest of the UK (p=0.065).

Table 2.3 UK cancer registry comparisons of % change in oral cancer incidence rates for all ages and significance of this change; for all ages combined: by sex, and for both sexes combined – period 1990-1999.

Registry	All ages					
	Males		Females		Both sexes	
	%change[2] incidence	p value for trend	%change[2] incidence	p value for trend	%change[2] incidence	p value for trend
East Anglia	54.0	0.95	0.9	0.94	5.1	0.640
Merseyside & Cheshire	55.1	0.60	20.7	0.14	11.4	0.213
North Western	8.1	0.24	36.9	**< 0.01**	19.8	**< 0.01**
N. Ireland (1993-1999)	-34.8	**< 0.01**	-4.7	**< 0.01**	-41.4	**< 0.05**
Northern & Yorkshire	3.6	**< 0.001**	26.1	**0.01**	12.2	**< 0.05**
Oxford	22.5	0.51	36.9	**< 0.001**	31.3	**< 0.01**
South & West	26.1	**< 0.001**	33.3	**< 0.001**	32.0	**< 0.001**
Scotland	27.9	**< 0.001**	36.0	**< 0.001**	32.6	**< 0.001**
Thames	33.3	**< 0.001**	28.8	**0.01**	34.7	**< 0.001**
Trent	13.5	0.09	28.8	**< 0.01**	21.5	**< 0.01**
Wales	13.5	0.12	42.3	**< 0.01**	24.9	**0.001**
West Midlands	6.3	0.43	36.0	**< 0.01**	19.1	**< 0.01**
England	16.2	**< 0.001**	29.1	**< 0.001**	23.4	**< 0.001**
UK[1]	17.6	**< 0.001**	30.4	**< 0.001**	24.2	**< 0.001**

[1] NI excluded from UK estimates;

[2] %change calculated between 1990 and 1999

significant values (p<0.05) in bold

For all ages combined across the UK (excluding Northern Ireland), incidence has been increasing by 1.8% per annum (p<0.001) for males and 3.0% per annum (p<0.001) for females. Similar significant increases were observed for males in five registries and for females in nine (Table 2.3). The difference in the increases between men and women across the UK was non-significant.

Figure 2.2 **Male trends in age-standardised (European population) incidence rates per 100,000 for oral cancer in the countries of the UK, 1990-1999.**

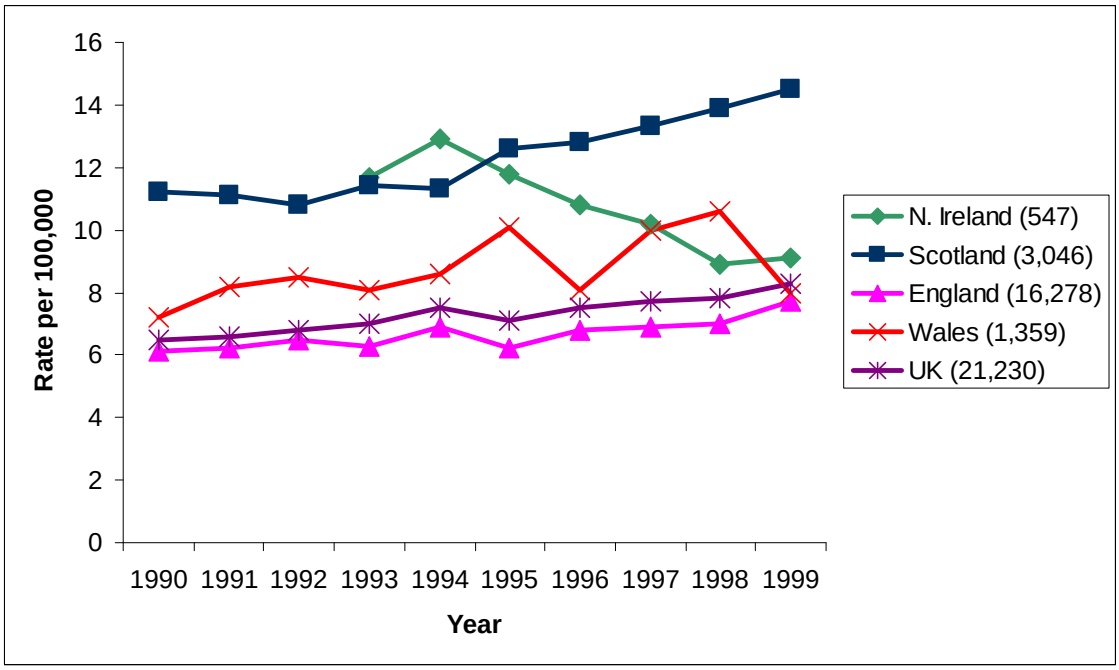
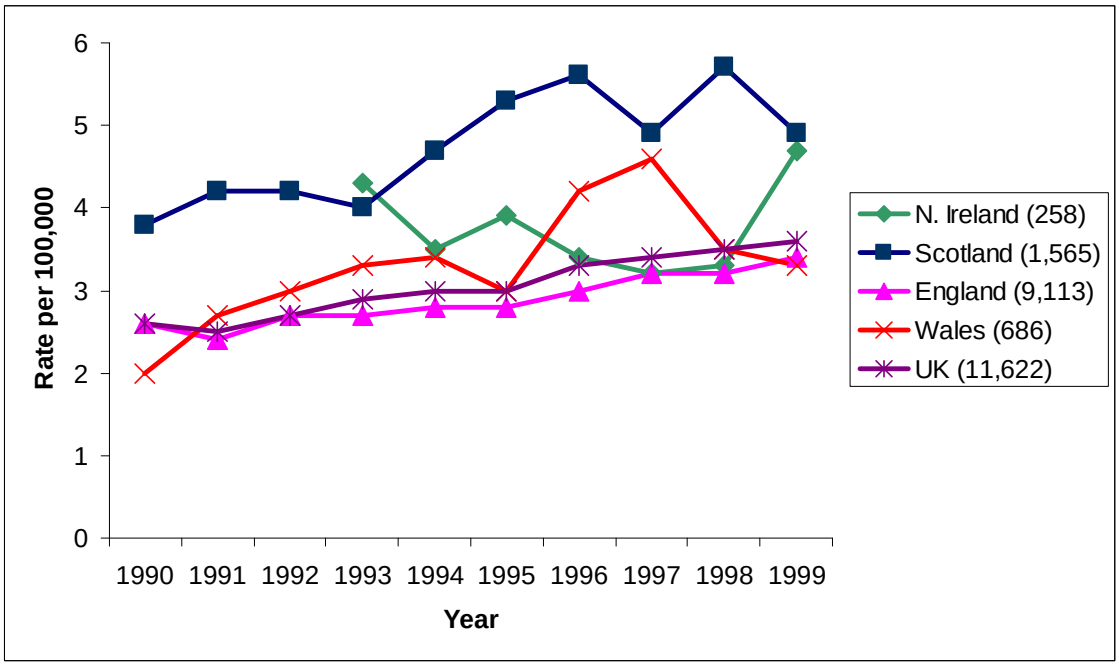


Figure 2.3 **Female trends in age-standardised (European population) incidence rates per 100,000 for oral cancer in the countries of the UK, 1990-1999.**



2.4.4.3 By age

The year on year change for combined male and female data has been significantly increasing ($p<0.001$) by 3.5% per annum in the younger age-group and 2.4% per annum in the older age-group (Table 2.4). For both sexes, the younger age-group trend over time varied across the cancer registries, with only three registries showing significant ($p<0.001$) increases. For the older age-groups, a modest upward trend was seen for most registries and this was significant ($p<0.01$) for six of the twelve registries. In the older age-group, the increasing trend was most marked for Scotland.

Table 2.4 UK cancer registry comparisons of % change in oral cancer incidence rates for all ages and significance of this change; for both sexes combined by age group (<45 years and +45 years) – period 1990-1999.

Registry	All sexes			
	Aged <45		Aged 45+	
	%change[2] incidence	p value for trend	%change[2] incidence	p value for trend
East Anglia	25.1	0.509	3.3	0.771
Merseyside & Cheshire	15.1	0.450	10.4	0.279
North Western	-19.4	0.453	21.7	**0.001**
N. Ireland (1993-1999)	-92.3	0.201	-38.2	0.310
Northern & Yorkshire	-4.0	0.864	13.2	0.190
Oxford	30.8	0.328	31.5	**<0.01**
South & West	60.6	**<0.001**	30.0	**<0.001**
Scotland	33.2	0.148	32.6	**<0.001**
Thames	64.1	**<0.001**	32.2	**<0.001**
Trent	8.7	0.732	21.9	**<0.01**
Wales	-4.8	0.884	27.4	0.001
West Midlands	96.2	**<0.001**	11.7	0.090
England	37.7	**<0.001**	22.1	**<0.001**
UK[1]	34.9	**<0.001**	24.4	**<0.001**

[1] NI excluded from UK estimates;

[2] %change calculated between 1990 and 1999;

significant values (p<0.05) in bold

2.4.4.4 By age and sex

The magnitude and significance of the trends in incidence for both males and females in younger and older age-groups are shown in Table 2.2. In the younger age-group, for the UK (excluding NI), incidence between 1990 and 1999 had increased by 24.7% in males ($p<0.01$) and 43.2% in females ($p<0.001$); while for the older age-group the increase was

less dramatic at 17.1% in males ($p<0.001$) and 29.4% in females ($p<0.001$). For the younger age-group, the trend over time varied considerably across cancer registries in both sexes, with three registries showing significant increases ($p<0.05$) in males and only two in females. For younger males: Thames, South West, West Midlands, and East Anglia had the highest percentage increases in the four countries. Comparison of the trends over time within this period, between registries and countries of the UK, found no significant differences between the trends in the younger groups and older groups. The increasing trend for the older age-group was seen for all the registries (with the exception of NI) and was significant ($p<0.05$) for males in five registries and for females in nine.

In Scotland there were increased incidence rates in younger adults (22.5% in men; 50.4% in women) although these rises were not statistically significant. However, the increases in incidence rates in older adults (27.9% in men; 32.9% in women) were significant ($p<0.001$).

2.5 Discussion

2.5.1 Key points and comparison with other work

The incidence of oral cancer in the UK continues to rise. This study found 32,852 cases of oral cancer diagnosed across the UK over a 10 year period. The numbers of reported oral cancers diagnosed each year increased each year from 2,813 in 1990 to 3,885 in 1999. Underlying this headline, there were significantly increased incidence rates of oral cancer across: geographic areas of the UK; in younger and older age-groups; and in both sexes.

The increases in rates were more marked in Scotland and in cancer registries in the North of England. The increases in incidence in the UK in general and Scotland in particular are consistent with previous reports (Johnson and Warnakulasuriya, 1993; Quinn *et al.*, 2001; Robinson and Macfarlane, 2003). The trends seen are also broadly consistent with data from other countries. The rising incidence of oral cancer in European countries was first noted in Denmark in the period 1943-1985 (Møller, 1989) and consistently repeated across Europe into the 1990s (Ferlay *et al.*, 2004).

The results of many studies from around the world also suggest that the incidence of oral cancer in young people is increasing more rapidly than for older people (Macfarlane *et al.*, 1992; Franceschi *et al.*, 1994; Hindle *et al.*, 1996; Shibski *et al.*, 2000; Robinson and Macfarlane, 2003), and similarly in females (of all ages) compared to males (Hindle *et al.*,

1996). Robinson and Macfarlane showed a dramatic increase in incidence rates for younger males in Scotland from the 1980s to the 1990s (Robinson and Macfarlane, 2003); while Quinn and colleagues reported a gradual rise across all age-groups in England and Wales (Quinn *et al.*, 2001). From the analyses presented here, the incidence rates (1990-1999) for Scottish younger males were significantly higher than the for the UK average (with only Mersyside & Cheshire being comparable) – although, the increase in incidence in younger adults in Scotland across the period was itself not significant. However, in comparison, significant increases in older people were observed in Scotland.

From the data for the whole of the UK, oral cancer remains a disease that occurs primarily in males in their 6th and 7th decades of life – remaining relatively rare in those aged 45 and younger. While the absolute percentage increases were greater in the younger than the older age-groups, there were no significant differences between these trends. Therefore, the recent concern that increases in younger adults were significantly more rapid were not corroborated in this detailed analysis which modelled the trends in incidence. Further, from these present findings, while the increase in incidence was greater in women than men, the difference was not significant; and incidence overall remained significantly higher in men than women.

2.5.2 Data quality

The importance of accurate statistical information on cancer incidence is important for planning cancer services, identifying potential future burden of care and highlighting areas for future investigation. As cancer registration is a dynamic process, the data presented here may differ from other published information relating to the same time period. Under-reporting of oral cancer by some UK cancer registries has previously been noted by Warnakulasuiya *et al.* (1994). They found this to be particularly important in the south of England, but was limited mainly to the 1980s. Consideration of the potential problem of underascertainment of (mainly historic) data and how it could affect national incidence rates and comparisons of this nature influenced the decision to focus on data from the 1990s only. Therefore a degree of caution is needed to ensure potential errors arising from underascertainment are considered.

Annually, the quality performance of each cancer registry in the UK is assessed and reported to the UK Association of Cancer Registries (UKACR) annual conference. Each report compares data on timeliness, quality, and completeness of each cancer registries' current and historic data. The tenth report was published in 2006 (Thomson, 2006) and

shows overall that (all site) cancer case ascertainment across the UK is mainly via microscopic verified tumours – with the proportion of cases being consistently greater than 80% through the 1990s and into the 21st century. This correlates with consistently low and falling proportions of Death Certificate Only (DCO) registrations – with the proportion of cases from this source consistently around 3%, although only four registries had met the 2% target of registrations as DCOs for UK cancer registries. Such a target emphasises the ethos of continually seeking to improve quality which is common in cancer registration across the UK. The mortality to incidence data ratio (M:I) is another quality indicator which records the proportion of deaths compared to cases – with a high M:I ratio suggesting underascertainment or genuinely worse survival. Overall, all cancer site M:Is are over 0.5 for the UK, with occasional outliers for specific cancer sites (e.g. lung) being continually investigated. There is no specific data reported on oral cancer (or head and neck cancer), but there is no indication that ascertainment of such cancers are a particular problem. Furthermore, a target for the timeliness of the cancer registries quality criteria was set in 2002 for 100% of cancers diagnosed in a calendar year being registered within 18 months of that year's end, and this is increasingly being met. By 2002, around 90% of cancer registrations had been completed within the target timeframe (although 100% had been reached by 2 years) (Thomson, 2006). Given the time-lag and to ensure that the time-frame of available data used in this present study was consistent for all cancer registries, the data, while requested in late 2002, were limited to the 10-year period 1990 to 1999.

2.5.3 Potential explanations for study findings

The reason for the rise in oral cancer incidence observed across Europe remains speculative, but an increase in the per capita consumption of alcoholic beverages since the 1950s has been proposed (Møller, 1989; Hindle *et al.*, 1996). The trends in oral cancer are potentially likely to be due to changing patterns of alcohol consumption and tobacco use since these are the main risk factors in Western populations (Blot *et al.*, 1996). However, it is suggested that the roles of nutrition and infection also require consideration (Møller, 1989; Hindle *et al.*, 1996).

On examination of the findings, however, it is apparent that these oral cancer trends are not easily explained by comparison to the descriptive trends in data available on the traditional lifestyle factors: particularly smoking and alcohol consumption. With regard to smoking, historical trends – more relevant to the temporal framework for the development of cancer – show a substantial fall in smoking prevalence since the 1970s, which began to slow in the early 1980s and into the 1990s. The most recent trends in adult cigarette smoking

continue to show a modest decline across the UK (Tobacco Advisory Group of the Royal College of Physicians, 2000; National Statistics, 2004; Northern Ireland Statistics and Research Agency, 2004). This is not necessarily consistent with an increased incidence of oral cancer from the 1990s.

However, tobacco smoking has been, and remains, more prevalent in the North of England and in Scotland (Tobacco Advisory Group of the Royal College of Physicians, 2000; National Statistics, 2004; Northern Ireland Statistics and Research Agency, 2004). In addition, despite the recent levelling out, these data on smoking to indicate an underlying polarisation of smoking to those from more disadvantaged backgrounds and areas (National Statistics, 2004). These patterns of smoking may help to explain the oral cancer trends observed, and indicate the pathway by which smoking may exert its continuing role in causation of oral cancer. Moreover, such data may also shed light on the greater increase in incidence of oral cancer seen in women as their smoking patterns have declined at a slower rate (Tobacco Advisory Group of the Royal College of Physicians 2000; Northern Ireland Statistics and Research Agency, 2004). It is unlikely, however that these smoking data hold the full explanation for the differences in oral cancer between these areas and the rest of the UK.

In terms of data on alcohol consumption, which has been recorded since 1978 across the UK, there has been a slight increase in overall weekly alcohol consumption among men and a much more marked one among women (Scottish Office, 1995; Scottish Office 1999; Tobacco Advisory Group of the Royal College of Physicians 2000; National Statistics, 2004; Northern Ireland Statistics and Research Agency, 2004). Therefore, the suggested role of alcohol in explaining the trends of increasing oral cancer in women may be a reasonable hypothesis. A history of heavy alcohol consumption (defined by greater than 20 units per week) was also observed in a ten-year observational case-series study of patients with oral cancer in Scotland (Llewelyn and Mitchell, 1994). It must also be noted that trend data on ‘multiple risk factors’ are not available for the UK. Of particular importance would be data on the combination of smoking and alcohol consumption behaviours, which are recognised as synergistically increasing oral cancer risk (Blot *et al.*, 1988).

Geographical inequalities in diet and nutrition do exist in the UK and are getting worse. There is a strong North / South gradient in terms of ‘healthier diets’, with people in the South East eating 33% more fruit and vegetables and significantly more fibre than those in the North West and Scotland (Department for Environment, Food and Rural Affairs,

2001). Diet has been shown to have a role in the aetiology of oral cancer (WCRF / AICR, 1997) and this could be a mediating factor for the effects of socioeconomic circumstances.

Descriptive epidemiology studies such as this are not an end in themselves, rather they generate further aetiological hypotheses. Rather than the issue of increasing incidence in younger age-groups, it was the geographic differences which jumped out – particularly those that seemed to have a socioeconomic dimension. Socioeconomic deprivation has been linked to the incidence of oral cancer in Scotland and the UK (Harris *et al.*, 1998; Edwards and Jones, 1999; Quinn *et al.*, 2001).

A detailed analysis of UK-wide socioeconomic data related to oral cancer registry information could not be undertaken at this time for two main reasons. Firstly, many registries did not collect postcode data or data which could be linked to a common socioeconomic measure as part of their cancer registration process. Secondly, the complexity of establishing a uniform measure of deprivation which could be used across the UK cancer registries was not available at the time.

However, many authors have described the 'North-South Divide' as a proxy for socioeconomic inequalities in the UK (Doran *et al.*, 2004). This North West / South East divide in socioeconomic inequalities is proposed to exist across the UK at the start of the 21st century. People of all socioeconomic classes have poorer health in Scotland compared to England; and those in Wales, the North East and North West regions of England have worse health than the South of England. This pattern was evident in the present study, in that those from the economically more prosperous South of England had significantly lower incidence rates of oral cancer than the rest of the UK for the older age-group ($p<0.001$). However, this was not seen in the younger age-group. Thus, a more detailed examination of the socioeconomic factors, from both a descriptive and analytical epidemiological perspectives seems to be the hypothesis warranting further investigation.

2.6 Conclusions

This descriptive epidemiological study of oral cancer incidence trends across the UK highlights that the burden of oral cancer is continuing to rise, which presents an increasing public health and health service challenge.

This study, as is the nature of descriptive epidemiology, leads to the generation of many further hypotheses for the explanation of the trends, rather than to strong conclusions.

From the analysis it seems that oral cancer incidence trends: are not significantly greater in younger population groups; are not readily explained by trends in behavioural risk factors; but that the general trend for a north-south divide across the UK warrants further exploration, particularly with regard to socioeconomic factors.

3 Descriptive epidemiology (II): Socioeconomic inequalities in incidence rates of oral cancer – Scotland, 1976-2002

3.1 Introduction

As described in the previous chapter, the incidence of oral and oropharyngeal cancer continues to rise across the UK: in younger and older age-groups, and in both sexes (Robinson and Macfarlane, 2003; Conway *et al.*, 2006). Changes in the traditional lifestyle risk factors of tobacco usage and alcohol consumption (Blot *et al.*, 1998; Bagnardi *et al.*, 2001a, 2001b) may not fully explain these increases, and a socioeconomic dimension may also be involved (Conway *et al.*, 2006). The risk of oral cancer appears highly correlated with socioeconomic factors, both in Scotland (Macfarlane *et al.*, 1996a; Harris *et al.*, 1998) and in the UK (Edwards and Jones, 1999; Quinn *et al.*, 2001), although this is not reflected across the world (Faggiano *et al.*, 1997). However, studies of the socioeconomic association with oral cancer tend to be cross-sectional and cannot account for changes over time (Greenwood *et al.*, 2003; Møller and Brewster, 2005) – correspondingly, these trends are less well understood.

3.2 Aims

While it was the initial intention to look at the socioeconomic related descriptive epidemiology for the whole of the UK – to follow-up the work detailed in Chapter 2, data were only readily and historically available from the Scottish Cancer Registry. Thus, the aims of this study were focused: to assess the relationship between oral cancer and an area-based measure of socioeconomic circumstances in Scotland; to assess the pattern and magnitude of any inequalities; and uniquely to look at whether this has changed over time.

3.3 Patients and methods

In accordance with the guidelines of the Scottish Cancer Registry, hosted within the Information and Statistics Division (ISD) of the NHS National Services Scotland (NHS NSS), access was requested (Appendix 2) and subsequently approved by the Caldicott Guardian for NHS NSS (Appendix 3), and a Confidentiality Statement was signed by the

author and Professor Jeremy Bagg, Head of the Dental School as study Sponsor (Appendix 4).

Incident cases of oral cancers (ICD-10 C00-C06) and cancers of the oropharynx (C09, C10, and C14) for the period 1976-2003 were requested (Appendix 5) and obtained from the Scottish Cancer Registry. Mid-year population estimates were derived from the Annual Reports of the Registrar General for Scotland for corresponding years (General Register Office for Scotland, 1977-2003). Annual and triennial age-standardised incidence rates by sex were calculated for the period 1977-2002 by direct standardisation to the European Standard Population (Waterhouse *et al.*, 1976).

This study utilised the Carstairs score to assess inequalities. It is an area-based (postcode sector) index of socioeconomic circumstances comprising four variables from the UK decennial census: social class, unemployment, overcrowding, and car ownership (Carstairs and Morris, 1991). Deprivation scores were categorised into five quintiles, from category 1 (the 'least deprived') to category 5 (the 'most deprived'), with each quintile containing an equal proportion of the population.

Firstly, 1981, 1991, and 2001 census-derived Carstairs deprivation categories were linked with cancer registration data relating to the periods of diagnosis 1976-1985, 1986-1995, and 1996-2002, respectively. Secondly, to validate this, the traditionally accepted and performed approach in Scotland, of using the 1991 census-derived Carstairs deprivation categories was applied to the whole period of diagnosis 1976-2002 (Information and Statistics Division, 2007b). There were no substantial differences observed between the two analysis methods linking the Carstairs Index to the oral cancer data. Therefore, only data from the first method, which utilised the Carstairs index calculated at the three census dates (1981, 1991, and 2001) are fully reported here. Evidence to support the similarity of the approaches is presented (at the end of the results section).

To assess the relationship between deprivation and oral cancer incidence over time and to test the significance of any differences, and of the gradients of any trends, a multilevel Poisson regression analysis model was used to incorporate the variables: age, sex, time / year, and deprivation quintile. The univariate effects of sex, age, time and deprivation were examined as categorical variables. The independent effects were analysed in a fully adjusted model, and 2-way, 3-way, and 4-way interactions were also analysed to look for more sophisticated relationships with deprivation. Statistical analyses were performed on

SPSS for Windows 7.5 (SPSS Inc.) and Poisson regression analyses were performed using the SAS statistical software package version 9.1 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

3.4.1 Time-trends: overall

The overall incidence of oral cancer for males was 11.1 per 100,000 (95%Confidence Interval 10.8, 11.3) and for females was 4.1 per 100,000 (3.9, 4.2) over the entire time period 1976-2002. Incidence in both males and females increased significantly over the period of the study. Comparing the three-year periods at the start and end of the study period, incidence in males increased from 10.1 (10.8, 11.3) to 13.3 (12.5, 14.1) per 100,000; and in females from 2.8 (2.5, 3.2) to 5.5 (5.0, 6.0) per 100,000. The median age of diagnosis was 65.1 years.

3.4.2 Time-trends: socioeconomic distribution

The relationship between deprivation and oral cancer incidence rates is demonstrated in the data in Table 3.1. For males of all ages, the ratio between the most and least deprived quintiles widened markedly across the period from 0.8 in 1976-78 to 2.6 in 1988-90, and flattened through the 1990s to 2.5 in 2000-02. In females of all ages, the ratios between the most and least deprived were somewhat lower than males, remaining stable at around 1.0 from 1976-78 to 1985-87, and increasing to between 1.3 and 1.9 thereafter.

Between 1976 and 2002, the widening gaps in oral cancer incidence between affluent and deprived socioeconomic groups by sex are clearly demonstrated in the summary graph – Figure 3.1. For males, there was a general increase in incidence of oral cancer with increasing severity of deprivation. From an inverse relationship in 1976-1978, the gap between the most and least deprived males appeared in the late 1970s and increased rapidly through to the 1990s. The gap is almost entirely explained by an increase in incidence (+196%, $p<0.001$) in the most deprived, with a (non-significant) reduction in the least deprived group over the period (-74%, $p=0.54$). A different pattern is seen for females in both magnitude and timing. The incidence increased in those from both the most and least deprived areas, with those women from the most deprived areas having the greatest increase (+163%, $p<0.001$), but a significant increase also apparent in the least deprived (+91%, $p<0.001$). The widening gap between the most and least deprived appeared in the

1980s and continued to increase until the late 1990s. Data from 2000-02 suggest that the gap had closed for women.

Table 3.1 Age-standardised incidence rates of oral and oropharyngeal cancer by sex, during nine consecutive triennia in Scotland, by Carstairs 1981 deprivation category quintile during consecutive triennia 1976-1985, Carstairs 1991 for 1986-1995 and Carstairs 2001 for 1995-2002.

Oral cancer cases	Age-standardized incidence rates per 100,000 person years at risk by period of diagnosis a and ratios 5 : 1								
	1976-1978	1979-1981	1982-1984	1985-1987	1988-1990	1991-1993	1994-1996	1997-1999	2000-2002
Males									
All	10.1	9.3	9.6	9.8	10.7	11.2	12.2	13.8	13.3
5 Most deprived	8.9	10.6	12.2	14.0	17.2	16.7	18.8	22.1	20.2
4	9.2	8.9	9.0	9.6	11.9	12.2	11.7	14.3	13.9
3	9.1	10.8	9.6	9.4	9.5	10.6	12.8	13.3	13.4
2	11.5	8.2	9.4	8.5	7.9	9.1	10.1	10.9	11.2
1 Least deprived	10.8	7.7	7.8	7.6	6.6	7.5	7.9	9.2	8.2
ratio 5 : 1	0.8	1.4	1.6	1.8	2.6	2.2	2.4	2.4	2.5
Females									
All	2.8	3	3.2	3.5	3.8	4.2	5.2	5.2	5.5
5 Most deprived	3.1	2.8	2.8	3.8	4.3	4.8	7.3	7.0	7.3
4	2.9	3.7	3.5	3.0	4.2	4.1	5.8	5.6	6.5
3	2.6	2.3	3.3	3.3	3.7	4.0	4.0	5.0	4.6
2	2.8	3.1	2.9	3.7	2.8	3.6	4.2	3.7	5.2
1 Least deprived	2.8	3.1	2.9	3.7	2.8	3.6	4.2	3.7	5.2
ratio 5 : 1	1.1	0.9	1.0	1.0	1.5	1.3	1.7	1.9	1.4

There appears to have been an almost ‘dose-like’ response relationship between socioeconomic deprivation and oral cancer. This is particularly apparent for males (Figure 3.2) where, with increasing severity of deprivation, the incidence of oral cancer has increased and this relationship has magnified from the late 1970s to the late 1990s. For females a broadly similar, but less pronounced, pattern was also observed for females, with increased incidence observed in women from all levels of deprivation (Figure 3.3). However, the numbers of cases and rates are much lower.

Figure 3.1 **Males and females age-standardised incidence rate (EASR) of oral and oropharyngeal cancer by Carstairs deprivation least and most deprived quintiles 1976-2002 in Scotland.**

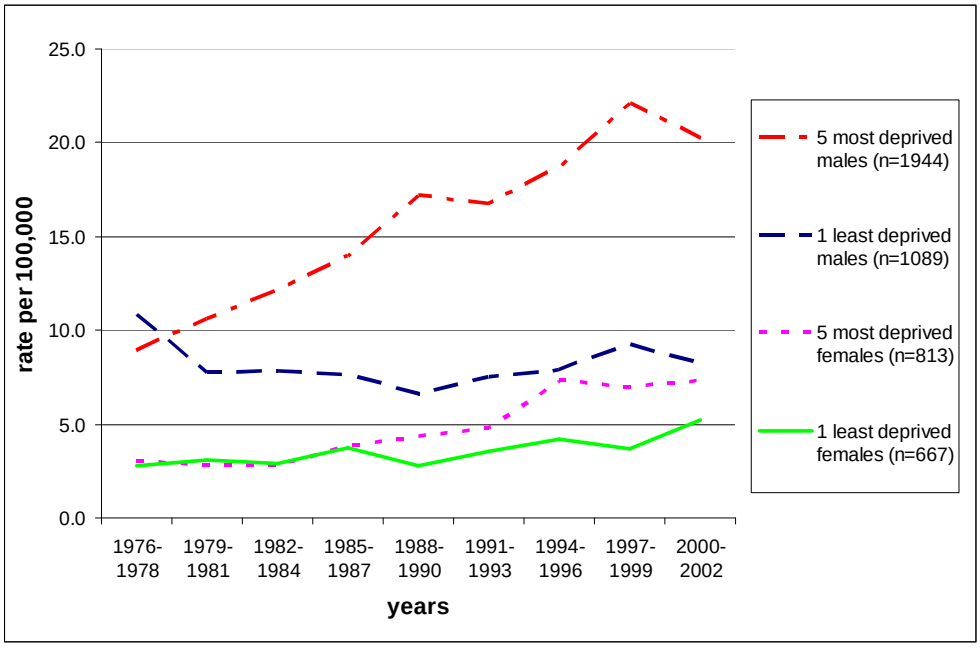


Figure 3.2 **Overall males age-standardised incidence rate (EASR) of oral and oropharyngeal cancer by Carstairs deprivation quintiles 1976-2002 in Scotland.**

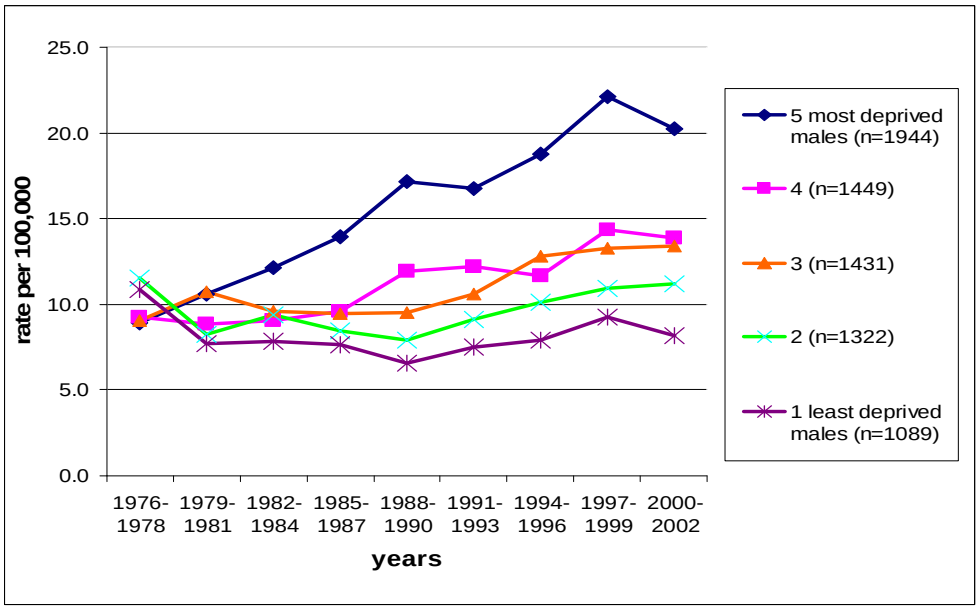
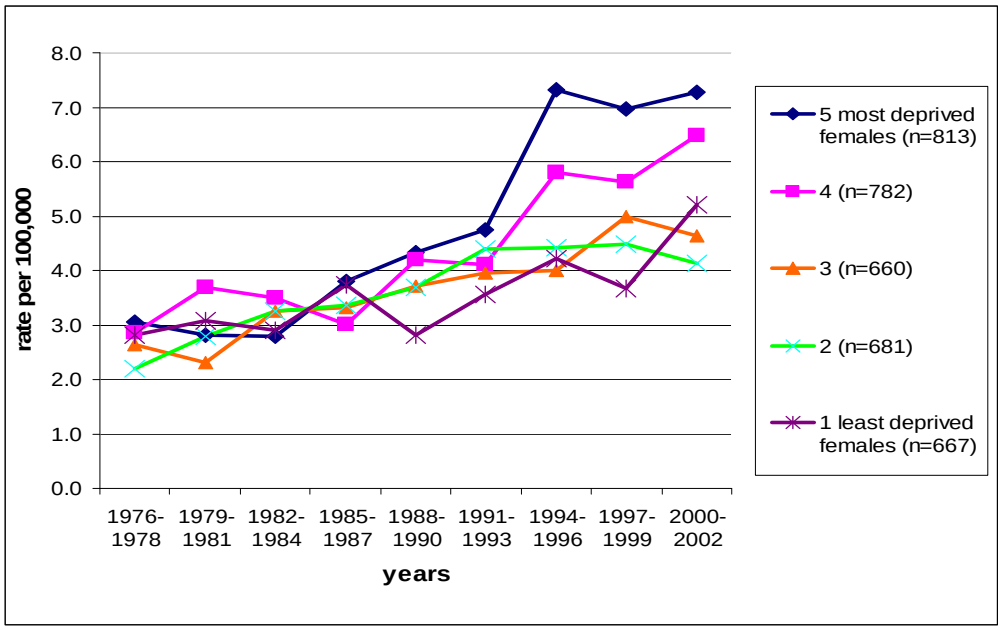


Figure 3.3 **Overall females age-standardised incidence rate (EASR) of oral and oropharyngeal cancer by Carstairs deprivation quintiles 1976-2002 in Scotland.**



3.4.3 Modelling determinants of time-trends

To begin to assess the relative importance of the determinants for these time-trends observed in oral cancer incidence from 1976 to 2002, the variables available related to these data were combined into a Poisson regression model. The variables available were: age, sex, year, and socioeconomic deprivation status. The results of the univariate unadjusted Poisson regression model (Table 3.2) show that risk of oral cancer increased with increasing socioeconomic deprivation ($p<0.001$); that oral cancer risk was vastly greater in older compared with younger age-groups ($p<0.001$); that there was a greater than two-fold risk in men than women ($p<0.001$); and that incidence had increased over the period 1976-2002 ($p<0.001$). When adjusting each variable for the others in the model (Table 3.2), the results were essentially unaltered, such that the risk of oral cancer increased with increasing levels of deprivation and remained significant ($p<0.001$) when controlling for age, sex, and year (Table 3.2).

Table 3.2 Summary of univariate and adjusted models of oral and oropharyngeal cancer by study variables: age-group, sex, year and deprivation (1976-2002).

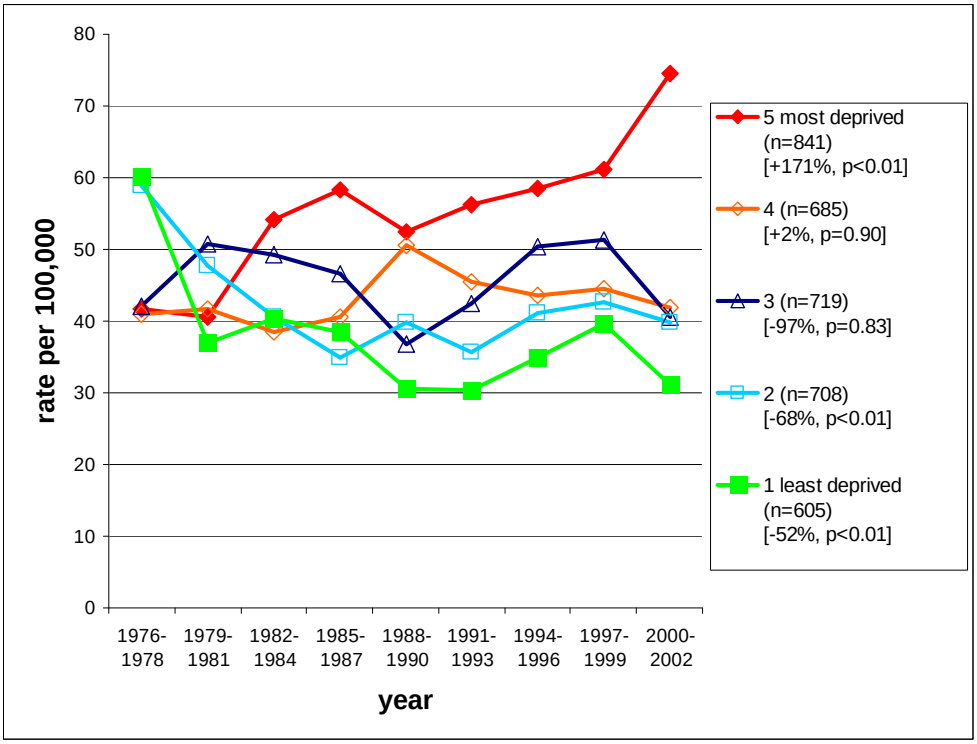
		Univariate		Adjusted	
Variable	**Level**	**Rate ratio (95%CI)**	***P*-value**	**Rate ratio (95%CI)**	***P*-value**
Age-group	<45 years	1 (ref)		1 (ref)	
	45 – 49 years	12.37 (11.04-13.86)	<.001	12.36 (11.04-13.86)	<.001
	50 – 54 years	20.57 (18.55-22.82)	<.001	20.63 (18.61-22.89)	<.001
	55 – 59 years	28.65 (25.96-31.66)	<.001	29.12 (26.39-32.18)	<.001
	60 – 64 years	33.33 (30.24-36.79)	<.001	34.20 (31.03-37.75)	<.001
	65 – 69 years	38.82 (35.24-42.82)	<.001	40.59 (36.86-44.78)	<.001
	70 – 74 years	41.58 (37.71-45.93)	<.001	44.85 (40.67-49.54)	<.001
	75 – 79 years	44.04 (39.79-48.81)	<.001	49.64 (44.85-55.02)	<.001
	80 – 84 years	52.40 (47.06-58.40)	<.001	62.59 (56.19-69.76)	<.001
	85 + years	61.16 (56.64-68.49)	<.001	78.91 (70.45-88.43)	<.001
Sex	Females	1 (ref)		1 (ref)	
	Males	2.17 (2.08-2.25)	<.001	2.74 (2.63-2.86)	<.001
Year	1976 – 1978	1 (ref)		1 (ref)	
	1979 – 1981	1.00 (0.91-1.10)	0.995	0.98 (0.90-1.08)	0.711
	1982 – 1984	1.08 (0.99-1.18)	0.095	1.04 (0.95-1.14)	0.375
	1985 – 1987	1.15 (1.06-1.26)	0.002	1.09 (1.00-1.19)	0.048
	1988 – 1990	1.26 (1.15-1.37)	<0.001	1.17 (1.07-1.28)	<0.001
	1991 – 1993	1.37 (1.26-1.49)	<0.001	1.25 (1.15-1.36)	<0.001
	1994 – 1996	1.58 (1.45-1.71)	<0.001	1.42 (1.31-1.55)	<0.001
	1997 – 1999	1.74 (1.60-1.89)	<0.001	1.53 (1.41-1.66)	<0.001
	2000 – 2002	1.79 (1.65-1.95)	<0.001	1.53 (1.41-1.66)	<0.001
Deprivation status	1 (least)	1 (ref)		1 (ref)	
	2	1.14 (1.07-1.21)	<0.001	1.12 (1.05-1.19)	<.001
	3	1.19 (1.12-1.27)	<0.001	1.21 (1.14-1.29)	<.001
	4	1.27 (1.19-1.35)	<0.001	1.29 (1.21-1.37)	<.001
	5 (most)	1.56 (1.47-1.66)	<0.001	1.65 (1.55-1.75)	<.001

3.4.4 Modelling determinants of socioeconomic trends

To assess in more detail the drivers for the socioeconomic trends in oral cancer incidence observed over time, 2-, 3-, and 4- way interactive models were successively built to assess the multiple potential interactions between the four variables of deprivation status, age, sex, and time.

Between 1976 and 2002, the widening gaps in oral cancer incidence between affluent and deprived socioeconomic groups by age and sex are clearly demonstrated in the interactive models plotted in Figures 3.4 to 3.7.

Figure 3.4 **Males 65+ years and over, incidence rate of oral and oropharyngeal cancer by Carstairs deprivation quintile 1976-2002 in Scotland [%change 1976 to 2002, p-value for trend]**

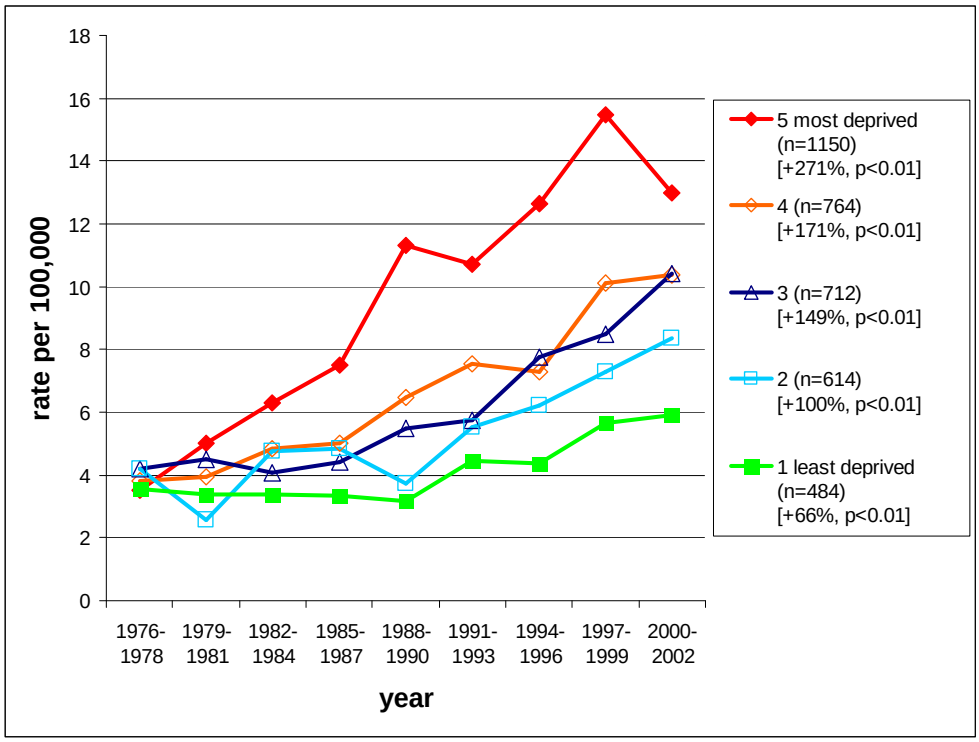


In males 65-years and over, there seems to have been a general increase in incidence of oral cancer with increasing severity of deprivation and this relationship magnified from the late 1970s to the late 1990s (Figure 3.4). In this age-group, increased incidence was only observed in the most deprived quintile. The widening gap between the most deprived and least deprived males in this age-group was clearly seen appearing in the late 1970s and rapidly increased through to the 1990s, although there was a slight inverse relationship between deprivation and oral cancer incidence in males between 1976 and 1978. The gap was almost entirely explained by an increase in incidence (+171%, $p<0.01$) in the most deprived, with substantial reduction in the least deprived group over the period (-52%, $p<0.01$).

For men under 65 years, the overall incidence rate was substantially lower than the older groups (Figure 3.5) and the patterns of change in inequality were somewhat different. There was no difference between those from all levels of deprivation in 1976-78. However, a widening gap between those from affluent and deprived areas appeared in the late 1970s and rapidly increased until the late 1990s. This widening was due to the considerable increase in oral cancer incidence in those from deprived communities (+271%, $p<0.001$) compared to the relatively modest increase in those from the least deprived areas (+66%,

p<0.01), albeit between 1997-99 and 2000-02 there was a reduction in incidence (-71%, p<0.01).

Figure 3.5 **Males <65 years, incidence rate of oral and oropharyngeal cancer by Carstairs deprivation quintile 1976-2002 in Scotland [%change 1976 to 2002, p-value for trend]**



A different pattern was seen for females in both magnitude and timing. For the over 65s, the incidence increased in those from all levels of deprivation (Figure 3.6), with those women from the most deprived areas having the greatest increase (+127%, p<0.01). However, a significant increase was also apparent in the least deprived (+73%, p<0.001). The widening gap between the most and least deprived appeared in the 1980s and continued to increase until the late 1990s. Data from 2000-02 suggest that the gap had begun to close for women over 65 years.

For women under 65 years, the overall levels are substantially lower than for the older age-group. The widening gap appears around 1985-87, with the increase again being mainly due to the increase in incidence in the most deprived. However, by 2000-02 those in the second most deprived quintile had reached the levels of the most deprived (Figure 3.7).

Figure 3.6 **Females 65+ years incidence rate of oral and oropharyngeal cancer by Carstairs deprivation quintile 1976-2002 in Scotland [%change 1976 to 2002, p-value for trend]**

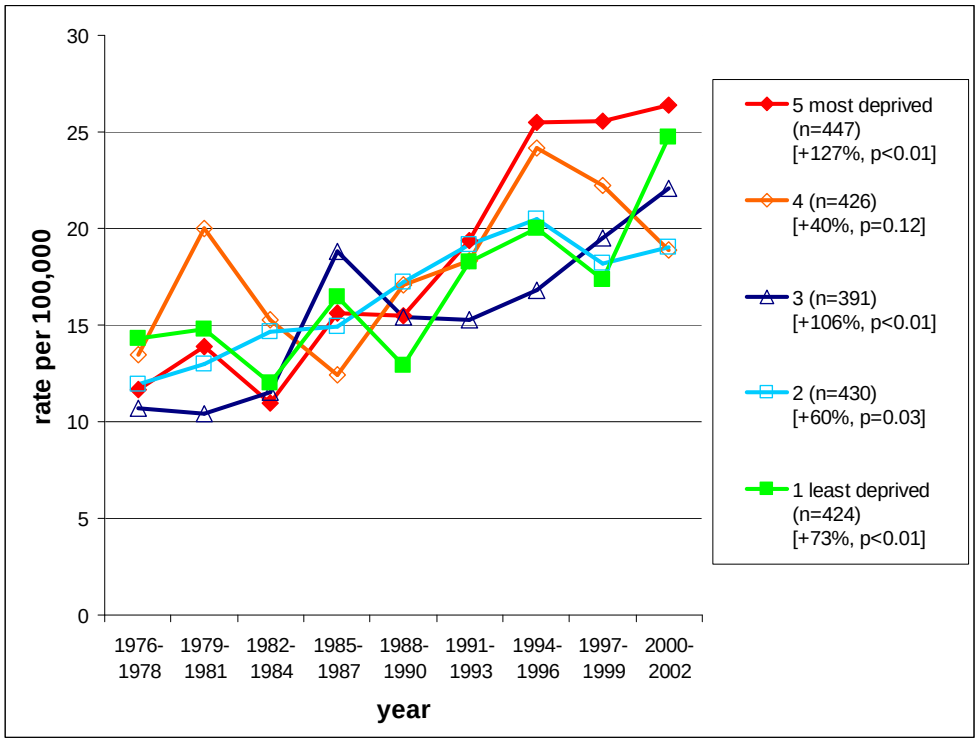
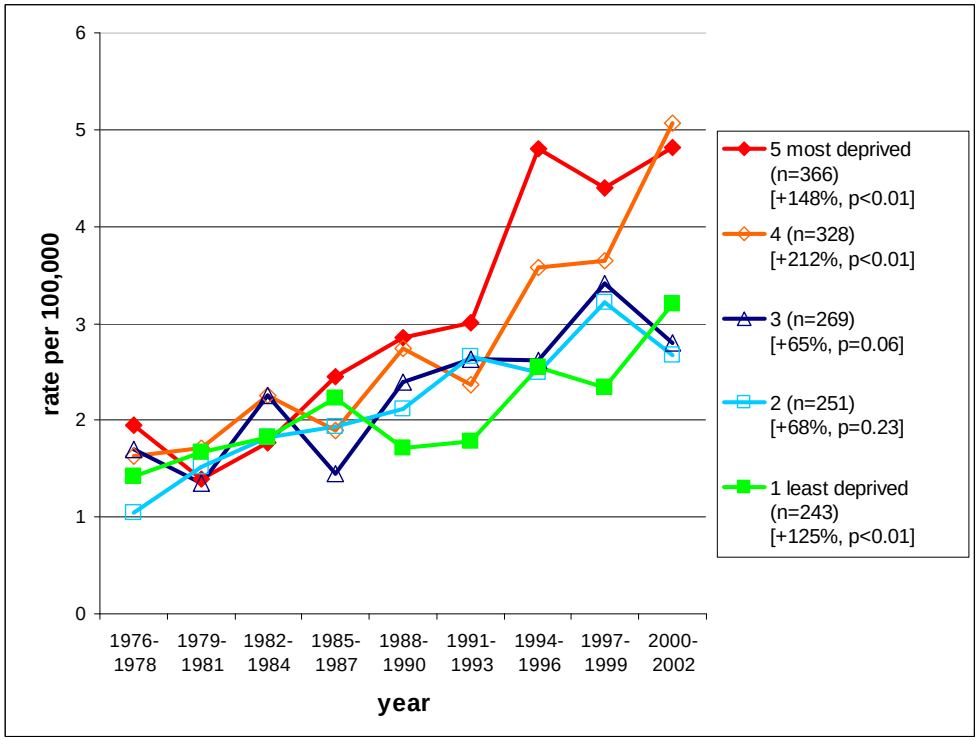


Figure 3.7 **Females <65 years, incidence rate of oral and oropharyngeal cancer by Carstairs deprivation quintile 1976-2002 in Scotland [%change 1976 to 2002, p-value for trend]**



3.4.5 Carstairs deprivation index methodology validation

Analysis was performed to compare the traditional deprivation method, linking the whole period (1976-2002) cancer data to Carstairs 1991, with the new approach, linking the cancer data to the nearest census time-point Carstairs 1981, 1991, and 2001 index i.e. Carstairs 1981 was used for cancer data from 1976-1985; Carstairs 1991 for 1986-1995; and Carstairs 2001 for 1995-2002. Table 3.3 summarises the distribution of the cancer data by deprivation quintile using both methods. A Spearman Correlation test provided a coefficient of 0.94 ($p<0.0001$) demonstrating a near perfect correlation of the data. Further, the adjusted multivariate model was run using both methods and the commensurate findings are demonstrated in Table 3.4

Table 3.3 Distribution of cases of oral cancer in Scotland (1976-1985) by deprivation quintile using two methods: (i) Carstairs 1991 linked to whole period data; and Carstairs 1981 linked to 1976-1985 data, Carstairs 1991 to 1986-1995 and Carstairs 2001 for 1995-2002.

Carstairs deprivation index method	Number	Percent
Carstairs 1991 (quntiles)		
1 (least deprived)	1647	15.42
2	2030	18.70
3	2091	19.26
4	2250	20.72
5 (most deprived)	2797	25.76
9 (unknown)	15	0.14
Carstairs 1981, 1991, 2001 (quntiles)		
1 (least deprived)	1756	16.17
2	2003	18.45
3	2091	19.26
4	2231	20.55
5 (most deprived)	2757	25.39
9 (unknown)	19	0.18

Table 3.4 Summary of adjusted models of oral and oropharyngeal cancer by study variables: age-group, sex, year and deprivation using Carstairs 1991 for whole period (1976-2002); and Carstairs 1981 linked to 1976-1985 data, Carstairs 1991 to 1986-1995 and Carstairs 2001 for 1995-2002.

		Carstairs 1991		Carstairs 1981, 1991, 2001	
Variable	**Level**	**Rate ratio (95%CI)**	***P*-value**	**Rate ratio (95%CI)**	***P*-value**
Age-group	<45 years	1 (ref)		1 (ref)	
	45 – 49 years	12.36 (11.04-13.86)	<.001	12.39 (11.06-13.88)	<.001
	50 – 54 years	20.63 (18.61-22.89)	<.001	20.66 (18.64-22.93)	<.001
	55 – 59 years	29.12 (26.39-32.18)	<.001	29.19 (26.45-32.26)	<.001
	60 – 64 years	34.20 (31.03-37.75)	<.001	34.25 (31.07-37.81)	<.001
	65 – 69 years	40.59 (36.86-44.78)	<.001	40.65 (36.91-44.84)	<.001
	70 – 74 years	44.85 (40.67-49.54)	<.001	44.98 (40.79-49.68)	<.001
	75 – 79 years	49.64 (44.85-55.02)	<.001	49.73 (44.93-55.11)	<.001
	80 – 84 years	62.59 (56.19-69.76)	<.001	62.71 (56.31-69.90)	<.001
	85 + years	78.91 (70.45-88.43)	<.001	79.10 (70.63-88.64)	<.001
Sex	Females	1 (ref)		1 (ref)	
	Males	2.74 (2.63-2.86)	<.001	2.74 (2.64-2.86)	<.001
Year	1976 – 1978	1 (ref)		1 (ref)	
	1979 – 1981	0.98 (0.90-1.08)	0.711	0.98 (0.90-1.08)	0.735
	1982 – 1984	1.04 (0.95-1.14)	0.375	1.05 (0.96-1.14)	0.328
	1985 – 1987	1.09 (1.00-1.19)	0.048	1.11 (1.01-1.21)	0.026
	1988 – 1990	1.17 (1.07-1.28)	<0.001	1.19 (1.09-1.30)	<0.001
	1991 – 1993	1.25 (1.15-1.36)	<0.001	1.28 (1.17-1.39)	<0.001
	1994 – 1996	1.42 (1.31-1.55)	<0.001	1.46 (1.34-1.58)	<0.001
	1997 – 1999	1.53 (1.41-1.66)	<0.001	1.53 (1.41-1.66)	<0.001
	2000 – 2002	1.53 (1.41-1.66)	<0.001	1.57 (1.45-1.70)	<0.001
Deprivation status	1 (least)	1 (ref)		1 (ref)	
	2	1.12 (1.05-1.19)	<.001	1.16 (1.09-1.24)	<.001
	3	1.21 (1.14-1.29)	<.001	1.24 (1.16-1.32)	<.001
	4	1.29 (1.21-1.37)	<.001	1.32 (1.24-1.41)	<.001
	5 (most)	1.65 (1.55-1.75)	<.001	1.66 (1.56-1.76)	<.001

3.5 Discussion

3.5.1 Key points and comparison with other work

Oral cancer is one of the few cancers for which rates have been reported to be on the rise in the UK – with the increases being more rapid in Scotland than in other areas of the UK (Møller and Brewster, 2005; Conway *et al.*, 2006). This present study showed that increases in incidence observed in Scotland from the 1970s and 1980s have continued over recent decades. The rise can be largely accounted for by individuals from the most deprived areas, with the strongest effect seen in men. For men, this widening

socioeconomic inequality gap first appeared in the late 1970s and increased through to the 21st century, while for women the association overall was not as strong and the divergence began later in the mid 1980s, but continued to increase again until the late 1990s – albeit at a much lower rate and it had begun to close by 2000-02. In the past decade, the gap has remained wide but was more stable. These findings mirror the wider pattern of general health inequalities in Scotland (Blamey *et al.*, 2002) which show widening inequalities in mortality rates in parallel with changes in income inequality from 1980 to 2000.

3.5.2 Data quality

As previously stated, the initial intention had been to look at the socioeconomic related descriptive epidemiology of oral cancer for the whole of the UK, as a follow-up to the work begun in Chapter 2. However, on exploring data available from the UK cancer registries, it was decided to focus only on the Scottish Cancer Registry data, as the other UK registries did not meet the criteria for inclusion. The criteria used to assess the data from the UK cancer registries for undertaking this detailed time-trends analysis of the socioeconomic trends included: availability of historic data (i.e. data for at least two decades), and availability of validated postcodes linked to the cancer registrations for subsequent linking to deprivation indices. Further, there was much uncertainty at the time with regard to standardising and comparing deprivation indices across the UK. It was therefore apparent that such data were only going to be readily and fully available for Scotland. Nevertheless, it was also clear that even a study limited to Scotland was not only going to be powerful, but was also going to be a considerable undertaking in itself.

The Scottish Cancer Registry data accessed in this study are considered to be of high quality and span more than 25 years. The accuracy of the postcodes, from which the Carstairs Deprivation Score was derived, in the Scottish Cancer Registry, is high (99.5%) (Brewster *et al.*, 2002). The quality indicators for registration of tumours of the oral cavity and oropharynx by the Scottish Cancer Registry have consistently been high over the past 20 years with: 95% microscopically verified registrations, and no greater than 2% Death Certificate Only registrations (Parkin *et al.*, 2002). The completeness of case-ascertainment in the Scottish Cancer Registry is also believed to be high, with evidence from several studies showing that data quality are consistently high, but yet steadily improving (Brewster *et al.*, 1994; Brewster *et al.*, 1997; Brewster *et al.*, 2002). This was maintained through a major reorganisation of the Scottish Cancer Registry between 1995 and 1997. Prior to this time, registration was undertaken largely manually by five autonomous regional registries. From 1997 onwards the national Scottish Cancer Registry took on

responsibility for all aspects of cancer registration. The registration system is now centralised at NHS NSS, ISD Scotland, with cases being ascertained from multiple sources, and the data from these multiple source records being linked through probability matching. Subsequently, diagnosis and other variables are manually verified by cancer registration officers (Harris *et al.*, 1998).

The subjects in this study were diagnosed with any malignant neoplasms of the oral cavity and oropharynx. The vast majority (over 90%) of these will be squamous cell carcinomas (SCC) (Johnson *et al.*, 2005). Other studies of these cancers do not distinguish morphology (Faggiano *et al.*, 1997). The observed rising trends are unlikely to be explained by changes in diagnosis or certification over the period as oral cancer is also a relatively straightforward diagnosis and no major changes in coding practices have occurred (WHO, 1992). The minor changes in the ICD coding system between ICD-9 and ICD-10 (which took place in 1992) were overcome by recoding all diagnoses prior to 1992 to the latest classification system (i.e. ICD-10). A specific potential problem was the possible inclusion of some non-oral pharyngeal cancers within the group of tumours defined as ill-defined sites in lip, oral cavity, and pharynx. However, such misclassification has been reported to affect less than 6% of cases in other descriptive epidemiological studies of oral cancers (Franceschi *et al.*, 2000).

The problem of misclassification of SES using a census-based measure is an important consideration in this kind of study. This is particularly an issue the further the date of cancer registration is from the census year. While this was to some degree unavoidable, it was felt that using data from the three census years available attempted to reduce this misclassification, linking the oral cancer data to SES at a closer point to the potential 'exposure' compared to the traditional method of linking the whole database to one (1991) census point. However, there were no differences in the results when the analyses were undertaken using either method. Moreover, if misclassification is random, it would be expected to lead to an underestimation of the association between socioeconomic deprivation and oral cancer incidence.

This newly developed method for utilising the Carstairs deprivation index employed in this study had not previously been carried out, but it was felt to be an intuitive and pragmatic way of examining the socioeconomic dimension of historic data. It was validated by comparison to the traditionally accepted method, and also confirms previous reports that the differences between the Carstairs-derived indices are minimal between censuses (Boyle *et al.*, 2004a).

Further future analyses could be done to take into account recently developed and piloted methods to create consistent geographic areas through time to overcome the problem of postcode changes between the census years (Boyle *et al.*, 2005), and also to investigate the use of recently developed area measures of multiple deprivation (Scottish Executive, 2004c).

A further limitation of this approach is the inevitable concern that the 'exposure' to socioeconomic status (as with other potential risk factors) will have been some time earlier than the development of cancer. This is a common problem in descriptive epidemiology and the study is unable to address this issue entirely as the cancer incidence data are linked via the postcode of the individual at diagnosis, with earlier residence information unavailable.

The approach taken to modelling the data in this study is worthy of some further explanation. The univariate and multivariate models permitted analyses of the indicator variables (age, sex, year, and deprivation status) to include all levels of the categorical variables (minus one for the referent level – for each variable). The initial levels were also chosen to ensure that no level had a very small number of events therein. Thus an age categorical variable of under 45 years was used as one of 10 levels (minus 1 for referent), sex had 2 categories (minus 1), year was grouped into 9 triennia (minus 1), and deprivation was divided into 5 quintiles (minus 1). Thus, in the multivariate model, the number of indicator variables included is the sum of each of these levels (minus 1 for the referent level in each case) which gave 23 variable indicators in the present study, which was evidently manageable.

However, to assess whether there were interactions between these variables, even more indicator variables are introduced *in addition* to those already included in the multivariate model. Thus, in this study to include all variable levels as categorised in the multivariate model above would equal (10 minus 1) times (2 minus 1) times (9 minus 1) times (5 minus 1) in addition to the 23 variables already included giving a colossal total of up to 311 in the 4-way interactive model. Thus the variables had to be rationalised.

Therefore, for the purposes of testing interactions, it is important that the variables are manipulated to reduce the numbers of levels or strata within them. Ideally, to ensure clarity and understanding, the number of interaction variables (levels) are limited to binary variables where possible. It was felt important with regard to the aims of this study to keep the 5 levels of deprivation as this variable did not naturally binarise, and it was also

considered important to maintain some detail in the time-line and not chunk the variable into a more crude (e.g. 10 year) time frame. Sex was already binarised, so the variable where we had to seek compromise was age.

Due to the relatively small numbers of cases of oral cancer in the <45 years age-group over the period, it was not possible to model the interactions of age on the cut-off criteria 'less than 45' compared to 'greater than 45'. However, it is considered essential that age is included in any explanatory model for descriptive cancer studies due to the integral relationship between age and cancer incidence (Clayton and Schifflers, 1987a, 1987b). Therefore, the median age (65 years) was adopted as the cut-off point in the models with the age binarised such that the 'younger' age-group was defined as those less than 65 years, and the 'older' age-group defined as those 65 years and over.

3.5.3 Potential explanations of study findings

The interaction between socioeconomic life circumstances and behaviours is complex. As well as socioeconomic circumstances affecting the individual empowerment in terms of education and health awareness, it also affects knowledge of and ability to make healthy choices (Evans and Stoddart, 1990). Smoking (Stead *et al.*, 2001) and alcohol consumption (Marmot, 1997) have been reported as coping mechanisms for the stress associated with deprivation. It is also well documented that diet is related to access and affordability of healthy foods as well as culture and cooking skills and not simply a lifestyle choice (Wrigley, 2002). So, in effect, socioeconomic circumstances may play a deeper role in the aetiology of the disease being potentially a 'cause of the cause'.

The important known 'lifestyle' factors cannot be overlooked as risk factors. For oral and oropharyngeal cancer, they are: smoking (Blot *et al.*, 1998), and alcohol consumption (Macfarlane *et al.*, 1996b; Bagnardi *et al.*, 2001a, 2001b), which together also have a synergistic effect (Brugere *et al.*, 1986; Macfarlane *et al.*, 1995). In addition, a diet low in fresh fruit and vegetables (WCRF / AICR, 1997; Pavia *et al.*, 2006) and Human Papillomavirus (Kreimer *et al.*, 2005) has been found to be associated with an increased risk of oral cancer. The question is: to what extent can the trends in socioeconomic inequality observed in this study be explained by the socioeconomic variation in these traditional factors? – although the time-lag between exposure and disease development further complicates the explanation.

3.5.3.1 Smoking behaviours and socioeconomic factors

Socioeconomic data for smoking prevalence and average weekly cigarette consumption for Scotland is limited, but is included in the data for Great Britain (GB). From 1970 to present, a consistent downward trend in smoking prevalence has been observed in all occupational social classes and in both sexes. For both sexes smoking prevalence, in social class I (professional) and II (employers and managers), remained substantially lower than in social class V (unskilled manual) and IV (semi-skilled manual and personal services) from 1972 to 1998 (Goddard and Green, 2004). However, there was no obvious widening of the inequality gap in smoking behaviour over the period. More recent data on the socioeconomic distribution of smoking from 1995 to 2003 are available for Scotland. They indicate that the overall downward trend in smoking prevalence continues, but widening inequalities in the distribution of smoking exist – with those from deprived areas increasingly less likely to give up (Bromley *et al.*, 2005). Oral cancer risk markedly declines after quitting smoking (La Vecchia *et al.*, 1999). Overall, it is difficult to demonstrate that the patterns in smoking behaviour related to socioeconomic status would fully explain the widening socioeconomic inequalities in oral cancer incidence observed in this study.

3.5.3.2 Alcohol consumption and socioeconomic factors

The association between alcohol drinking in Scotland and socioeconomic factors is somewhat mixed. The series of Scottish Health Surveys published from 1995 to 2003 (Dong and Erens, 1997; Shaw *et al.*, 2000; Bromley *et al.*, 2005) consistently show that while more people in Scotland were drinking alcohol excessively, there was no clear relationship between socioeconomic factors and reported drinking behaviour. This is similar to the equivocal association in findings for Britain from the 1980s (Goddard *et al.*, 2004). However, between 1998 and 2003 there was a 19% rise in the number of alcohol-related hospital episodes in general hospitals in Scotland and this was strongly related to area-deprivation – with those from deprived areas more likely to be admitted (Bromley *et al.*, 2005). In this regard, it should be noted that self-reported excessive drinking may be poorly recounted (Leon and McCambridge, 2006). Unfortunately there is no detailed socioeconomic breakdown on alcohol consumption data, but the overall increasing levels of alcohol consumption since the early 1970s cannot be ignored as a potential cause for the increase in oral cancer. As Leon and McCambridge (2006) detailed in their explanation for liver cirrhosis: per capita alcohol consumption more than doubled over this period – mostly attributable to increases in wine and spirit drinking with beer consumption being stable

(Academy of Medical Sciences, 2004). These liver cirrhosis trends for Scotland also have a strong deprivation association (Morrison *et al.*, 2006) and oral cancer and liver cirrhosis mortality trends have been shown to positively correlate (Hindle *et al.*, 2000). Thus, alcohol may have a role in socioeconomic inequalities, although evidence to support the widening trends is incomplete.

Given the well reported synergistic relationship between smoking and heavy drinking (Brugere *et al.*, 1986; Macfarlane *et al.*, 1995), this combined behaviour may be related to socioeconomic status and could be a potential explanation – however, there are limited data available to examine this.

3.5.3.3 Diet and socioeconomic factors

Recent data on dietary behaviour in Scotland have shown that daily fruit and vegetable consumption has significantly increased between 1995 and 2003. However, there were marked inequalities in this behaviour with men consistently less likely to eat fruit and vegetables daily than women, and those from deprived areas increasingly eating less than their counterparts from affluent areas (Bromley *et al.*, 2005). Earlier available UK data from the 1980s do not contradict this finding and have shown a particularly poorer diet in those who were unemployed (Braddon *et al.*, 1988). There were no available data on trends in dietary behaviour across the whole period of the study. Therefore, it is difficult to draw strong conclusions on the role of diet in the overall widening gap seen in this study.

3.5.3.4 HPV and socioeconomic factors

There seem to be contradictory relationships between HPV infection and sexual behaviour and social class. Data on sexual behaviour are not published for Scotland, but from the Sexual Attitudes and Lifestyles survey in the UK, it was found that both men and women in high social classes reported having more sexual partners than those in low social classes (Johnson *et al.*, 1994). However, it is well known that Human papillomavirus infections are associated with the number of sexual partners and lead to increased risk of developing cervical cancer (Mueller *et al.*, 1996), a cancer, which in Scotland, exhibits a strong positive association with deprivation (Scottish Cancer Registry, 2007). Therefore, in terms of oral cancer, sexual behaviour and HPV may be associated with the socioeconomic inequalities, although the evidence available is inconclusive.

3.5.3.5 Socioeconomic factors per se

The effects of socioeconomic circumstances themselves are also an interesting possible explanation worthy of consideration. In terms of societal changes over time, there were underlying trends in socioeconomic circumstances in Scotland (Devine, 2006). These changes occurred throughout the period of the study, and were seemingly responsible for the widening socioeconomic gap between affluent and deprived individual members of society, and affluent and deprived communities. Potential explanations for this include the effect of the post-industrial decline in economic activity in Scotland which brought with it massive unemployment and polarization of poverty to pockets of the country – particularly to the West of Scotland (Devine, 2006). Similarly, in self-reported health from the census in 2001 – the gap between the highest and lowest social classes was greater in Scotland than in the rest of the UK (Doran *et al.*, 2004).

The association between oral cancer and socioeconomic circumstances is complex and the explanation of increasing trends over time adds another dimension. Socioeconomic circumstances may play an important role in influencing behaviour but may also have a more direct role. This will be explored in the subsequent meta-analysis and analytical studies, as well as discussed in more detail in Chapter 7.

3.6 Conclusions

The explanations for the relationship between socioeconomic factors and oral cancer incidence and the widening inequalities over time demonstrated are complex. While some of the relationship between socioeconomic circumstances and some of the trends over time could be explained by known aetiological risk factors, the role of socioeconomic inequality remains unexplained by the known risk factors and perhaps could be related to the effects of deprivation itself.

More work is required to determine why, overall, there is a continuing increase in incidence in oral cancer and why increasing inequalities are seen. This could include assessing the importance of individual and area measures of socioeconomic status. At the very least, studies on risk factors for oral cancer need to take into account socioeconomic status as a serious potential confounding factor.

4 Systematic review and meta-analysis: Socioeconomic inequalities and oral cancer risk

4.1 Introduction

In 2000, oral cancer was estimated to be the eighth most common cancer worldwide – with the greatest burden in developing countries (Parkin *et al.*, 2001). Despite the significant global inequality in the distribution of oral cancer; and despite a wealth of literature on the effects of poverty and inequality on health (Marmot, 2005), the effect of socioeconomic circumstances on oral cancer is given little recognition in a predominant medical model approach to research on the aetiological risks of the disease (Mucci and Adami, 2001). Published work, reviewed in Chapter 1, on the relationship between socioeconomic status (SES) and oral cancer has mainly been in the form of descriptive epidemiology studies linking routine registry data to census data. From such studies, increased risk of oral cancer appears associated with low socioeconomic factors (Edwards and Jones, 1999; Conway *et al.*, 2007), although this was not reflected in a review of incidence studies from across the world (Faggiano *et al.*, 1997). These routine data are, however, liable to the 'ecological fallacy' whereby individuals are allocated socioeconomic status based on their area of residence.

While analytical epidemiological studies often mention or control for SES, it is rarely the focus of the research. The few studies which have explored the relationship between SES and oral cancer provide equivocal findings, and are also complicated by the multiple definitions of oral cancer employed (Moore *et al.*, 2000). In summary, Greenberg and co-workers (1991) found no relationship between oral and pharyngeal cancer and education or occupational social class, while several case-control studies have shown an increased risk with lower occupational social class (Elwood *et al.*, 1984) and lower education levels (Ferraroni *et al.*, 1989). Conversely, occasional studies point to a higher oral and pharyngeal cancer risk in more educated young subjects (Rodriguez *et al.*, 2004). Socioeconomic correlates have also recently been found to be changing over time, with the positive relationship with poorer socioeconomic circumstances through the 1990s disappearing, as reported in a review of Italian case-control studies (Bosetti *et al.*, 2001). Generally, differences in cancer risk between socioeconomic groups can be interpreted as an example of inequality (Kogevinas *et al.*, 1997).

4.2 Aims

In light of this relatively variable picture, the aim was to assess the association between SES and oral cancer via a systematic review of the literature and meta-analysis of published and unpublished case-control studies. This included investigating the relationship between SES and risk of oral cancer by: the different SES measures employed, and where possible: by sex, by age-group (younger vs older), by definition of oral cancer, by global region, by developmental status of the country, over time, and by taking into account behavioural confounding factors where possible. In addition, methodological aspects of case-control studies were taken into account in the interpretation of the findings.

4.3 Methods

4.3.1 Approach

The methodology was adapted from guidelines for systematic reviews (Sutton *et al.*, 1998; Stroup *et al.*, 2000; Centre for Reviews and Dissemination, 2001; Higgins and Green, 2006) and from examination of similar reviews in other fields (Petticrew *et al.*, 1999; Bagnardi *et al.*, 2001a, 2001b; Parikh *et al.*, 2003). Reporting follows the guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (Stroup *et al.*, 2000).

4.3.2 Search strategy

In September 2006, the following databases were searched: Medline 1950-; Medline In-Process & Other Non-Indexed Citations Subject Headings; Embase 1980-; CINAHL 1982-; PsychINFO 1806-; CAB Abstracts 1973-; EBM Reviews-ACP Journal club 1991-; Cochrane Register of Controlled trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; HMIC Health Management Information Consortium; and Pubmed. Relevant key words and search terms were used to find papers containing case-control studies of oral cancer (Appendix 6). There was no language restriction imposed (Grégoire *et al.*, 1995). Bibliographies were also hand-searched.

4.3.3 Inclusion criteria

All identified studies were reviewed independently by two reviewers the author (David I Conway - DIC) and supervisor (Lorna MD Macpherson – LMDM). Inclusion criteria at this stage were: (i) it was a study of oral and/or oropharyngeal cancer – but wider definitions or groupings which may include oral cancer were accepted at this time – e.g. cancer of the head and neck, or upper-aerodigestive tract (UADT); (ii) the study used case-control methodology. Any studies identified by only one reviewer were included at this stage.

Full text copies were obtained for all selected studies. The two reviewers (DIC and LMDM) assessed each paper. Studies continued to be included if (i) any SES information (including all data on: educational attainment, occupational social classification, or income) for both cases and controls was presented; (ii) the Odds Ratio (OR) for any SES measure was presented or could be calculated. Corresponding authors were contacted where (a) there was an indication that data on oral and/or oropharyngeal cancers could potentially be obtained from the wider cancer definition or grouping presented in the paper; or (b) that SES data were collected but had not been presented in the paper.

4.3.4 Methodological assessment of included studies

Two reviewers (DIC and LMDM) independently assessed the individual methodological characteristics of the selected studies according to ten criteria (Sutton *et al.*, 1998; Petticrew *et al.*, 1999) based on the main sources of bias in case-control studies (as outlined in Chapter 1, Section 1.2.3) (Table 4.1). Assessment discrepancies between the reviewers were resolved through discussion and re-reading.

Table 4.1 Quality assessment criteria questions

	Quality criterion
1	Was the case definition explicit (defined by ICD codes or descriptors)?
2	Did the study include newly diagnosed ('incident') cases only?
3	Did the study design utilize population rather than hospital-based controls?
4	Was there evidence of an *a priori* sample size calculation?
5	Was there evidence of identical data collection methods in both cases and controls?
6	Was there a description of 'baseline' characteristics of both cases and controls?
7	Were there adjustments for potential confounders by matching or adjusting (minimum age + one or more confounders)?
8	Was the response rate defined, and >70% in both cases and controls?
9	Was there avoidance of over-matching (of SES) factors in (cases and) controls?
10	Were there appropriate statistical analyses of SES data?

4.3.5 Data extraction

The country where the study was undertaken was extracted and classified according to level of development and income as defined by the World Bank (Soubbotina, 2005). Where available, the adjusted OR (or crude OR) with corresponding 95% Confidence Intervals (CIs) were extracted, or were calculated for low compared to high SES categories. Since the studies included reported SES using different measures and different scales, the lowest category was compared to the highest (reference) category as reported by the authors of the studies. This approach measures the extent of inequality and accounts for the variation in SES measurements.

4.3.6 Meta-analysis

All analyses were performed on Comprehensive Meta-analysis (Version 2) (Borenstein *et al.*, 2005). Separate meta-analyses were performed for: monthly household income, occupational social class, and education level. For each measure, the effect of low SES on the risk of oral cancer was calculated. Where possible, subgroup analyses based on: age, sex, definition of oral cancer employed, global region, global development status, study time-period, and estimates adjusted / unadjusted for other risk factors were performed. Where data were available for more than one SES measure within the same study, these data were pooled and compared. Potential sources of heterogeneity were examined using the Inconsistency Index (I^2) (Higgins *et al.*, 2003). Heterogeneity was estimated among studies grouped according to socioeconomic measure and within subgroups. Data were pooled by means of a random effects model, unless heterogeneity was absent – when both random and fixed effects were compared (Normand, 1999). For the purposes of reporting, random effects findings were used, and there was significant heterogeneity ($p<0{\cdot}001$) present in the meta-analyses unless otherwise stated. A summary OR with 95% Confidence Intervals (CI) was calculated, together with a hypothesis test on summary effect estimates based on a *z*-statistic, for comparison within each subgroup analyses.

Four sensitivity analyses were performed to address study heterogeneity by limiting the meta-analysis to studies satisfying key methodological criteria: (1) those with population-based compared to hospital-based data sources; (2) samples of higher sample size (≥ median case sample size); (3) those with the same number of SES strata. (4) In addition, influence analyses were performed in which the summary OR was computed omitting one study at a time to assess for any single study's effect on the overall estimate.

4.3.7 Publication bias

Publication bias was assessed via a funnel plot – in which the log odds ratio was plotted against the standard error for all studies included. The Begg and Mazumbar test (Begg and Mazumbar, 1994) and Egger's regression intercept test (Egger *et al.*, 1997) were used to evaluate publication bias.

4.4 Results

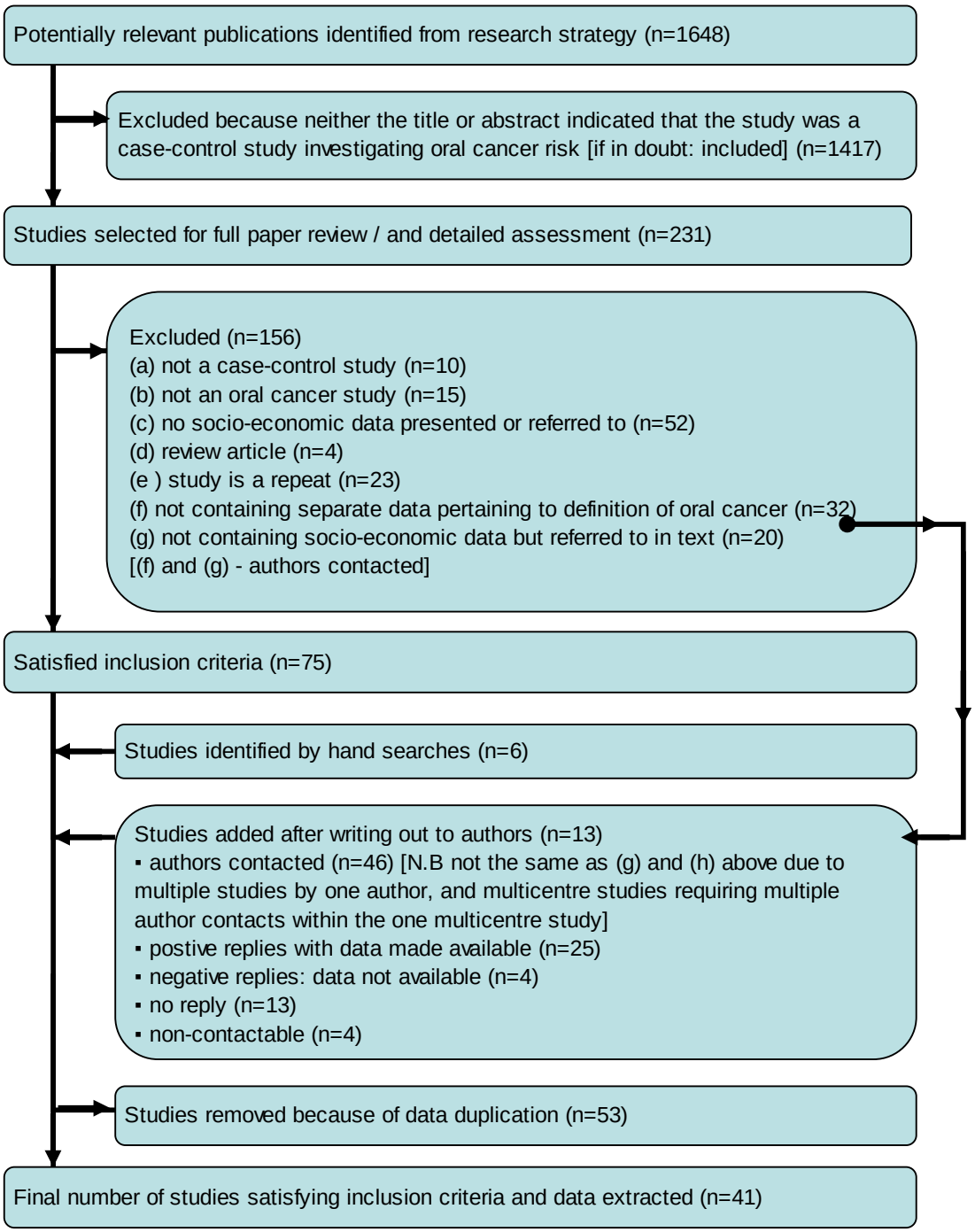
4.4.1 Search

The search strategy retrieved 1648 studies (Figure 4.1). Of these, 231 were selected for further examination of the full article. Fifty two were initially excluded and the authors were contacted either directly or via the International Head and Neck Cancer Epidemiology (INHANCE) consortium (INHANCE, 2007). This resulted in 24 positive responses (all from INHANCE) which comprised authors from multicentre studies and led to data from an additional 13 studies being included. Where there were multiple papers reporting data from the same study, the paper presenting SES data as per the inclusion criteria was chosen, if more than one study reported SES data, the most recent paper was chosen. Forty one studies (including one unpublished) were eventually included (Appendix 7).

4.4.2 Study characteristics

Forty-one case-control studies, including a total of 15,344 individuals with oral cancer and 33,852 control subjects, were finally included and their characteristics are summarised in Table 4.2. One study was undertaken between the 1960s and 70s, 12 studies were completed in the 1980s, 18 studies in the 1990s, and nine studies since 2000. Ten were European, 15 were North American, nine Asian, five South or Central America, one African, and one was a world-wide multicentre study. Fourteen studies were based in lower-income and 26 in high-income countries, with the multicentre study including both classes of countries.

Figure 4.1 Flow chart of study selection



Only two studies focused on a particular age-group (<45 years), while 19 studies provided a mean age which ranged from 38-60 years, and eight studies gave an open ended age-range (e.g. >20 years, or <76years). A further 15 studies included adults only, but the age range was not specified. In one study, age-range was not detailed.

Table 4.2 Characteristics of included studies

STUDY ID	STUDY YEARS	STUDY BASE	COUNTRY STATUS	SEX	AGE yrs (mean, or range)	CANCER DEFINITION	STUDY DESIGN	TOTAL NO. OF CASES	TOTAL NO. CONTROLS	SES MEASURE (no. of strata)	ADJUSTED
Andreotti et al, 2006	1999-2002	Brazil	L	M & F	55	OC & OP	H	325	468	E (4)	0
Choi and Kahyo, 1991	1986-1989	South Korea	H	M + F	55	OC	H	157	471	E (5), O (8)	0
Cui et al, 2006 *	1999-2004	Los Angeles, USA	H	M & F	na all	OC + OP	P	205	1005	E (4)	A, S, T, Al
Dikshit and Kanhere, 2000	1986-1992	Bhopal, India	L	M & F	na	OC	P	148	260	E (2)	A, T
Elahi et al, 2002 *	1999-2001	Tampa, USA	H	M & F	60	OC + OP	P	79	897	E (4)	A, S, T, Al
Elwood et al, 1984	1977-1988	Canada	H	M & F	62	OC	H	87	374	O (2)	S, Al
Franceschi et al, 1990 *	1986-1989	Northern Italy	H	M	na all	OC	H	157	1272	E (4), O (3)	A, S, T, Al
Franceschi et al, 1999 *	1992-1997	Northern Italy	H	M & F	58	OC + OP	H	598	1491	E (3)	A, S, T, Al
Franco et al,1989	1986-1988	Brazil	L	M & F	na all	OC	H	232	464	E (4), I (5)	0
Greenberg et al, 1991	1984-1983	USA	H	M	na all	OC & OP	P	762	837	E (3), O (3)	A, S, L, T, Al
Guneri et al, 2005	1998-2001	Turkey	L	M & F	56	OC	H	79	61	E (3), O (4), I (3)	0
Hashibe et al, 2006 *	2000-2002	Eastern Europe	L	M & F	na all	OC + OP	H	282	698	E (4)	A, S, T, Al
Hayes et al, 1999 *	1992-1995	Puerto Rico	L	M & F	na all	OC + OP	P	236	521	E (4)	A, S, T, Al
Herrero et al, 2003 *	1996-1999	International	?	M & F	na all	OC + OP	H	1175	1676	E (4)	A, S, T, Al
Kabat et al, 1994	1977-1990	USA	H	M + F	<80	OC & OP	H	1560	2948	E (4), O (5)	0
Ko et al, 2003	1992-1993	Taiwan	H	M & F	48	OC	H	107	200	E (3), O (3)	0
Levi et al, 1998 *	1992-1997	Switzerland	H	M & F	?75	OC + OP	H	289	883	E (3)	A, S, T, Al
Llewellyn et al, 2004a	1990-1997	South East England, UK	H	M + F	38	OC & OP	P	116	207	O (3)	0
Llewellyn et al, 2004b	1999-2001	South East England, UK	H	M + F	38	OC & OP	P	53	91	O (3)	0
Lu et al, 1996	1990-1992	Taiwan	H	M & F	na all	OC	P	40	160	E (3), O (3)	0
Maden et al, 1992	1985-1989	Washington state, USA	H	M	42	OC	P	131	136	E (2), O (3), I (2)	A
Marshall et al, 1992	1975-1983	New York, USA	H	M & F	na all	OC	P	290	290	E (6)	0
Mashberg et al, 1993	1972-1983	New Jersey, USA	H	M	57	OC & OP	H	359	2280	O (3)	A, L, T, Al
Merchant et al, 2000	1996-1998	Pakistan	L	M & F	49	OC	H	79	149	E (5)	0
Merletti et al, 1989	1982-1984	Torino, Italy	H	M + F	na all	OC & OP	P	122	606	E (3)	0
Moreno-Lopez et al, 2000	1995-1998	Madrid, Spain	H	M & F	na all	OC & OP	P	75	150	E (2), O (3)	0
Muscat et al, 1996 *	1981-1990	New York, USA	H	M & F	na all	OC + OP	H	670	1037	E (4)	A, S, T, Al
Nandakumar et al, 1990	1982-1984	Bangalore, India	L	M & F	55	OC	H	348	348	E (2)	0
Olshan et al, 2000 *	1994-1997	North Carolina, USA	H	M & F	na all	OC + OP	H	86	202	E (4)	A, S, T, Al
Pacella-Norman, 2002	1995-1999	South Africa	L	M & F	<74	OC	H	87	804	E (3)	A, T, Al
Rao et al, 1994	1980-1984	Bombay, India	L	M & F	50	OC	H	713	635	E (2)	A, L
Rogers et al, 1991	1983-1987	Washington state USA	H	M & F	<74	OC	P	379	514	E (3)	0
Rosenquist, 2005	2000-2004	Sweden	H	M + F	na all	OC & OP	P	132	320	E (3)	0
Schwartz et al, 1998 *	1990-1995	Washington state USA	H	M + F	42	OC + OP	P	393	607	E (3), I (5)	A, S, T, Al
Smith et al, 1998 *	1994-1996	Iowa, USA	H	M & F	>20	OC + OP	H	402	759	E (3)	A, S, T, Al
Unpublished *	2000-2003	South America	L	M + F	15-79	OC + OP	H	854	1706	E (4)	A, S, T, Al
Toporcov et al, 2004	1997-1999	Brazil	L	M & F	57	OC	H	70	70	E (3), I (3)	0
Wynder and Stellman, 1977	1969-1975	USA	H	M + F	60	OC	H	873	3350	E (4), O (3)	0
Zhang et al, 2004 *	1995-2003	Texas, USA	H	M & F	57	OC + OP	H	627	865	E (4)	A, S, T, Al
Zheng et al, 1990	1988-1989	Beijing, China	L	M + F	na all	OC	H	404	402	E (4)	A, S, T, Al
Znaor et al, 2003	1993-1999	Kerala, India	L	M	>25	OC	H	1563	3638	E (5)	0

*** International Head and Neck Cancer Epidemiology INHANCE Consortium studies**
H = high-income country, L = lower-income country.
M + F = separate data for males and females, M & F = sex data combined.
na = not available, na all = not available but evidence of a full age-range.
OC = oral cavity cancer; OC + OP = separate data for oral cavity and orophaynx available, OC & OP = oral Cavity and oropharynx data combined.
H = hospital controls, P = population controls.
E = education, O = occupational social class, I = monthly household income, (with number of strata of each SES measure in brackets).
0 = unadjusted, A = age, S = sex, T = tobacco use, Al = alcohol consumption, L = location.

The definition of oral cancer employed in the included studies was variable: 19 studies presented only oral cavity cancer data (typically ICD 10: C00-06), while 21 studies presented oral cavity and oropharynx data (typically ICD 10: C00-C06, C09-10, C14 combined) – although separate oral cavity data were available within 12 of these studies. The cancer was defined by ICD codes in 33 studies. The measurement of socioeconomic circumstances varied between the studies. Education attainment was available from nearly all studies (n=37), occupational social class data were present in 14 studies while monthly household income data were available from five. Twenty six studies included hospital-based controls, while 15 studies included population-based controls. The median sample size was 23 cases and 464 controls.

4.4.3 Methodological quality characteristics

The methodological aspects of the studies are detailed in Table 4.3.

All studies showed evidence of identical data collection methods for cases and controls and only one study did not present base-line characteristics. The response rate was defined and was >70% for both cases and controls in 18 studies, and statistical analyses of the socioeconomic data, which included adjusting for potential confounders, were performed in 19 studies.

4.4.4 Association between low income and oral cancer

4.4.4.1 Overall

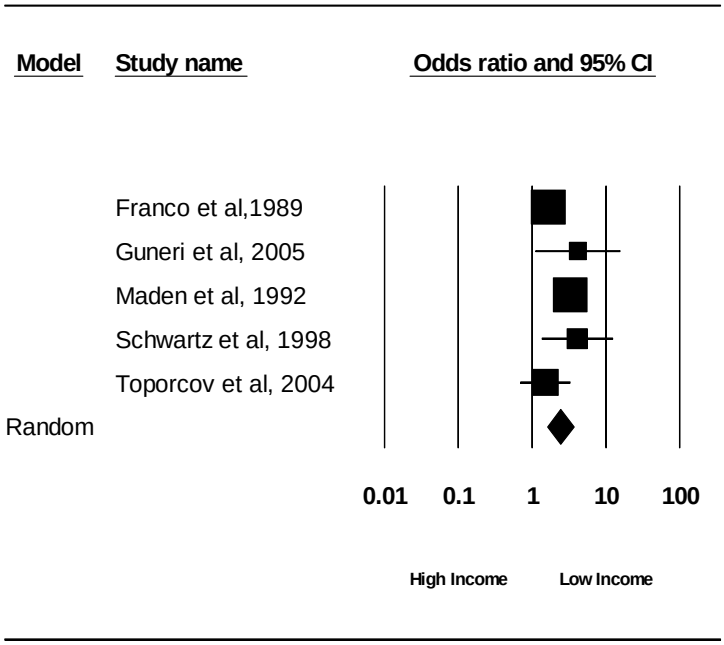
Five studies with monthly household income estimates included 905 cases and 1,338 controls. There was a moderate degree of heterogeneity among these studies (I^2=36.20%, p=0.18). A random-effects model provided an overall estimate for low income relative to high income category associated with increased risk of oral cancer OR 2·41 (95%CI 1·59, 3·65; p<0·001) (Figure 4.2).

Table 4.3 Methodological characteristics of included studies

STUDY ID	Methodological aspect									
	A	B	C	D	E	F	G	H	I	J
Andreotti et al, 2006	1	1	0	0	1	1	1	1	1	0
Choi and Kahyo, 1991	1	1	0	0	1	1	1	0	1	0
Cui et al, 2006	1	1	1	0	1	1	1	0	1	1
Dikshit and Kanhere, 2000	1	0	1	0	1	1	1	0	1	1
Elahi et al, 2002	1	1	1	0	1	1	1	1	1	1
Elwood et al, 1984	1	1	0	0	1	1	1	0	1	1
Franceschi et al, 1990	1	1	0	0	1	1	1	1	1	0
Franceschi et al, 1999	1	0	0	0	1	1	0	1	1	1
Franco et al,1989	1	1	0	0	1	1	1	0	1	0
Greenberg et al, 1991	0	0	1	0	1	1	1	1	1	1
Guneri et al, 2005	0	1	0	0	1	1	0	0	1	0
Hashibe et al, 2006	1	1	0	0	1	1	1	0	1	1
Hayes et al, 1999	1	1	1	0	1	1	1	1	1	1
Herrero et al, 2003	1	1	0	0	1	1	1	1	1	1
Kabat et al 1994	0	1	0	0	1	1	1	0	1	0
Ko et al, 2003	1	0	0	0	1	1	1	0	1	0
Levi et al, 1998	0	0	0	0	1	1	1	1	1	1
Llewellyn et al, 2004a	1	1	1	0	1	1	1	0	1	0
Llewellyn et al, 2004b	1	1	1	0	1	1	1	1	1	0
Lu et al, 1996	0	1	1	0	1	1	1	1	0	0
Maden et al, 1992	1	0	1	0	1	1	1	0	1	1
Marshall et al, 1992	0	1	1	0	1	1	1	0	1	0
Mashberg et al, 1993	0	1	0	0	1	1	1	0	1	1
Merchant et al, 2000	0	1	0	1	1	1	1	0	1	0
Merletti et al 1989	1	1	1	0	1	1	1	0	1	0
Moreno-Lopez et al, 2000	1	1	1	0	1	1	0	0	1	0
Muscat et al, 1996	1	1	0	0	1	1	1	1	1	1
Nandakumar et al, 1990	1	1	0	0	1	1	1	0	1	0
Olshan et al, 2000	1	1	0	0	1	1	1	1	1	1
Pacella-Norman, 2002	1	1	0	0	1	1	1	0	1	1
Rao et al, 1994	1	0	0	0	1	1	1	0	1	1
Rogers et al, 1991	1	0	1	0	1	1	1	1	1	0
Rosenquist, 2005	1	1	1	0	1	1	1	1	1	0
Schwartz et al, 1998	1	1	1	0	1	1	1	0	1	1
Smith et al, 1998	1	1	0	0	1	1	1	0	1	0
Toporcov et al 2004	1	1	0	0	1	1	1	0	1	0
Unpublished	1	1	0	0	1	1	1	1	1	1
Wynder and Stellman, 1977	1	0	0	0	1	1	0	1	1	0
Zhang et al, 2004	1	1	0	1	1	0	1	0	1	1
Zheng et al, 1990	1	1	0	0	1	1	1	1	1	1
Znaor et al, 2003	1	0	0	0	1	1	0	1	1	0

1 – Present; 0 – Absent.
A – Explicit case definition (defined by ICD codes or descriptors);
B – Limited to newly diagnosed ('incident') cases only;
C – Utilised population- rather than hospital-based controls;
D – Evidence of *a priori* sample size calculation;
E – Evidence of identical data collection methods in both cases and controls;
F – Description of 'base-line' characteristics of both cases and controls;
G – Adjustments for potential confounders by matching or adjusting (minimum age + one or more confounders);
H – Defined response rate, and >70% in both cases and controls;
I – Avoidance of over-matching (of SES) factors in (cases and) controls;
J – Appropriate statistical analyses of SES data.

Figure 4.2 Meta-analysis of odds ratio estimates of low vs high monthly household income associated with risk of oral cancer



4.4.4.2 Sex and age

Subgroup analysis on the income data by sex was limited with only one study providing separate data on females and two studies with separate data for males. The two studies with male data gave a higher OR 4.04 (95%CI 2.65, 6.16; p<0.001) for oral cancer risk, but it was not significantly different (p=0.10) from the study with female data or the combined estimate. Therefore, there were no differences by sex in relation to SES and no studies available with separate age-group estimates.

4.4.4.3 Lower- vs. high- income countries

There were three studies from lower income countries and two studies from high income countries, and within each grouping there was no observed heterogeneity. A fixed-effects model found that low monthly household income had a significantly (p=0·04) greater effect in high-income countries (OR 3·41; 95%CI 2·14, 5·44; p<0.001) compared to lower income countries (OR 1·77; 95%CI 1·18, 2·66; p=0·01) – although in the latter there was still an increased risk associated with low income.

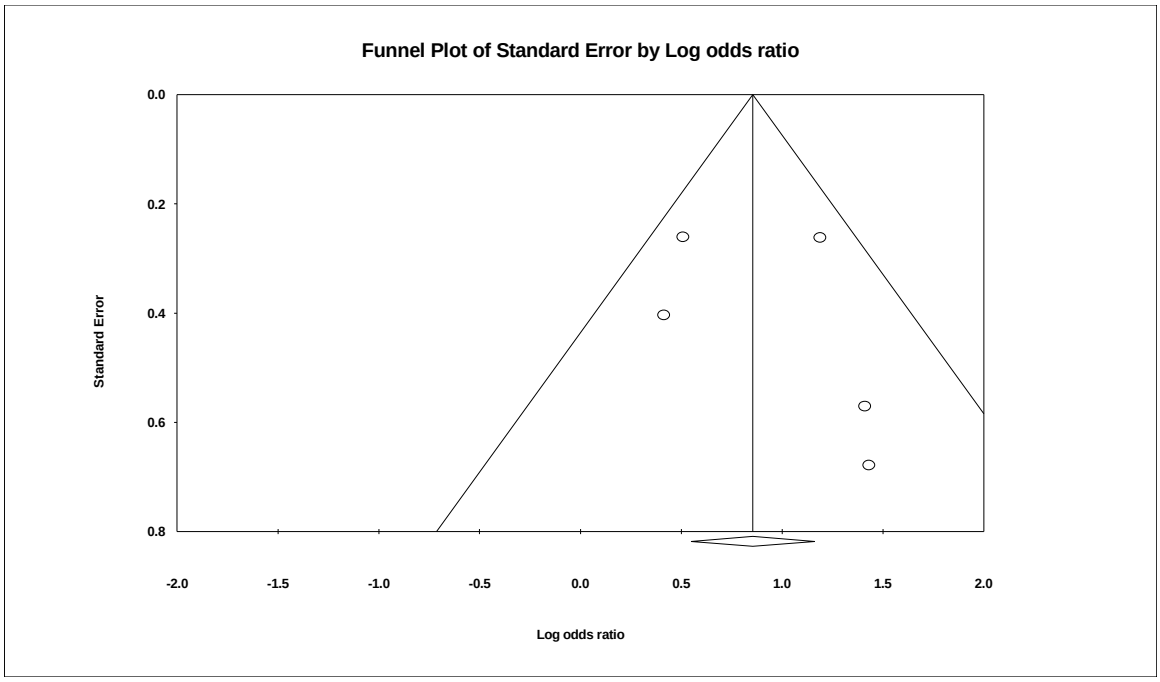
4.4.4.4 Sensitivity analysis

The two studies from high income countries were the same two which utilised a population-based approach, and which adjusted for potential confounding risk factors. So, after pooling, they also had a significantly (p=0·04) greater risk association with low income. Sample size did not affect the estimates, and influence analysis demonstrated that no single study in the 5-study meta-analysis significantly altered the summary OR. There were also no significant differences (p=0·64) between studies by number of SES levels reported (Table 4.4).

4.4.4.5 Publication bias

Begg's test (p=0·40) and Egger's test (p=0·29) for publication bias within the income data studies were both non-significant. Figure 4.3 assesses publication bias via a funnel plot: the vertical line depicts the log of the overall meta-analytic OR for income level. The x-intercept of this line is >0, indicating greater risk for oral cancer with lower income levels (OR 2.41). The diagonal lines represent pseudo-95% CIs around the log OR. Begg's adjusted-rank correlation test (p=0.40) rejects any significant correlation between the effect estimates and their variances. Thus, no obvious skew in the distribution of published studies is observed and no evidence of publication bias is present. However, there was low power, given the small number of studies with income data.

Figure 4.3 Funnel plot for publication bias (Income meta-analysis).

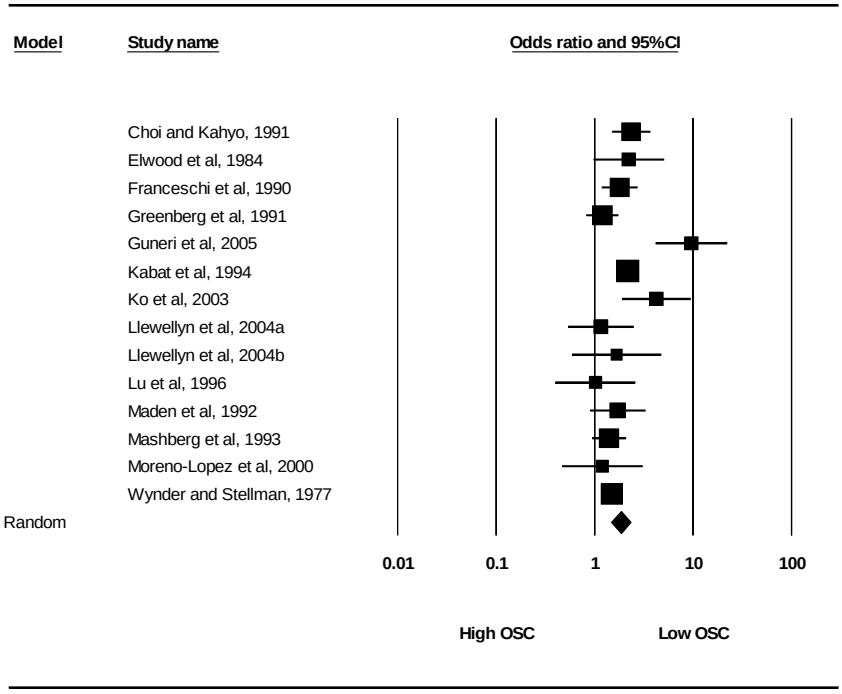


4.4.5 Association between low occupational social class (OSC) and oral cancer

4.4.5.1 Overall

The 14 studies reporting occupational estimates included 4,556 cases and 12,537 controls. All studies reported an increased risk of oral cancer with low OSC compared to high social class. There was significant heterogeneity across the studies (I^2=63·54%, p=0·001). The combined OR was 1·84 (95%CI 1·47, 2·31; p<0·001) (Figure 4.4).

Figure 4.4 Meta-analysis of odds ratio estimates of low vs high occupational social class associated with risk of oral cancer



4.4.5.2 Oral cancer definition

There were no significant differences (p=0·10) in the summary OR estimates based on the definition of oral cancer employed, although the estimate for oral cavity OR 2·25 (95%CI 1·56, 3·26; p<0·01); was higher than for oral cavity with oro-pharynx combined OR 1·52 (95%CI 1·13, 2·03; p=0·005).

4.4.5.3 Sex and age

The estimated OR 1·88 (95%CI 1·48, 2·39; p<0·001) for low OSC risk for oral cancer in males from nine studies was slightly lower (not significantly, p=0·35) than for females OR 2·31 (95%CI 1·61, 3·30; p<0·001) from five studies.There was no heterogeneity in the female studies, but significant heterogeneity in the male group. Two studies provided separate OSC data on young age-groups with zero heterogeneity between them: OR 1·32 (95%CI 0·71, 2·45; p=0·384). However, this was notsignificantly different (p=0·277) from the non-age differentiated data.

4.4.5.4 Global position

There were no significant differences between regions of the world (p=0·55): five studies were from Europe OR 2·09 (95%CI 1·04, 4·22; p=0·04); six from North America OR 1·63 (95%CI 1·31, 2·04; p<0·001); and three from Asia OR2·26 (95%CI 1·17, 4·36; p=0·02). Only one study presenting OSC data was from a lower income country.

4.4.5.5 Adjusting for potential confounding risk factors

For the four studies which had OSC data adjusted for age, sex and behaviour risk factors, there was no heterogeneity observed, and the fixed-effect model provided an OR 1·41 (95%CI 1·10, 1·79; p=0·01). This was lower (but notsignificantly p=0·06) than for the remaining 10 studies, which did not have adjusted estimates, with a combined OR 2·03 (95%CI 1·52, 2·72; p<0·001).

4.4.5.6 Sensitivity analyses

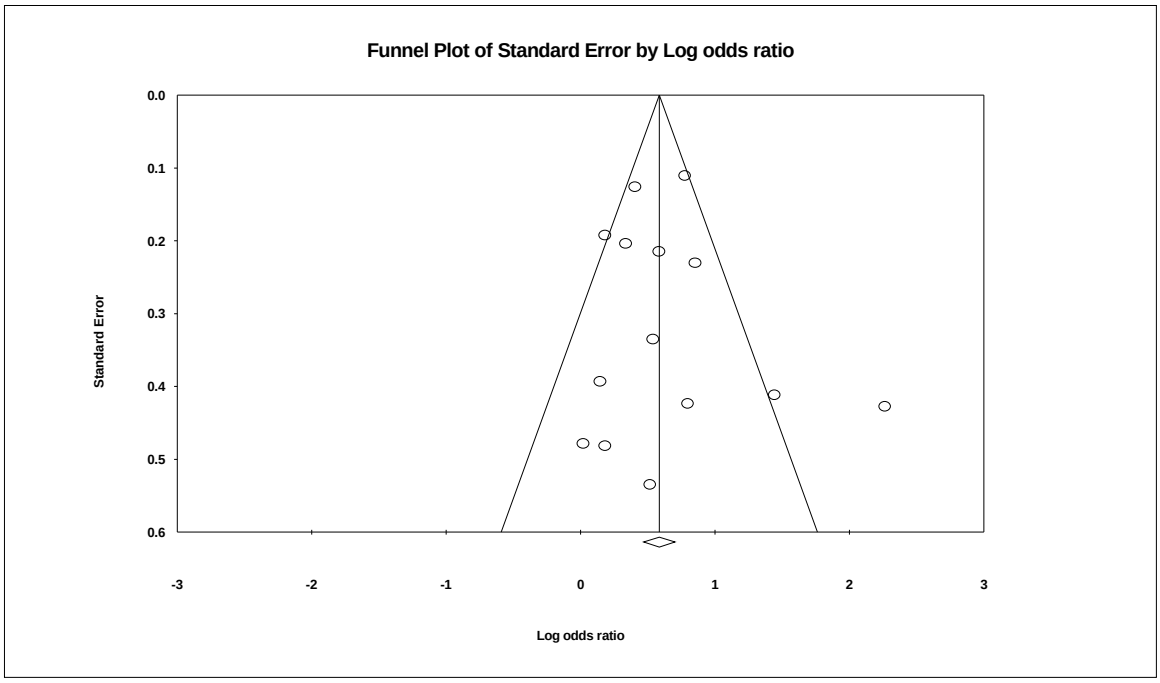
Study-base had a significant effect on the estimates. Of the 13 studies with OSC data, eight were hospital-based studies providing OR 2·22 (95%CI 1·66, 2·97; p<0·001) associated with low OSC. This was significantly (p=0·006) higher than the summary OR 1·28 (95%CI 0·98, 1·67; p=0·07) of the six population-based studies which had zero heterogeneity between them. There was no effect (p=0·21) comparing studies by sample size (≥median sample). There were six studies with higher quality scores (≥median) where heterogeneity was absent, giving a summary OR 1·50 (96%CI 1·19, 1·89; p=0·001). This was lower (but not significantly p=0·103) than the OR 2·10 (95%CI1·50, 2·93; p<0·001) for the lower quality studies. There were also no significant differences (p=0.06) between studies by number of occupational SES levels reported (Table 4.4). Influence analysis demonstrated

that no single study in the meta-analysis of all 14 OSC studies significantly altered the summary OR.

4.4.5.7 Publication bias

There was no apparent publication bias in the studies presenting OSC data: Begg's test (p=0·19) and Egger's test (p=0·70) for publication bias within the 14 studies were both non-significant. Figure 4.5 assesses publication bias via a funnel plot: the vertical line depicts the log of the overall meta-analytic OR for occupational social class. The x-intercept of this line is >0, indicating greater risk for oral cancer with lower occupational social class (OR 1.84). The diagonal lines represent pseudo-95% CIs around the log OR. Begg's adjusted-rank correlation test (p=0.19) rejects any significant correlation between the effect estimates and their variances. Thus, no obvious skew in the distribution of published studies is observed and no evidence of publication bias is present.

Figure 4.5 Funnel plot for publication bias (occupational social class meta-analysis).



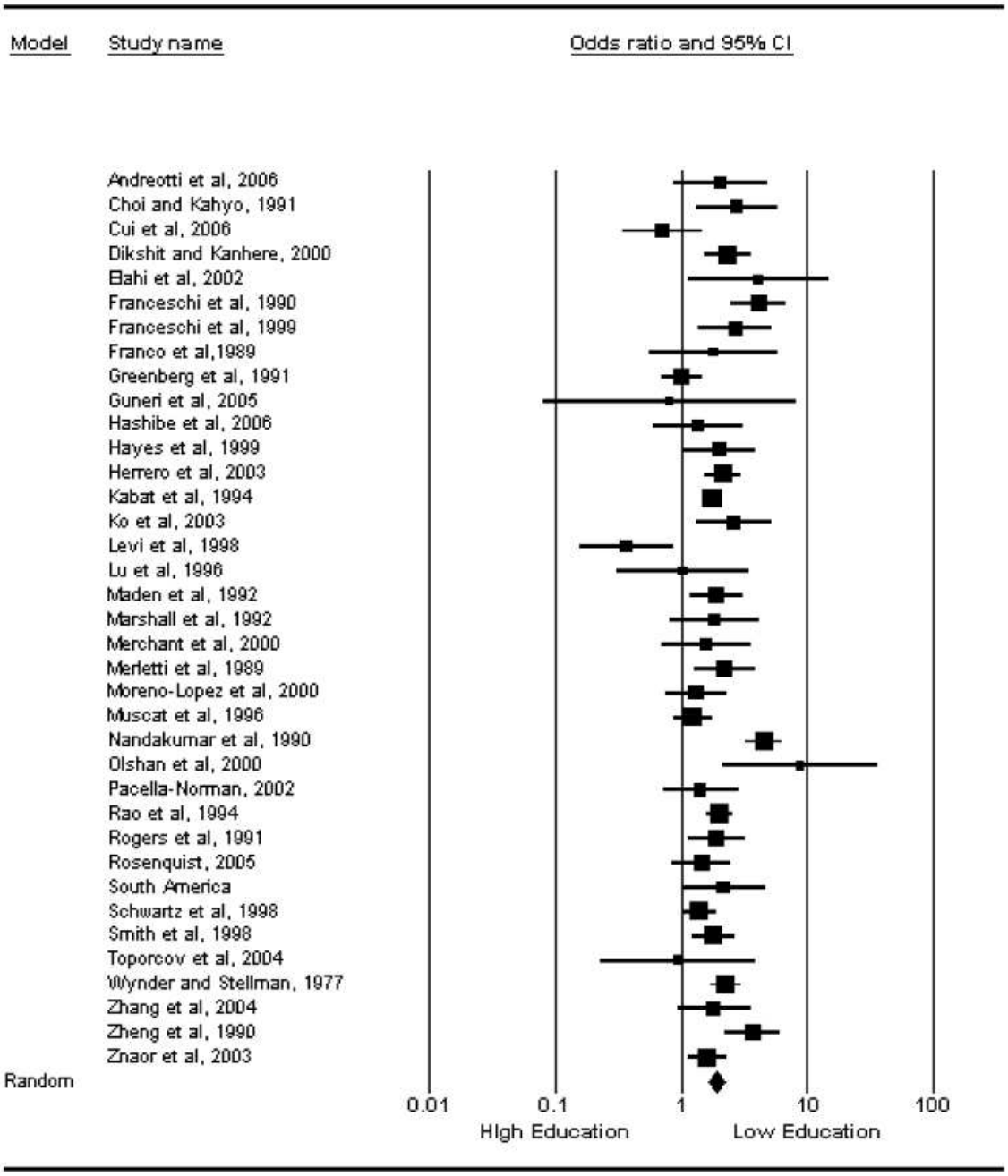
4.4.6 Association between low educational attainment and oral cancer

4.4.6.1 Overall

Thirty seven studies with 14,845 cases and 31,107 controls in total, provided data on the association of education with oral cancer risk. There was significant heterogeneity across

the studies (I^2=65.52, p<0.001). The combined OR was 1·85 (95%CI 1·60, 2·15; p<0·001) for increased risk associated with low educational attainment. Only four studies provided an OR which suggested high education levels were associated with increased risk for oral cancer (Figure 4.6, Table 4.4).

Figure 4.6 Meta-analysis of odds ratio estimates of low vs high educational attainment levels associated with risk of oral cancer



4.4.6.2 Sex and age

There were no differences by sex and no studies available with separate age-group estimates. The estimated OR 2·04 (95%CI 1·61, 2·58;p<0·001) for low education risk associated with oral cancer in males from 11 studies was higher (not significantly p=0·29)

than the females subgroup OR 1·62 (95%CI 1·25, 2·10, p<0·001) from seven studies. There was no observed heterogeneity in the female studies group. There were no studies which provided separate education data for younger and older age-groups (Table 4.4).

Table 4.4 Summary relationship between low socioeconomic status and oral cancer

Subgroup / sensitivity analysis		SES level	SES Measure OR (95% CI); n=number of studies		
			Income	Occupational social class	Education
		high	1•00	1•00	1•00
Overall		low	2•41 (1•59, 3•65); n=5	1•84 (1•47, 2•31); n=14	1•85 (1•60, 2•15);n=37
Cancer defintion	OC	low	–	2•25 (1•56, 3•26); n=8	1•93 (1•63, 2•30); n=31
	OC&OP	low	–	1•52 (1•13, 2•03); n=6	1•58 (1•23, 2•02); n=13
Sex	M	low	4•04 (2•65, 6•16); n=2	1•88 (1•48, 2•39); n=9	2•04 (1•61, 2•58); n=11
	F	low	–	2•31 (1•61, 3•30); n=5	1•62 (1•25, 2•10); n=7
Age	younger	low	–	1•32 (0•71, 2•45); n=2	–
Global development	High-income	low	3•41 (2•14, 5•44); n=2	–	1•71 (1•42, 2•07); n=22
	Lower-income	low	1•77 (1•18, 2•66); n=3	–	2•09 (1•63, 2•68); n=14
Region	N America	low	3•41 (2•14, 5•44); n=2	1•63 (1•31, 2•04); n=6	1•62 (1•34, 1•96); n=13
	Europe	low	–	2•09 (1•04, 4•22); n=5	1•59 (0•97, 2•59); n=8
	Asia	low	1•77 (1•18, 2•66); n=3	2•26 (1•17, 4•36); n=3	2•38 (1•76, 3•21); n=9
	S / C America	low	1•62 (1•05, 2•48); n=2	–	1•90 (1•29, 2•79); n=5
Time-period	1970s-1980s	low	–	1•58 (1•35, 1•86); n=7	2•31 (1•76, 3•03); n=12
	1990s	low	2•58 (1•49, 4•45); n=3	1•79 (1•15, 2•80); n=5	1•65 (1•38, 1•96); n=17
	2000s	low	2•17 (0•84, 5•64); n=2	4•18 (0•75, 22•91); n=2	1•53 (1•12, 2•10); n=8
Adjusted for confounders	yes	low	3•41 (2•14, 5•44); n=2	1•41 (1•10, 1•79); n=4	1•74 (1•33, 2•27); n=17
	no	low	1•77 (1•18, 2•66); n=3	2•03 (1•52, 2•72); n=10	1•99 (1•70, 2•27); n=20
Methodological criteria	Higher	low	3•41 (2•14, 5•44); n=2	1•50 (1•19, 1•89); n=6	1•88 (1•50, 2•35); n=16
	Lower	low	1•77 (1•18, 2•66); n=3	2•10 (1•50, 2•93); n=8	1•83 (1•50, 2•24); n=21
No. of levels of SES	2	low	–	–	2•25 (1•50, 3•37); n=5
	3	low	2•17 (0•84, 5•64); n=2	1•50 (1•25, 1•81); n=9	1•47 (1•15, 1•88); n=13
	4	low	–	4•14 (0•75, 22•91); n=3	2•04 (1•63, 2•56); n=15
	5	low	2•26 (0•98, 5•23); n=2	–	1•72 (1•27, 2•32); n=3

OR = Odds ratio; CI = Confidence Interval
OC = Oral cavity cancer; OC&OP = oral cavity and oropharyngeal cancer combined
M = Male; F= Female
N = North; S = South; C = Central

4.4.6.3 Oral cancer definition

The subgroup analysis of the 30 studies, which provided education data for 'oral cavity' defined cancer, provided a greater (p=0·06) pooled OR 1·94 (95%CI 1·638, 2·29; p<0·001)

compared to the combined OR 1·51 (95%CI 1·24, 1·85;p<0·001) from the seven studies where there were no separate oral cavity data available (Table 4.4).

4.4.6.4 Lower- vs. high- income countries

The risk of oral cancer associated with low educational attainment was similar across lower and high-income countries and between European and North American countries. Pooled estimates from the 14 studies in lower-income countries were not significantly greater (p=0·21) than the 22 studies from high-income countries (Table 4.4). The pooled estimate for the nine studies from Asia OR 2·38 (95%CI 1·76, 3·21; p<0·001) was not significantly (p=0·39) higher than the estimate from the eight European studies OR 1·63 (95%CI 1·00, 2·66; p=0·05); or the 13 North American studies which gave an OR 1·61 (95%CI 1·33, 1·95; p<0·001).

4.4.6.5 Trends over time

There was a moderately significant (p=0·04) reduction in education-related inequalities over time comparing the subgroups of 12 studies completed in the 1970s and 1980s to the 17 studies completed in the 1990s and to the eight studies completed in the 21st century. However, there was no significant (p=0·70) change between the last two decades. This change was also observed, but not to a significant extent, when limiting the analysis to both lower income countries (p=0·08), and also to high-income countries (p=0·29). However, limiting the analysis to studies meeting less than half of the methodological criteria did produce a significantly lower OR in recent years (p=0·002), which was not significant (p=0·24) when limiting to studies meeting most methodological criteria.

4.4.6.6 Adjusting for potential confounding risk factors

There were 17 studies which had education estimates adjusted for smoking and alcohol consumption. These were not significantly different (p=0·39) to the 20 studies not adjusting for these risk factors.

4.4.6.7 Sensitivity analysis

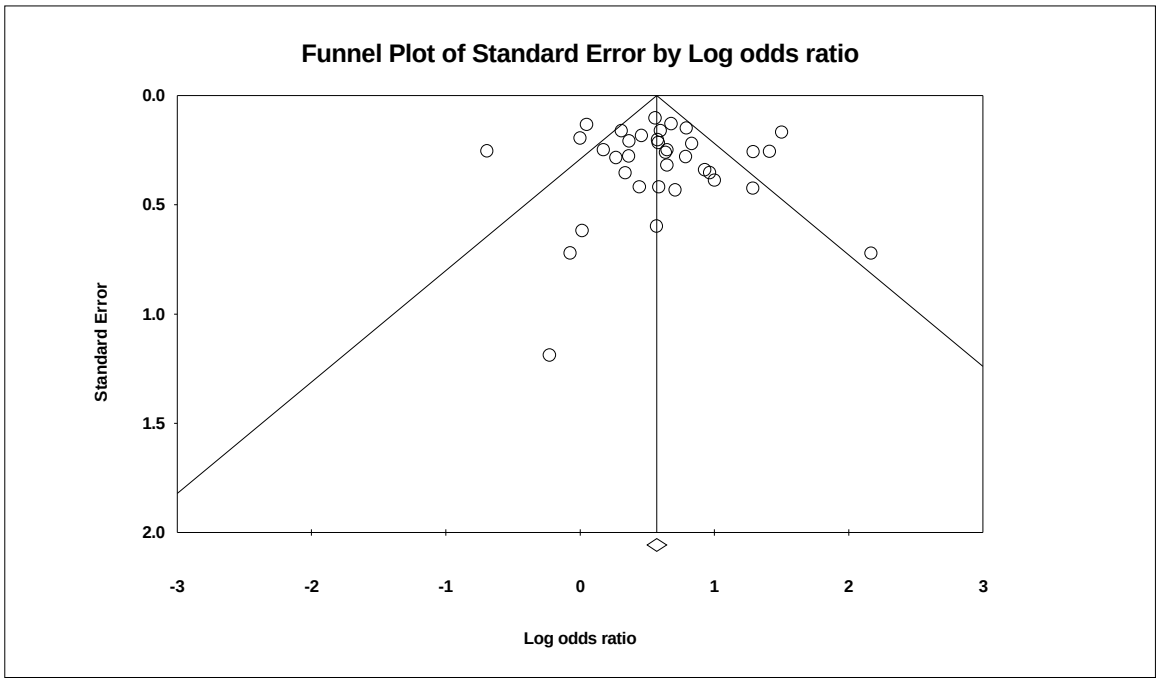
Data source did not have a significant effect on the estimates. Of the 37 studies with education estimates, 24 were hospital-based studies providing an overall estimate OR 2·03 (95%CI 1·68, 2·45; p<0·001) associated with low education attainment. This was similar

(p=0·06) to the summary OR 1·59 (95%CI 1·28, 1·90;p<0·001) from the 13 population-based studies. There were also no significant differences (p=0·28) between studies by number of educational SES levels reported (Table 4.4). Influence analysis, demonstrated that no single study in the meta-analysis of all 37 studies with education data significantly altered the summary OR.

4.4.6.8 Publication bias

There was no apparent publication bias in the 37 studies presenting education data: Begg's test (p=0·67) and Egger's test (p=0·71) for publication bias were both non-significant. A funnel plot of the effect size (log OR) versus precision estimated as the reciprocal of the effect size demonstrates a symmetrical pattern with no suggestion of publication bias in this analysis (Figure 4.7). In the funnel plot, the vertical line depicts the log of the overall meta-analytic OR for education level. The x-intercept of this line is >0, indicating greater risk for oral cancer with lower educational attainment (OR 1.85). The diagonal lines represent pseudo-95% CIs around the log OR. Begg's adjusted-rank correlation test (p=0.33) rejects any significant correlation between the effect estimates and their variances. Thus, no obvious skew in the distribution of published studies is observed and no evidence of publication bias is present.

Figure 4.7 Funnel plot for publication bias (education meta-analysis).



4.4.7 Comparison between SES measures

There were 10 studies with both education and occupation data which provided similar pooled estimates. The education OR 1·88 (95%CI 1·44, 2·46; p<0·001) was marginally lower (but not significantly, p=0·81) than the occupation SES OR 1·97 (95%CI 1·49, 2·61; p<0·001). Five studies contained both education and income data (zero heterogeneity) and the low income provided a higher (p=0·05) OR 2·41 (95%CI 1·59, 3·65; p<0·001) compared to the low educational attainment OR 1·48 (95%CI 1·15, 1·91; p=0·002).

4.5 Discussion

4.5.1 Key points

As far as could be ascertained, this is the first systematic review and meta-analysis of socioeconomic inequality and oral cancer undertaken. Low relative to high SES is associated with increased risk of developing oral cancer. This is repeated across all SES measures used, is consistent across sexes, global regions, country economic development status, and definitions of oral cancer employed. These findings also hold when only examining studies meeting specific methodological criteria, and when adjusting for potential confounding factors.

4.5.2 Limitations

The review findings are as far as possible robust. A thorough search was undertaken, which tapped into a world-wide head and neck cancer research network resource to identify unpublished analyses. Nevertheless, the limitations of meta-analyses are well documented and are acknowledged here (Blettner *et al.*, 1999; Stroup *et al.*, 2000; Higgins and Green, 2006) – particularly their dependency on the level of evidence of the summarised studies. Therefore, this study is subject to potential bias, including: publication bias, bias associated with case-control study methodology, and confounding (Blettner *et al.*, 1999; Higgins and Green, 2006).

Publication bias is the selective publication of studies based on the magnitude and direction of their findings and is a significant threat to the validity of meta-analyses – particularly those of observational studies (Stroup *et al.*, 2000). Publication bias was systematically assessed, via funnel plots and a series of sensitivity and influence analyses,

and was not observed. However, the power of the tests to detect publication bias may be low for some of the small meta-analyses so publication bias may still operate within this set of data.

The main limitations of case-control studies, including selection and recall bias (Breslow and Day, 1980), were addressed through a thorough assessment of key methodological issues associated with case-control studies. However, it has been shown that recall of SES information is reliable, and independent of social class (Krieger *et al.*, 1998). Sensitivity analyses limiting to those studies meeting methodological criteria aimed at limiting bias did not materially affect the results.

The presence of significant heterogeneity in most of the pooled analyses was expected as the included studies used different: SES measures, oral cancer definitions, potential confounding factors; and came from different data sources and populations from across the world. Study heterogeneity was primarily addressed and explored through pooling the data by means of a random effects model (Higgins and Green, 2006) and through subgroup and sensitivity analyses.

SES data were usually presented stratified into several levels but with limited uniformity of data presentation. It was felt that the best indicator of the extent of relative inequality was the difference between the highest and lowest strata, as reported by the authors of the selected study (Shaw *et al.*, 1999). However, this ratio has been criticised as not giving a full picture of inequalities (Wagstaff *et al.*, 1991). Despite this, it was felt that it would not be possible to collapse the mid-categories into meaningful social strata. SES also must be seen in the context of the country and culture where it is being observed. Low SES may have a different meaning and implication in a low- compared to a high-income country and it was therefore felt that standardisation of levels of SES was not possible. For example, education categories in studies from lower-income countries often had ‘no education’ as the lowest level and ‘ever education’ as the highest level, while in high-income countries the lowest level was ‘high school’ and the highest level was ‘university education’. Similar inter-study variability was observed for occupational social class and income categories. Therefore, it was decided that the most appropriate assessors of the socioeconomic strata were the authors of the original included studies. Further, sensitivity analyses based on the number of SES strata reported did not affect the results materially, such that estimates based on dichotomising SES data compared to studies with multiple levels of SES were similar.

4.5.3 Comparison with other work

Potential confounding by risk factors need to be considered in studies investigating the effects of SES. For oral cancer the important known 'lifestyle' behaviour factors include smoking / tobacco use and alcohol consumption (which together also have a synergistic effect), a diet low in fresh fruit and vegetables, and HPV infection. A recent INHANCE pooled analysis of cigarette smokers who never drank alcohol found an increased risk for oral cancer (OR 1·4) and among never smokers, alcohol consumption offered a similar risk (OR 1·2) (Hashibe *et al.*, 2007). An earlier IARC monograph review found a higher oral cancer risk (4.0-5.0) for tobacco smoking (IARC, 2004a). A meta-analysis investigating bidi smoking (a south Asian traditional tobacco habit) gave an increased estimated risk of oral cancer for bidi smokers (OR 3·1) compared to never smokers but a non-significant increased risk compared to cigarette smokers (OR 1·1) (Rahman *et al.*, 2003). Also, a meta-analysis of 15 studies found an increased risk of oral and pharyngeal cancer with increasing alcohol consumption: from OR 1·9 for 25g/day to OR 6·5 for 100g/day (Corrao *et al.*, 2004). In relation to diet, a recent pooled analysis of 16 studies showed that each portion of fruit (OR 0·5) or vegetables (OR 0·5) consumed per day reduced oral cancer risk (Pavia *et al.*, 2006). Furthermore, a recent international multi-centre case-control study found an increased risk associated with HPV infection (OR 1·5) for oral cavity cancer and (OR 3·5) for oropharyngeal cancer (Herrero *et al.*, 2003).

4.5.4 Potential explanations for study findings

In the context of these pooled risk estimates, the oral cancer risk from low SES was found to be significant and comparable. This relationship remained when behaviour risk factors were adjusted for (as far as was possible) – although it may be reasonable to assume that residual confounding persisted unaccounted for or underestimated. Smoking, alcohol, diet, and sexual history (with regard to HPV-exposure) are associated with inequality themselves and may go part of the way to explain SES gradients in oral cancer (Marmot, 1997). The interaction between low SES and these risk behaviours themselves is complex as discussed in the previous chapter.

SES is based on three inter-related dimensions, according to Weber: (i) class – incorporating ownership and the economic dimension, (ii) status – prestige or honor in the community, and (iii) power – political influence (Weber, 1914). The measurement of SES via the indicators of education, occupation, and income capture these dimensions (Liberatos *et al.*, 1988), but it is evident that these three indicators are also intertwined:

with education generally leading to occupation and on to income. The mechanisms for increasing disease risk – in this case, oral cancer – are complex.

The hypotheses for the association of low education attainment and poor health have yet to be fully 'unbundled' (Berkman and Macintyre, 1997; Yen and Moss, 1999). In terms of the association with oral cancer risk, potential hypotheses include education: (i) as a potential direct causal effect – being generally fixed in early life it may also reflect childhood experiences (Lynch *et al.*, 1994); (ii) influencing position in society and the inferred stresses (Marmot, 2002); (iii) reflecting income and access to health care, health information (Berkman and Macintyre, 1997); (iv) influencing occupation (Berkman and Macintyre, 1997); (v) determining values for the future – and so 'risky' behaviours (Murphy and Topel, 2006); (vi) as a means of developing cognitive skills – and so decision-making (Lynch *et al.*, 1994; Berkman and Macintyre, 1997); (vii) affecting preferences – and so locus of control (Berkman and Macintyre, 1997); and (viii) determining social networks (Berkman and Macintyre, 1997).

Low OSC may reflect exposure to harmful physical environments and agents which could increase the risk for oral cancer (Riechelmann, 2002; Menvielle *et al.*, 2004). Low OSC may also bring with it a work environment more associated with harmful psychological or social environments with 'work stresses' (Marmot *et al.*, 1991) which may also increase cancer risk. Low OSC may also increase risk through poorer terms and conditions, increased short-term employment (Stewart *et al.*, 1990) and increased periods of unemployment (Bartley, 1994).

Household income may have a direct impact on the housing and living environment which in turn affects health (Lynch *et al.*, 2000; Marmot, 2002). It may also determine access to: health services, social facilities, and to the affordability of quality food (Wrigley, 2000). These factors affect health and could potentially explain the association with increased oral cancer risk.

It has been suggested that low SES, by all measures, potentially infers some form of 'stress' (Marmot, 2005). These stresses may come from a range of sources e.g. insecurity of work, unemployment, fear of crime, debt, low social capital and community cohesion (Macintyre *et al.*, 1993). The biological basis for the pathway between the stresses associated with low SES, inequalities and cancer development is not entirely clear but emerging hypotheses include the "biological ageing" effects resulting from poor

socioeconomic circumstances (Adams and White, 2004), perhaps being mediated by telomere shortening (Cawthon *et al.*, 2003).

While the present study indicated a reduction in inequalities over time – no evidence was found that they had completely disappeared as previously reported (Bosetti *et al.*, 2001). This trend was not explained by limiting to studies from high- or lower-income countries, although it was most apparent when limiting the analyses to studies with low methodological criteria. Nevertheless, the increased oral cancer risk associated with low SES is significant and persistent.

The complex interactions and potential explanations of the relationship between oral cancer and SES have been outlined. These will be discussed further and drawn together in Chapter 7.

4.6 Conclusions

Although often ignored, this study has shown the socioeconomic perspective to be potentially a major factor in the aetiology of oral cancer. Recently, there has been an ever-growing focus on the genetics and molecular epidemiology of oral cancer, with a continued acceptance of traditional risk behaviours as ‘lifestyle choices’ – often viewed independently of and considered unaffected by the socioeconomic circumstances in which people live. Further research is necessary to tease out the hypotheses and components of low SES associated with increased oral cancer risk.

5 Analytical epidemiology (I): Socioeconomic aspects of selection and participation in a population-based case-control study of head and neck cancer in Scotland

5.1 Introduction

The late Sir Richard Doll (2003), in an address to the University of Glasgow, described falling participation as ‘one of the important challenges facing case-control studies’.

Population case-control study design is vulnerable to bias, particularly that associated with the effects of non-participation (Stang *et al.*, 1999; Olson 2001; Rogers *et al.*, 2004). A number of hard-hitting commentaries in the epidemiological literature have also discussed the increasing threat to the future of case-control epidemiology from population non-participation, and point to limited research on the non-participation issue (Sandler, 2002; Stang, 2003; Bernstein, 2006; Hartge, 2006).

The main effect of non-participation is bias resulting in non-comparability of cases and controls (Breslow and Day, 1980). This potential bias can affect both exposure and outcome measures, in addition to the assessment of association between exposure and outcome (Crique, 1979; Rothman and Greenland, 1998). However, participation bias will affect the findings (i.e. the odds ratio) only when it has a combined effect on both the exposure and outcome (Austin *et al.*, 1981).

It is in the selection or sampling of controls, intended to be representative of the population, where there is also potential for bias. However, in population-based control sampling, via, for example, General Practice patient registers held by health administration authorities, the response or participation rate holds the main potential source of bias (Law *et al.*, 2002). It has been argued that hospital-based controls improve participation, although this more convenient sample may lead to selection bias through over- or under-selection of individuals exposed to the risk factors of interest, while population controls have to struggle more with motivation to participation (Wacholder *et al.*, 1992; Bernstein, 2006). The issue of participation also feeds into the on-going wider debate on defining the roles of epidemiology. On one hand, the argument is to ignore the population perspective in the search for risk factors, and to ensure the representativeness of controls with respect

to cases (Rothman and Greenland, 1998); while on the other hand, the call is to broaden the scope of epidemiology, and to take a population perspective which extends to the selection of controls representative of and generalisable to the wider population (Pearce, 1997).

Despite the significant impact participation has on case-control studies, reporting of response and participation is inconsistent, often poor, and under explored (Olson *et al.*, 2002; Morton *et al.*, 2006). Investigation of non-participation in epidemiological studies is often constrained by limitations imposed by ethical research committees (Smith *et al.*, 2004a), particularly when the research is focused on following up non-participants for their reasons for non-participation. If non-participants differ from those who participate or who actively decline to participate this will impact on the strength of the validity and the generalisability of the results to the target population.

In addition, there is often limited information available on population-based controls who do not participate, particularly if random-digit dialing methods – common in North America – are employed. Active follow-up is usually required, with the corresponding additional research resource, to approach for an additional time those who did not participate (Law *et al.*, 2002). Furthermore, few studies have attempted to assess the socioeconomic impact of both selection bias and participation bias in both cases and controls.

5.2 Aims

The main aims of this study were to assess the socioeconomic effects on selection and participation in the Glasgow centre of the Alcohol Related Cancers and Genetic susceptibility in Europe (ARCAGE) study. ARCAGE is a 15 centre (in 11 countries) collaborative case-control study investigating the genetic, behavioural, and socioeconomic risk factors for head and neck cancer in Western Europe (IARC, 2002). All centres followed a common protocol and Greater Glasgow (Scotland) was a participating centre, contributing data from a population-based case-control study. Data were collected via face-to-face interviews and blood sampling in the subject's home by three trained interviewers. Full details of the case-control study methods will be documented in Chapter 6.

Specifically, the aims of this present study are: (i) to assess the extent by which socioeconomic circumstances are associated with the relative participation rates in cases and controls; (ii) to determine whether General Medical Practice (GP) lists are an adequate sampling frame for selection of a population-based case-control study; and (iii) to

investigate whether participants in the study are representative of the target population (i.e. Glasgow) from where they have been drawn.

5.3 Methods

5.3.1 Case ascertainment

The population-base for Glasgow was defined by residence in the health administration boundary 'NHS Greater Glasgow Health Board' – and registered with a GP. Incident case ascertainment ran from April 2002 to December 2004 and involved identification of patients aged 18-80 years with a histologically confirmed squamous cell carcinoma of the oral cavity, pharynx, or larynx and with no history of previous or other synchronous malignancy. This was conducted through weekly monitoring of pathology departments, hospital clinics and communication with the Head and Neck Cancer Liaison Nurses who had a city wide remit. Reasons for non-participation of cases were monitored.

5.3.2 Control selection

Control selection followed identification and participation of a case. The patient's GP was contacted, and all people from the practice list, matched for sex and age (5-year age band) were selected by the practice management team and the GP. Of those, ten were then randomly (via random number tables) selected and sequentially ordered 1 to 10 (with '1' being the first choice control) by the practice team. The researcher then contacted them one-at-a-time in numerical order via a letter of invitation to participate which contained an information leaflet on the study. This invited them to participate by responding via telephone or letter to the named researcher to arrange an appointment for interview. If the researcher had received no response within two weeks a follow-up letter was sent out (Ethical Committee Approval did not permit telephone follow-up). If there was no response within a further week from the '1st choice control' then the next person on the list was contacted. Of the 10 control subjects, only each of those approached prior to the individual who agreed to participate, were registered as controls (and hence considered as the denominator for the response calculation). This process was repeated until a positive response was received and interview consent secured. Postcodes were obtained for all controls, therefore it was possible to assign the area-based measures of socioeconomic circumstance, whether the control participated or not.

5.3.3 Deprivation scores

The primary measure of neighbourhood deprivation used was the recently developed Scottish Index of Multiple Deprivation (SIMD), created by the Scottish Executive (government) for monitoring and planning purposes. The SIMD is calculated using Census data including six domains of: income, employment, housing, health, education, geographical access to services / telecommunications – which are derived from 31 individual indicators of deprivation at the level of 'data zones' (Scottish Executive, 2004c) – detailed in Section 1.3.3.11.

Data zones are defined as stable and consistent small geographical areas in Scotland. They are groups of 2001 Census Output Areas which have populations of between 500 and 1,000 residents nested within Local Authority boundaries. They are intended to be effective at identifying small areas with similar social and economic characteristics (Scottish Neighbourhood Statistics, 2004).

Also used in this investigation were the traditionally reported area-based measures of deprivation (based on data from the 2001 Census): (i) the Carstairs-2001 deprivation scores (Carstairs and Morris, 1991) – detailed in Section 1.3.3.7; and (ii) the Townsend-2001 deprivation scores (Townsend *et al.*, 1988) – detailed in Section 1.3.3.8.

Deprivation scores were calculated by linking subjects' postcodes to 2001 Census output areas and data zones using the National Statistics Postcode Directory (2006). Postcodes which had not been assigned an output area or data zone were checked using the subject's address with the Royal Mail's postcode finder (Royal Mail, 2006). Lower (including negative) deprivation scores (for Townsend, Carstairs, and SIMD) represent areas with higher (affluent) socioeconomic levels and higher values represent higher levels of socioeconomic deprivation.

5.3.4 Statistical analyses

Comparative deprivation distributions were plotted on histograms and boxplots for: participants and non-participants in both the cases and controls (including 1st selected and non-1st selected controls); and for the Glasgow and Scotland (excluding Glasgow) populations. Comparisons were carried out using two-sample Wilcoxon tests. To assess the effect on participation of choice position (i.e. 1st choice vs non-1st choice), a linear model of ranked data was performed. As there were more than two factors, the Wilcoxon test was

not suitable – an accepted method for modelling skewed data is to model ranks (Conover and Inman, 1982). Statistical analyses were performed on SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

5.4 Results

Similar results and trends for the deprivation score distributions of the population-base, cases, controls, participants, and non-participants were observed for the SIMD, the Carstairs, and the Townsend indices. Therefore, for the purposes of clarity, the full range of all comparisons is presented for the SIMD distributions only. Evidence is presented to demonstrate the similar distributions for all the indices.

5.4.1 Response

Of the 298 eligible cases identified, permission to approach was not granted by a health care professional for only four subjects, and the overall participation rate for the cases was 34.9% (n=104). Of the 262 registered and approached controls from the GP lists, 91 (34.7%) agreed to participate. Reasons for non-participation are detailed in Table 5.1.

Table 5.1 Participation rates and reported reasons for non-participation of cases and controls.

	Cases n (%)	**Controls n (%)**
Total	298 (100)	262 (100)
Participants	104 (34.9)	91 (34.7)
Non-participants	194 (65.1)	171 (65.3)
Non-participation reasons n (% of non-participants)		
Deceased	38 (19.6)	-
Severe chronic disease	5 (2.6)	-
Severe disability	20 (10.3)	24 (14.1)
Consultant refusal	3 (1.5)	-
Self-reported ill health	23 (11.9)	-
Other (nurse refusal)	1 (0.5)	-
Subject refusal (with no reason)	66 (34.0)	43 (25.1)
Unable to contact	38 (19.6)	104 (60.8)

The comparative SIMD distributions of the study population (Glasgow), target population (Scotland excluding Glasgow), interviewed cases, non-interviewed cases, interviewed controls and non-interviewed controls are shown in the data in Table 5.2 and Figures 5.1 and 5.2.

Table 5.2 Summary Scottish Index of Multiple Deprivation (SIMD) scores for cases and controls by control selection position and participation status, and for the Glasgow and Scotland (excluding Glasgow) populations.

Group	Mean	Median	Lower quartile	Upper quartile
Scotland population excluding Glasgow	19.4	16.0	9.0	26.5
Glasgow population	33.3	28.3	11.0	52.9
All controls	36.7	33.2	15.9	53.3
All controls interviewed	30.0	23.5	10.7	46.8
All controls not interviewed	40.8	39.8	22.9	59.3
1st choice controls	32.1	31.3	10.8	50.5
1st choice controls interviewed	24.5	14.1	8.1	46.1
1st choice controls not interviewed	36.4	34.3	17.0	51.4
Non 1st choice controls	37.9	34.7	18.2	55.2
Non 1st choice controls interviewed	31.4	25.2	12.5	46.8
Non 1st choice controls not interviewed	42.0	39.5	25.3	61.6
Cases	43.0	41.7	23.3	64.5
Cases interviewed	39.7	39.0	19.7	62.9
Cases not interviewed cases	44.9	43.7	25.7	64.7

Figure 5.1 Boxplots for Scottish Index of Multiple Deprivation (SIMD) distributions by interview status

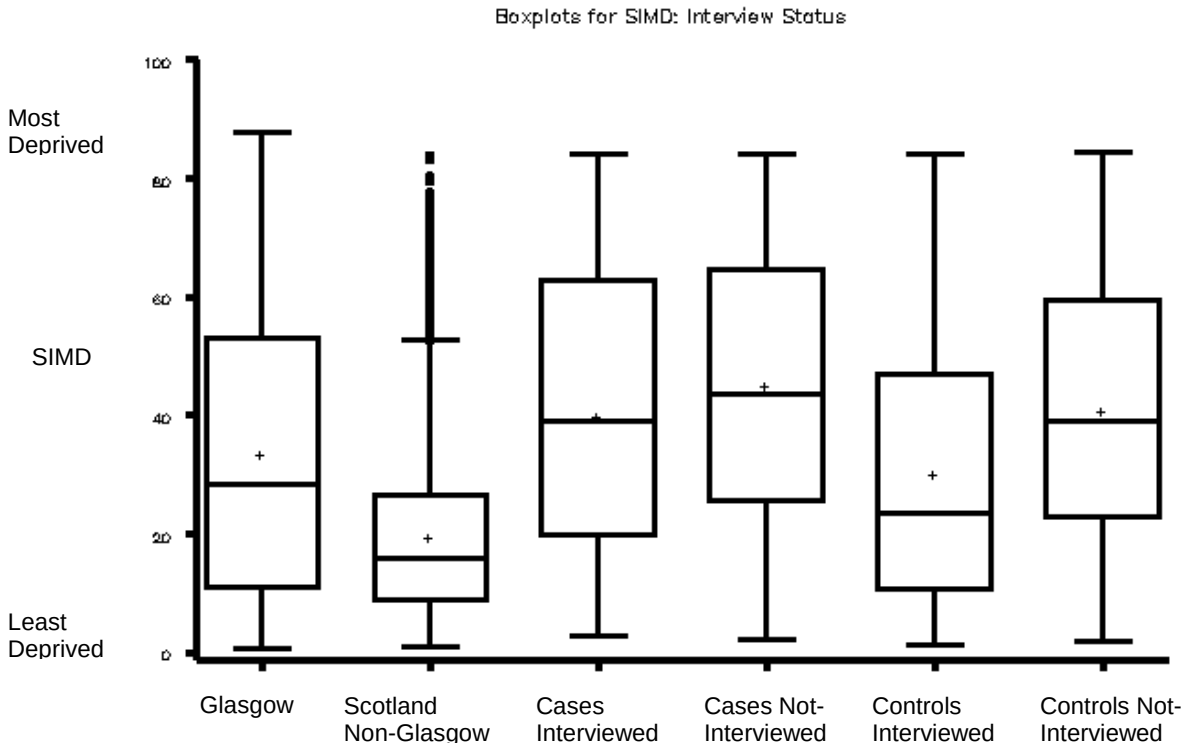
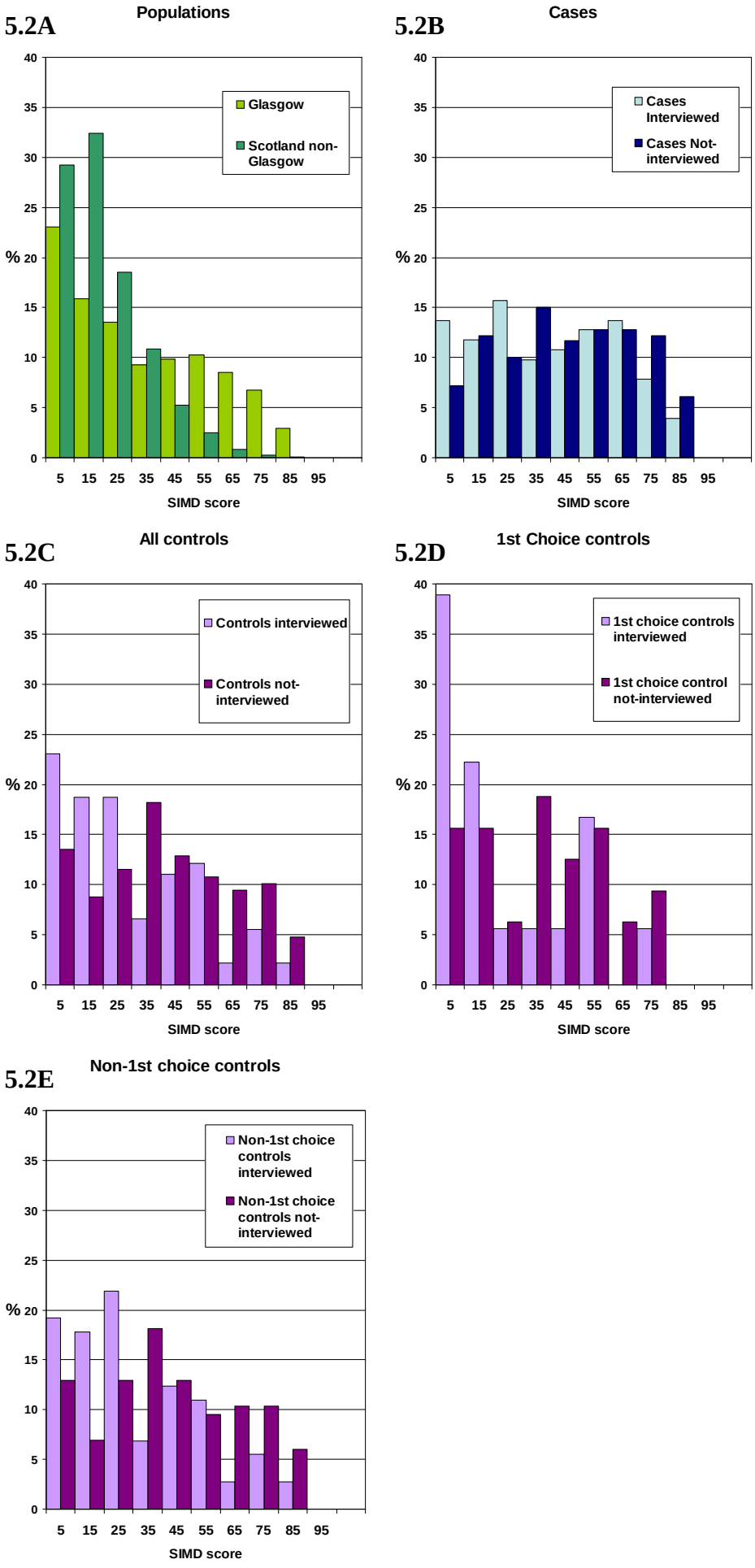


Figure 5.2 **Comparative distributions of the Scottish Index of Multiple Deprivation (SIMD) scores for cases and controls by control selection position and participation status, and for the Glasgow and Scotland (excluding Glasgow) populations.**



5.4.2 Study and target populations

The SIMD distribution of the Glasgow population was significantly ($p<0.001$, Wilcoxon test) more deprived than that of the population of the rest of Scotland (excluding Glasgow). This further demonstrates, what has previously only been presented using the Carstairs index (McLoone, 2004) that those living in Glasgow live on average in more relatively deprived areas than those living in other parts of Scotland (Figure 5.1, Figure 5.2A).

5.4.3 Cases

The overall group of cases were from significantly ($p<0.001$) more deprived areas than the general Glasgow population. With regard to participation: non-participant cases were from significantly ($p<0.001$) more deprived areas than participant cases (Table 5.2; Figure 5.1, Figure 5.2B). Those cases who were not interviewed were also more likely ($p<0.001$) to live in more deprived areas than the Glasgow population. Similarly, interviewed cases were also from significantly ($p=0.007$) more deprived areas than the distribution of the Glasgow population (Table 5.2).

Cases were significantly ($p=0.002$) more likely to live in more deprived areas than the study controls (Table 5.2; Figure 5.2).

5.4.4 Controls

The overall group of controls (participants and non-participants) were living in marginally more deprived ($p=0.028$) areas than the Glasgow population (Table 5.2). The controls, as with the whole Glasgow population, were from significantly ($p<0.001$) more deprived areas than the Scottish population excluding Glasgow.

On examination of participation of controls: interviewed controls were from significantly ($p<0.001$) more affluent areas than controls who were not interviewed (Figure 5.2C). The non-participant controls were from significantly ($p<0.001$) more deprived areas than the wider Glasgow population. However, the interviewed controls were not significantly different ($p=0.311$) to the Glasgow population in terms of area-deprivation.

First choice controls (irrespective of participation) were not significantly different ($p=0.149$) from non-first choice controls overall, and they were not from significantly

different (p=0.850) socioeconomic backgrounds than the Glasgow population in terms of relative deprivation. However, the non-first choice controls were from significantly (p=0.009) more deprived areas than the average for the Glasgow population (Table 5.2, Figure 5.2D, Figure 5.2E).

These relationships held in the linear model of ranked data to the same magnitude, suggesting there was no association with participation and choice-position. Thus, participation was confirmed as not being affected by choice position on the randomly matched 10 controls.

5.4.5 Comparison of deprivation Indices

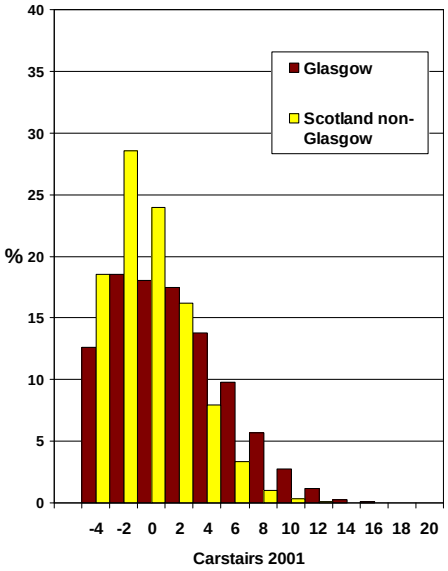
There were no significant differences in the distribution of deprivation scores for the population, the cases, and the controls between all the SIMD, Carstairs, and Townsend deprivation indices (Figure 5.3, Figure 5.4). Similar control socioeconomic distributions were computed from two-sample Wilcoxon tests using each index (Table 5.3).

Table 5.3 Two sample Wilcoxon tests for comparison of controls to Glasgow population by Carstairs 2001, Townsend 2001, and SIMD.

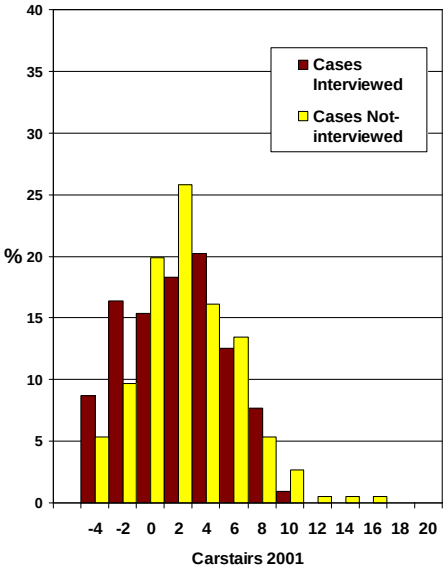
	Glasgow population		
	SIMD	**Carstairs 2001**	**Townsend 2001**
Controls	**p = 0.028**	**p = 0.032**	**p = 0.041**
Controls interviewed	**p = 0.311**	**p = 0.320**	**p = 0.621**
Controls not interviewed	**p < 0.001**	**p = 0.004**	**p = 0.002**

Figure 5.3 **Comparative distributions of the Carstairs (2001) scores for cases and controls by participation status, and for the Glasgow and Scotland (excluding Glasgow) populations.**

5.3A **Populations**



5.3B **Cases**



5.3C **Controls**

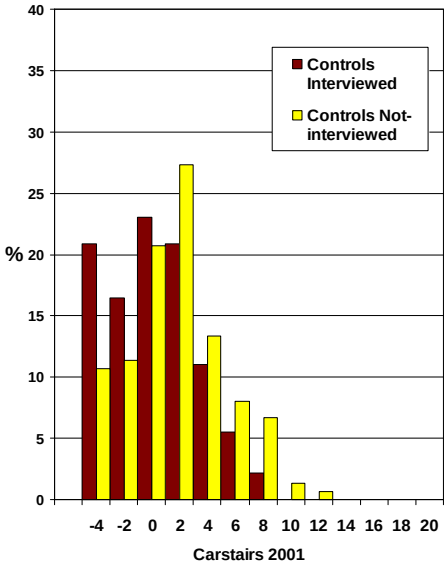
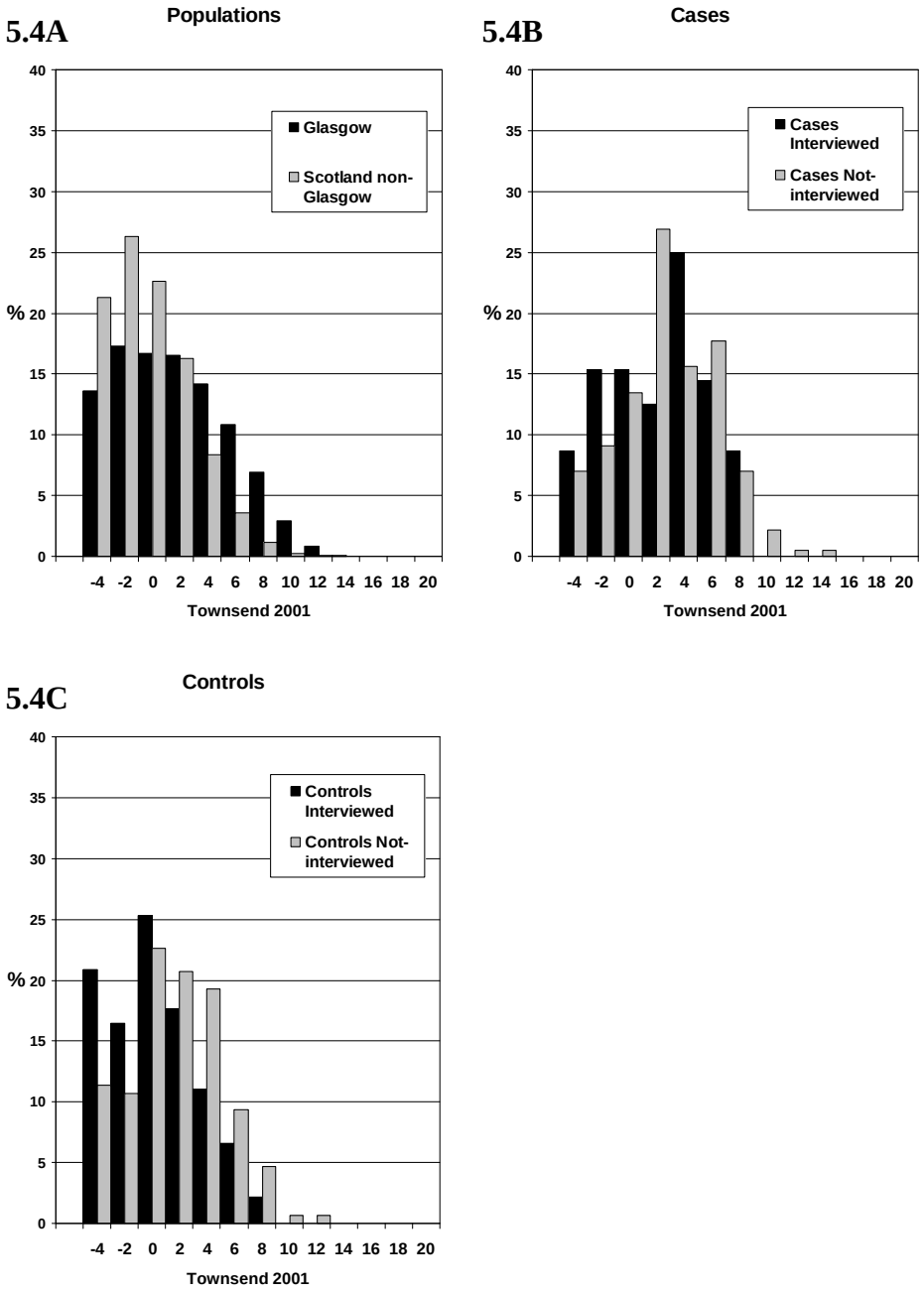


Figure 5.4 **Comparative distributions of the Townsend (2001) scores for cases and controls by participation status, and for the Glasgow and Scotland (excluding Glasgow) populations.**



5.5 Discussion

5.5.1 Key points

The response rate from both cases and controls was low in this study. There was evidence of selection bias and participation bias in both the cases and controls from a socioeconomic perspective. Interestingly, the controls who participated were socioeconomically similar to the population-base. The explanation for this is complex.

The study recruited incident cases from the Glasgow population and because head and neck cancers are more prevalent in the lower social groups (Macfarlane *et al.*, 1996a; Conway *et al.*, 2007) more cases (as expected) were from deprived areas compared to the population. Randomly sampled from cases' GP practice lists (matched only for age and sex), the overall control group was from more deprived areas than the Glasgow population. In addition, socioeconomic participation bias existed with both the interviewed cases and controls being from less deprived areas than their non-participant equivalents. These different types of bias associated with deprivation operated in different directions with the result that the interviewed controls were from similar socioeconomic areas as the 'target' Glasgow population.

The study was not initially designed to match on socioeconomic circumstances as this was a potential explanatory variable of interest – rather a true population representative sample of controls was intended. Selecting controls from the GP practice of the case had a stronger socioeconomic effect on the control sample than originally anticipated.

Firstly, while there was always a potential risk of broadly matching on socioeconomic circumstances through GP practices, there was evidence to suggest that GP practices were not homogenous with respect to their socioeconomic profiles. Rather the socioeconomic distribution of patients registered within an individual General Practice in Glasgow was broadly similar to the distribution of the Glasgow population (with 93% of the variation in deprivation of the Glasgow population being observed within General Practices in Glasgow (McConnachie *et al.*, 2003)). Nevertheless, while aware of this potential problem, the study design was practically constrained by the Health Board Caldicott Guardian and Ethics Committee, who did not permitting access to the GP register (i.e. the Community Health Index numbers) of the whole Glasgow population, or randomly to all General Practices in Glasgow (rather controls had to be matched to the cases' GP). Therefore, matching through GP practices were chosen as a proxy to accessing the population-base.

Despite these problems, quite fortuitously, the aim of obtaining a group of controls socioeconomically representative of the Glasgow population-base was achieved. This was due to the combined effects of selection bias and participation bias working in opposing directions – with the selection effect initially making the controls initially more deprived than the population (due to the effect of matching on the cases GP practice list / area); and the participation bias effect of interviewed controls being from more affluent areas than non-participants.

5.5.2 Comparison with other work

These findings in relation to participation bias are consistent with other studies investigating the socioeconomic aspects of participation using area-based measures of deprivation where active follow-up was also not possible and detailed information on individual non-participants not available (Law *et al.*, 2002; Smith *et al.*, 2004a). They also agree with the literature on non-response where individual socioeconomic data are available, which consistently finds that low educational attainment and low occupational social class leads to lower participation rates (Giordano *et al.*, 1990; Madigan *et al.*, 2000; Richardi *et al.*, 2002).

Further, with regard to selection bias, GP practice lists had previously been shown to be a suitable source of controls in a previous large UK-wide case-control study (Law *et al.*, 2002). This investigation of childhood cancer interviewed 3838 cases and 5530 controls and had high participation rates of 87% and 72% respectively (Law *et al.*, 2002). The authors concluded that GP practices in the UK are a robust source of population representative controls, although socioeconomic participation bias needs to be taken into consideration. More recently, from the same data, an investigation of the socioeconomic risk associated with childhood cancer, found no significant differences in levels of area-based deprivation between cases and controls (Smith *et al.*, 2006).

These results are in contrast to a study which investigated participation and selection bias, with regard to area-based socioeconomic circumstances, by the same research group (Smith *et al.*, 2004a). They found similar findings to those reported in this chapter. In their investigation of acute leukaemia (in all ages) across England, 838 cases and 1658 controls were interviewed – with participation rates higher in cases (79%) than in the control group (47%) (Kane *et al.*, 1999; Smith *et al.*, 2004a). They found that non-participant cases and controls were more likely to live in deprived areas (Smith *et al.*, 2004a). However, the cases were significantly more likely to live in deprived areas than their corresponding

controls (Kane *et al.*, 1999). They concluded that GP registers, although popular and convenient, should be used with caution to sample population controls, particularly with regard to generalising results (from controls) to the population.

5.5.3 Limitations

A main study limitation is the potential for 'ecological fallacy' in using area-based socioeconomic indicators where individuals are allocated an area socioeconomic status based on their residence. There is a wealth of literature debating this issue and it has been argued that people who live in the same area can share many of the socioeconomic circumstances not reflected by individual measures, in that the socioeconomic environment confers risk apart from or over and above that of their individual social class (Evans and Stoddart, 1990; Berkman and Macintyre, 1997). Individuals living in the same area are collectively exposed to socioeconomic factors rather than individually as a result of their individual socioeconomic position (Macintyre *et al.*, 1993). While individual measures of occupational social class, educational attainment, or income may have provided more detailed information, such indicators were simply not available for non-participants and could not have been obtained without active follow-up.

One potential limitation of using the new index of multiple deprivation is the concern of mathematical coupling whereby the index (exposure) includes a health domain and the outcome (cancer) is also a health-related and this may lead to false correlations. While this has not been assessed for the SIMD, a recent study by Adams and White (2006) of the effect of health domain within the IMD-2004 for England (which is constructed with the same domains as the SIMD) found that removing the health domain had practically little effect on the assessment of inequalities. They conclude that the health domain had a sound theoretical base – particularly when considering a full definition of deprivation, however, they did urge some caution in its utility when measuring and interpreting health inequalities. In our study it is unlikely this had a major effect on the analysis as the SIMD distributions were similar to the traditional deprivation indices (e.g. Carstairs and Townsend) which do not contain a health component.

A further major limitation of this study is the relatively small numbers of both cases and controls recruited which limits the overall power of the study both in analytical terms but also in terms of the ability to draw strong conclusions about the methodological issues that have been highlighted. It may be an easy criticism to dismiss the study based on the small numbers recruited, however, the numbers are not insubstantial, and such an assessment

does not acknowledge the enormous effort that went into recruiting subjects. Furthermore, the numbers were limited first and foremost by the ability to recruit case subjects – the control recruitment followed. The cases' non-participation reasons have been documented, but case-ascertainment, in the first instance was also compounded by the challenge of accessing case subjects in a seemingly disparate city-wide model of care for head and neck cancer care with multiple specialties, working in multiple hospital locations, and with multiple pathology laboratories.

Ultimately, the concern associated with selection and participation biases are the potential threat to the validity and precision of the study (Breslow and Day, 1980). Low participation rates can have a serious impact, due to the increased risks associated with differences associated with participants and non-participants – potentially in terms of differences in socioeconomic factors (observed in this study), or behaviours, or health status (Austin *et al.*, 1981). Selection bias has the potential to influence the generalisability (external validity) of the findings directly through the effects of the source of the controls, but also through how this impacts on participation (Rothman and Greenland, 1998). In the present study a fortuitous series of effects led to a socioeconomically representative control group. This could be considered, in the philosopher Immanuel Kant's terms as, 'the right answer for the wrong reasons' – an outcome which he did not favour, and which led him to caution against being enamoured by the outcome before understanding the process of getting there (Creel, 2001).

5.5.4 Potential explanations of study findings

5.5.4.1 Overall

The new SIMD scores used were based on small areas grouped on the premise of the common socio-demographic characteristics of their residents (Scottish Executive, 2004c). So the potential explanations for the association between low socioeconomic circumstances and participation observed could also be drawn from inferring individual socioeconomic characteristics such as education levels, and occupational social class. Low educational attainment may affect understanding of the request for participation, distrust and suspicion of health services, low confidence and self-esteem. Low occupational social class may also mean that the kind of work (e.g. shift work, working away from home) may not lend itself to time being available to participate (Hartge, 2006).

5.5.4.2 Cases

A low overall response for the cases was also observed. However, participants and non-participants were both more likely to live in relatively deprived areas compared to the Glasgow population. Non-participation of cases was also heavily influenced by the health status of the individual, including the significant number who had died. This may reflect the poorer prognosis and survival in those from deprived backgrounds (Macfarlane *et al.*, 1996a).

The cases, on average, were more likely to live in deprived areas than the controls, and this was irrespective of case or control participation. This is consistent with descriptive epidemiological findings of the socioeconomic inequalities observed in the distribution of oral cancer in the Scottish population (Conway *et al.*, 2007). The potential explanations for this are the socioeconomic determinants of the known aetiological risk factors: smoking, alcohol consumption, and diet – although the interactions between socioeconomic life circumstances and these behaviours are complex. As well as socioeconomic circumstances affecting an individual's empowerment in terms of education and health awareness, it also affects knowledge of and ability to make healthy choices (Giordano *et al.*, 1990). These factors and the components of the socioeconomic risk will be more fully investigated in Chapter 6.

5.5.4.3 Controls

Part of the explanation for low response may also have been the nature of the health outcome under investigation. The study control-recruitment information sheet which was sent out focused on, what is commonly referred to (medically) as 'head and neck cancer'. This is perhaps an ambiguous and misleading term for the public. On reflection, terms like 'mouth and throat cancer' may have been more recognisable. This is in keeping with a review on factors that affect willingness to participate which suggested that 'salience of the topic' exerted the strongest effect on willingness to participate (Hartge, 2006).

Two diametrically opposite potential interpretations could be given to and conclusions drawn from the findings regarding selection and participation in the control subjects. Firstly, that GP practices provide a representative population sample for population-based case-control study design when the condition under investigation has a known skewed socioeconomic distribution towards deprived communities; and conversely, that GP practices do not provide such a representative sample under such conditions.

Firstly, the intention was not to match on socioeconomic circumstances, due to the aim to explore the components of the socioeconomic risk on oral cancer within the ARCAGE study. However, it was inevitable (although this can only fully be acknowledged with hindsight, even with the assumption that practices were likely to be more heterogenous with respect to the socioeconomic profile of their patients) that the population-based case-control study design approach was going to sample controls from broadly the same areas as the cases. Due to the location of the GP practices these areas were likely to have similar socioeconomic area-profiles. Thus, the utilisation of community-based medical practice lists provided a sample frame which introduced an element of matching on area-socioeconomic circumstances. It was known that deprived communities carry a greater burden of head and neck cancer, therefore, the cases were more likely to attend GP practices in more deprived areas. So matching on and selecting controls from such practices would skew the GP sampling frame to those who were more deprived than the original target population. It was also expected that participation of controls would also be biased to those more likely to be socioeconomically more affluent. Both of these factors played out and ultimately gave a population representative sample of interviewed controls. Further, it is likely that if a population sampling frame did not match on socioeconomic area of the study case then the effect of socioeconomic participation bias would have resulted in controls which were not representative of the study-base. This interpretation could lead to the conclusion that provided the condition under investigation in a case-control study is related to deprivation, and then GP practice lists could potentially provide a valid and population-representative source of controls.

However, the main issues that do not hold up in this interpretation are the completely unquantifiable nature of the socioeconomic biases which operated throughout this study process. This began with the cases – who were as expected from more socioeconomically deprived areas than the Glasgow population. However, the participation bias effect on those cases who participated brought the socioeconomic distribution of the cases more towards that of the target population.

The controls were then selected from the participating case's GP practice. The nature of the matching aimed to ensure that the selected controls were representative of the GP list – with the inference in the study-design that such lists are representative of the wider population. However, they were skewed to the deprivation level of the cases (but the extent of this is unquantifiable). The effect of the subsequent, albeit expected, skew to those from more affluent areas being more likely to participate is also unquantifiable, and would likely vary depending on the participation rate (again undeterminable at the outset of a study).

The extent of the biases related to both selection and participation, in the expectation that they would provide a representative population sample is too imprecise and risky to be a valid recommendation from these findings. Therefore, the only conclusion that can be drawn is that selecting controls in a 'population-based' case-control study from case GP practices needs to be undertaken with caution. This approach may not be an appropriate method when the disease in question has a known skewed socioeconomic distribution. Future designs should bear this aspect of socioeconomic matching in mind, when the aim is for a 'population-based' case-control study design.

Selecting controls from GP practice lists could be argued as an approach to matching on (socioeconomic) area of residence, as patients in the UK practices usually live in surrounding defined catchment areas. Therefore GP lists may be of limited value in providing controls representative of the population-base, and due consideration of the socioeconomic distribution of the study disease needs to be given in deciding the method of selecting a control group.

However, as described earlier, the deprivation distribution of the patients within GP practices in Glasgow has been shown to be representative of the deprivation distribution of the Glasgow population (McConnachie *et al.*, 2003). Therefore, the catchment area of GP practices are more heterogenous with regard to deprivation, which may reflect that they are larger geographic areas than the small areas (data zones) utilised to measure the SIMD.

5.5.5 Alternative options for control selection

Selection of controls has perennially been debated and reviewed, most thoroughly in a series by Wacholder *et al.* (1992a, 1992b, 1992c), then by Lasky and Stolley (1994), and most recently by Grimes and Schulz (2005). These reviews outline the commonly used sources of controls as: hospital patients, death certificate or disease registry lists, friends or neighbours, relatives, and the 'general population'.

5.5.5.1 Hospital controls

Hospital controls are supported by Wacholder *et al.* (1992b) on three counts: (i) to select controls from the same referral pattern assumes the controls come from the same base-population; (ii) to gather the same quality of information as the cases; and (iii) for convenience. However concern has been expressed on that first point – the comparability of hospital controls with the population-base (Lasky and Stolley, 1994). On the few

occasions where both hospital and community controls were both selected in the same analytical case-control study, variable findings have been observed. One US study investigating coronary artery disease found both sources to be valid and comparable (Tell *et al.*, 1982); while an investigation of smoking behaviours from a US cancer case-control study found greater prevalence in hospital controls compared to those from the community (Morabia *et al.*, 1996). Furthermore, a recent South American head and neck cancer case-control study which utilised hospital controls found limited selection bias even when utilising controls with tobacco and alcohol related diseases (Nishimoto *et al.*, 2002).

More recently hospital visitors were also found to be a potentially valid and feasible source of controls for a case-control study investigating breast cancer in Brazil (Mendonça and Neto, 2001).

5.5.5.2 Controls with similar diseases

Controls with similar diseases are occasionally used in cancer studies, wherein controls are selected from patients with different forms of cancer. The main advantage put forward is the reduction of recall bias with regard to exposures, although in the review by Lasky and Stolley (1994) the evidence was equivocal.

5.5.5.3 Friend or neighbour controls

The use of friends as controls, also known as peer-nominated controls, was studied and reviewed by Kaplan and colleagues (1998). They noted high response rates could be obtained (although not as high as one would expect) and advised that such controls should be considered a selection option in the current era of confidentiality restrictions on accessing population registers. They also suggested two particular problems: (i) a ‘halo effect’ is a possibility with people generally nominating friends who were ‘better off’ or ‘more acceptable’ than themselves; and (ii) conversely, overmatching to an unknown extent based on behaviours or other factors is also a possibility.

Neighbour controls have been used to describe neighbours either selected by the patient (Lasky and Stolley, 1994), or canvassed from a finite proximity to or ‘neighbourhood’ of the patient (Grimes and Schulz, 2005). The former definition may provide a ready source of controls willing to participate, however, they may also introduce selection biases related to the exposure under investigation or particularly matched on socioeconomic and ethnic factors (Lasky and Stolley, 1994). The latter definition of neighbourhood controls has been

viewed positively as a way of obtaining socioeconomically matched controls to reduce confounding, but that non-response was also a particular issue (Grimes and Schulz, 2005).

5.5.5.4 Relative controls

Goldenstein *et al.* (1989) developed a model to assess the potential selection bias in the use of relatives (siblings) of cases in case-control studies and reports no selection bias provided the exposure-specific risks remain constant over time – although this is a major assumption in their model. Furthermore, other authors point to genetic confounding, and to the common physical environment, lifestyles, and socioeconomic status inherent in relatives of cases (Grimes and Schulz, 2005). The methodological issues in the use of 'non-blood' relatives in epidemiological research do not seem to have been fully explored since the theoretical issues related to the common environment were described by Wacholder *et al.* (1992b).

5.5.5.5 Population controls

Obtaining 'population controls' defined as those representative of the target population could be described as the 'holy grail' of case-control studies, given the volume of concern in recent years on the topic (highlighted in the many editorials reviewed in the introduction of this chapter). The principle behind population controls, according to Wacholder *et al.* (1992b) is that when a roster which identifies all individuals in the target population is available, controls can be selected at random from that roster. The advantages of population controls are related to the overarching aim of analytical epidemiology that the study (sample) can be related back to the population, in particular population controls provide a means of obtaining representativeness and generalisability to the target population – including calculation of the population attributable risk. The disadvantages are mainly around the practicalities of obtaining such controls both in terms of general population response and participation, but also in terms of the ethical and confidentiality issues around accessing population rosters and contacting selected individuals. Differential recall bias between 'healthy' population controls and cases has also been described as an issue (Wacholder *et al.* 1992a).

The methods used to select population samples are also well rehearsed in the literature (Wacholder *et al.*, 1992b; Lasky and Stolley, 1994) and include: population rosters e.g. tax lists, voting registers, telephone directories, national population registers, random digit (telephone) dialing (in the US), 'neighbourhood controls', and general medical practices

GP lists (in the UK) or other primary care ‘health units’ where the whole population are registered. Although only RDD, neighbourhood controls, and GP lists have received much attention in the review literature. The main consideration in the choice of such lists is the completeness of the roster – the more complete the more straightforward the task of selecting controls (Wacholder *et al.*, 1992b).

Random-digit dialing is widely used in the US where there are limited population rosters – while it is convenient and can provide an immediate response (via speaking to the individual directly in the first instance), it has a number of well documented disadvantages (Grimes and Schulz, 2005). These weaknesses relate to the socioeconomic factors that determine ownership and access to a telephone, and increasing use of mobile phones in society further complicate this approach. The present study did not consider this approach suitable.

Neighbourhood controls described above, are a non-random, or rather pre-determined mechanism of obtaining population or community controls, usually where no local population roster is available. This approach involves canvassing or knocking on adjacent or proximal residences in the same block or street as the case – to a pre-determined pattern (rather than to the interviewers’ discretion) (Grimes and Schulz, 2005). This mechanism is increasingly being considered where population rosters are not available or inaccessible. In the present study, the Ethics Committee did not approve this approach.

In the UK, as described above, GP lists are often used as sources of selecting population controls, given the assumption that almost the whole population is registered with a GP. Most recent data show that registration covers approximately 98% of the population (Royal College of General Practitioners (RCGP, 1987). Similarly, in Scotland, the most recent data available from ISD showed that the whole population seem to be universally registered with a GP (Information Statistics Division, 2007c) – although the data are somewhat limited in that more people are recorded as being registered than are on the population estimates.

As observed in the present study, selecting controls via GP practice lists may not be suitable, in every case, due to the selection bias associated with the geographical area populations registered with each practice. One potential solution may be to sample from the full target population roster i.e. all those registered with a GP in the target population. Such a roster exists in Scotland, via the Community Health Index (CHI) number. In the present study the Caldicott Guardian (a senior member of the NHS staff in the locality who

oversees the protection of patients' health information) refused permission to access the CHI roster to recruit patients – preferring access to patient rosters to be facilitated by General Practitioners.

In conclusion, with regard to future options for control selection: population controls are the ideal aim, but participation and restrictions to population rosters are proving major challenges, in addition to the expense and time-consumption involved. The use of GPs as a source of population controls is a well trodden path and a pragmatic choice, for epidemiologists in the UK, and while this method should be used with caution and careful monitoring, it should not be completely rulled out. Other potential sources of population registers also need to be explored. This could include re-exploring access and use of the population GP register (in Scotland recording with the Community Health Index number). However, failing that, hospital controls could also be considered for future studies in this area of oral cancer epidemiology, although the benefits of improved participation of controls need to be carefully weighed against the risks of them being unrepresentative of the population. Interestingly, a hospital approach has been adopted in the other European ARCAGE study collaborating centres outside of the UK (IARC, 2002).

5.6 Conclusion

Low participation rates in case-control studies remain a problem with socioeconomic factors strongly affecting participation. These effects need to be considered in the analysis and interpretation of risk.

Selecting controls from case GP practices needs to be implemented with care and attention paid to obtaining evidence on the underlying socioeconomic characteristics of GP practice populations, specifically when the disease in question has a skewed socioeconomic distribution.

In the present study, a control sample selection biased in one direction was offset by participation bias in the opposite direction fortuitously providing a representative control sample. It remains unresolved as to whether these findings were due to matching on the cases' GP.

Epidemiologists may also need to explore other potential sources of study controls for case-control studies and study design needs to ensure there are systems in place to monitor and take into account potential participation bias related to socioeconomic circumstances.

6 Analytical epidemiology (II): An exploratory study of the components of socioeconomic risk associated with head and neck cancer – results from a population-based case-control study in Scotland

6.1 Introduction

Head and neck carcinomas include the subsites: oral cavity, pharynx, and larynx. Despite the morphological differences, they have many common features and are often grouped together in: descriptive epidemiology studies (Soutar and Robertson, 2001; Stewart and Kleihues, 2003; Döbrõssy, 2005), aetiological analyses (Kreimer *et al.*, 2005; Peters *et al.*, 2005), and clinical management literature (Pignon, 2000; NHS National Institute for Clinical Excellence, 2004; Scottish Intercollegiate Guidelines Network, 2006).

Worldwide, cancer defined as head and neck cancer is estimated to be the sixth most common cancer for both sexes and the third most common in developing nations. However, it is relatively rare in European and North American countries, being around the 10th most common site for cancer (Sankaranarayanan *et al.*, 1998; Parkin *et al.*, 1999). In Scotland in 2004, head and neck cancers were the fifth most common cancer overall, with European age-standardised incidence rates of 25.4 and 9.2 per 100,000 in males and females, respectively (Cancer Information Programme, 2006). While the overall incidence trend is decreasing in the United States (Ries *et al.*, 2004), head and neck cancer seems to be on the rise across Europe (Parkin *et al.*, 2003), in the UK and Scotland in particular (Soutar and Robertson, 2001, Scottish Cancer Registry, 2007). Here the trend has been predicted to continue, with the greatest burden seeming to fall upon those living in the most deprived communities (Soutar and Robertson, 2001).

The relationship between socioeconomic status (SES) and head and neck cancer has not been extensively studied and is correspondingly poorly understood. Ecological descriptive epidemiological studies utilising record linkage of cancer registries to census data have previously demonstrated social inequalities in the distribution of oral and oropharyngeal cancer (Conway *et al.*, 2007), oral and pharyngeal cancer (Macfarlane *et al.*, 1996a), and laryngeal cancer (Faggiano *et al.*, 1997) – with those from lower socioeconomic groups

having a higher incidence. Data from analytical epidemiological studies were previously reported to show a more equivocal relationship with SES in the case-control studies which focused on this area (Elwood *et al.,* 1984; Ferraroni *et al.,* 1989; Greenberg *et al.,* 1991; Bosetti *et al.,* 2001). However, in the systematic review and meta-analysis undertaken earlier (reported in Chapter 4), a more convincing relationship with lower socioeconomic status (by all measures) was associated with increased oral and oropharyngeal cancer.

Smoking or chewing tobacco, together with alcohol consumption, are considered to be the main risk factors for head and neck cancer (Blot *et al.,* 1996), and to a lesser extent, diets low in fruits and vegetables (Pavia *et al.,* 2006), and human oncogenic papillomavirus infection (perhaps associated with sexual history) (D'Souza *et al.,* 2007) have also been associated. However, these behavioural or 'lifestyle' risks are often viewed in isolation from the underlying social context.

6.2 Aims

It is widely accepted routine practice to adjust for SES in analyses of risk factors for head and neck cancer, but this study aimed to flip this logic on its head and take an alternative perspective *a priori*: to examine SES as the main risk factor of the disease. Uniquely it also aimed to explore this in terms of both individual and area-based SES effects to assess specific components of socioeconomic risk. In addition, these SES factors will be examined to see if they persist when adjusting for behavioural risk factors. And vice versa: are the behavioural risk factors explained by socioeconomic determinants.

The specific objectives of this study include investigating the importance of:
- occupational social class and social mobility across the life course
- experience of unemployment as a risk factor
- educational status (level of educational attainment and years in full time education)
- area-based measures of socioeconomic circumstances (Carstairs, Scottish Index of Multiple Deprivation)
- the relationship between SES and behavioural risk factors (particularly smoking, alcohol, and diet)

In addition, as a separate exercise, this study will also test the methodology employed to investigate:
- the relationship between individual and area-based measures
- the relative effects of individual and area effects on the risk of oral cancer

However, these aims have to be viewed within the context of the wider Alcohol Related Cancers and Genetic susceptibility in Europe (acronym ARCAGE) study aims, which are to determine ‘genetic, lifestyle, and environmental risk factors for head and neck cancer in adults’ (IARC, 2002). Specifically, the study objectives are to test the hypothesis that the large differences in the incidence of head and neck cancer throughout the European Union are due to one or more of the following factors:

- different genetic susceptibility to alcohol metabolism, tobacco metabolism, DNA repair and other factors between European populations;
- different patterns of alcohol consumption and types of alcoholic beverage European populations;
- interaction between alcohol consumptions and other dietary and lifestyle factors, including low consumption of fruit and vegetables and tobacco consumption.

While the overarching hypotheses and objectives of the thesis are focused on ‘oral cancer’ and on ‘socioeconomic circumstances and inequalities’, the utilisation of the ARCAGE study requires compromise to accept the wider ‘head and neck cancer’ definition, and to accept that the study design (including questionnaire) was not designed primarily to look at social and economic factors. Furthermore, due to the design and study numbers in the local centre (Glasgow), it was also never going to be possible to undertake subsite analysis to focus on the oral cancer cases. It is the intention, however, to ensure that this is taken into consideration in the interpretation of the findings.

6.3 Participants and methods

6.3.1 Overview

This population-based case-control study was conducted in Glasgow, Scotland as a participating centre contributing data to the ARCAGE study. ARCAGE is a 15 centre collaborative case-control study (in 11 countries) with a common protocol investigating the lifestyle and genetic risk factors for head and neck cancer in Western Europe. The study geographical boundary was the health administrative authority of NHS Greater Glasgow Health Board with a population, in 2004, of 867,083 comprising 17.1% of the Scottish population (Registrar General for Scotland, 2005). Ethical approval for the study was given by the NHS North West Multicentre Research Ethics Committee.

6.3.2 Case ascertainment

Cases were patients aged 18-80 years with a primary histopathological diagnosis made between April 2002 and December 2004. Diagnosis included malignant cancers of the oral cavity (ICD-O-3 topography: C00-06), oropharynx (C09-10), hypo-pharynx (C12, 13), or larynx (C14, C32) (WHO, 2000). 'Incident' cases (diagnosed within six months prior to interview) were ascertained through weekly monitoring of head and neck cancer clinics in hospital departments and confirmed by pathology department records. In Glasgow, there were multiple clinics across the city – and case accrual was greatly assisted by head and neck cancer patient liaison nurses who had a city wide remit.

6.3.3 Control selection

Controls were randomly selected in a standard way, as described in detail in the previous chapter. The general medical practices of the case-subjects were the sampling frame with 10 people individually matched for age (5-year age band) and sex being selected by the practice management team and the GP. These 10 were randomly (via random number tables) sequentially contacted until a positive response was received and interview appointment secured. Invitation to participate was via a letter from the medical practitioner and the study was introduced as an investigation of risk factors for head and neck cancer.

6.3.4 Data collection

Interviewers were trained and calibrated to ensure standard data collection (this included tape recording and reviewing interviews). Identical data collection methods were used for both cases and controls, with a structured questionnaire (Appendix 8) including information on socio-demographic characteristics, anthropometric measures, lifestyle behaviours such as smoking and alcohol consumption, a brief medical and dental history, frequency of intake of selected foods, and an occupational history. Questionnaire data were coded and entered into a preformed Microsoft Access database.

6.3.5 Individual measures of SES

The socioeconomic variables collected included two education measures: level of educational attainment (secondary school only, further education, and higher education), and number of years of full time education (computed as a binary variable ≤10 years, 11+ years, and a continuous variable).

The detailed life-time occupational history section collected data on every occupation, including: start date, end date, job title, industry, and nature of work. Each job title and associated industry was coded manually according to the 1990 Standard Occupational Classification (Office of Population Censuses and Surveys, 1990) and the 1992 Standard Industrial Classification of Economic Activities (Central Statistical Office, 1992), respectively. The Registrar General's Social Class (RGSC) and the Socio-economic Group (SEG) were then allocated for all jobs in the occupation history according to the 1990 Standard Occupational Classification (Office of Population Censuses and Surveys, 1990).

The RGSC and SEG data were each dichotomised into two levels of SES – manual and non-manual categories, and high and low groups respectively. They were explored in several ways, including RGSC / SEG of the: (i) first job; (ii) last job; (iii) longest occupation; and (iv) 'ever' manual RGSC / 'ever' low SEG. Lifetime experience of unemployment was also assessed. In addition occupational social class mobility was assessed comparing the RGSC of the first occupation compared to the present occupation or last occupation before retirement as per Menvielle and colleagues (2004). Social mobility categories were upward mobility (crossing from manual to non-manual), downward mobility (crossing from non-manual to manual), continuous non-manual, and continuous manual.

6.3.6 Area-based measures of SES

Deprivation scores were calculated by linking subjects' postcodes to 2001 Census data zones and output areas using the National Statistics Postcode Directory (National Statistics, 2006). Postcodes which had not been assigned a data zone or output area were checked using the subjects' addresses within the Royal Mail's Postcode Finder (Royal Mail, 2006).

The current postcode of residence of the study participants was linked to two area-based measures of socioeconomic circumstance: (i) The Scottish Index of Multiple Deprivation (SIMD), and Carstairs-2001 as described in the Chapter 5. The SIMD and Carstairs variables were computed as continuous variables and also in quintiles.

6.3.7 Smoking data

Exposure to tobacco was defined as: 'current' (smoking at the time of interview as well as stopped within one year of the interview), 'ex-smokers' (stopped over 12 months ago), and 'never' smoked – cigarettes, cigars, a pipe, or any other tobacco product at least once a

week for a year. For each type of tobacco smoked, data collected, included: age began; average amount smoked; and age of any major change (defined as +/- 50% change, no change, or stop) in smoking pattern. The data for each period were summed to provide a lifetime smoking history. Smoking history data (including details of cigarette, cigar and pipe habits) were converted into 'cigarette equivalents' by multiplying smoking duration with daily tobacco consumption (with one cigar = 4 cigarettes; 1 pipe = 3.5 cigarettes (Hashibe *et al.*, 2007). Smoking variables computed included: the total lifetime duration of smoking in years; the total number of cigarette equivalents smoked in life-time; and these variables were used to calculate 'pack-years' – where 1 pack-year is the equivalent of smoking 1 pack (of 20) cigarettes each day for 1 year (Bernaards *et al.*, 2001).

6.3.8 Alcohol data

Alcohol consumption was recorded as 'ever' / 'never', and for each category of alcoholic beverage (beer, wine, hard liquor, aperitifs, other), data included: age began; type of drink; frequency; quantity; age of any major change (defined as +/- 50% change, no change, or stop) in drinking pattern; and details for any subsequent periods. Quantity was converted into units of alcohol (approximately, 1 unit of alcohol = 8g of ethanol) (Inter-departmental Working Group, 1995) via a pre-developed look-up table which took into consideration alcohol strength which standardised all categories of beverage. Alcohol variables computed cumulatively for all beverage categories, included: lifetime duration of drinking; and average weekly alcohol consumption over lifetime (units/week) (Rehm *et al.*, 2001).

6.3.9 Diet data

Food frequency diet histories were collected for a range of food and drink items. For each item, frequency was recorded as number of occasions per 'day', 'week', 'month', 'year' or 'never'. The key items utilised for the purpose of this study were the summary fruit and vegetable consumption items. These were converted into total weekly consumption of fruit, and separately, of vegetables.

6.3.10 Statistical analysis

Variables as detailed above were selected based on *a priori* hypotheses developed from literature review and clinical opinion. Variables were manipulated blind to case or control status. They were divided based on the distribution of the data equally across the control distributions.

The primary statistical method was unconditional logistic regression (to permit inclusion of unmatched cases and controls, and to maximise power) adjusted for age and sex, for the estimation of odds ratios (OR) and corresponding 95% confidence intervals (95% CI) (Breslow and Day, 1980). This model was repeated following adjustment for smoking and alcohol consumption – to assess for potential independent effects of the range of socioeconomic components.

Interactions between smoking and alcohol consumption; and between individual and area-based measures for SES were also evaluated with the use of the likelihood ratio test within the regression model.

Forward stepwise conditional logistic regression analysis was also conducted separately for the socioeconomic variables (adjusting for age and sex), and for the lifestyle variables (adjusting for age and sex) to identify the most important socioeconomic and lifestyle factors independently associated with head and neck cancer.

Finally, those variables identified via the stepwise conditional logistic regression, and those variables that had demonstrated significance at the 5% level, together with an alcohol consumption variable (which, although non-significant, was of *a priori* interest), were adjusted for in the multivariate analysis.

Throughout, the ORs and 95% CIs shown are based on the likelihood ratio test procedure. All statistical analyses were performed on SAS version 9.1 (SAS Institute Inc., Cary, NS, USA).

6.4 Results

6.4.1 Response and sample characteristics

Overall response rates were 35% for cases and 35% for controls. Exclusion of those who could not be contacted gave response rates of 40% for cases and 58% for controls. The main reasons for non-participation were death before interview (cases 20%; controls 0%); ill-health / disability / health professional refusal (cases 27%; controls 14%); subject refusal (cases 34%; controls 25%); and unable to contact (cases 20%; controls 61%).

In total, 103 cases and 91 controls were included. There were broadly similar distributions by: sex between cases (38 women, 65 men) and controls (39 women, 52 men); and age

between cases (24-79 years, mean 58 years) and controls (25-80 years, mean 61 years). Of the 103 cases, 71 were classified as oral / oropharyngeal cancers (ICD-10 C00-06, 09, 10, and 14), and 32 as hypopharyngeal / laryngeal cancer (C12, 13, 32) (WHO, 1992).

6.4.2 Age and sex adjusted analysis of Socioeconomic components

In the age and sex adjusted analysis, the area-based socioeconomic factors statistically significantly associated with head and neck cancer included: residence in the most deprived communities (SIMD quintiles 4, and 5; and Carstairs quintile 5) (Table 6.1) – this was confirmed by the trend of increased risk of cancer with increasing levels of deprivation by modelling the area-deprivation scores as continuous variables (data not shown). The individual socioeconomic factors were: lifetime experience of unemployment associated with increased head and neck cancer risk; and high education level associated with a protective effect (Table 6.1). There were no significant associations with the other individual measures of SES. However, examination of the social class and socioeconomic group data from across the occupational histories found a consistent direction and trend of a potential increased risk in manual occupational social classes and lower socioeconomic groups. Social mobility was also not significantly associated, although there was a trend to suggest that both upward social mobility and stability in non-manual social classes conferred a reduced risk.

6.4.3 Age and sex adjusted analysis of behavioural risk factors

The behavioural factors associated with increased head and neck cancer risk were: current smoking, and a history of smoking of any duration – with an increasing risk with increasing duration smoked. Smoking was further confirmed as a significant risk with increasing pack-years – which takes into account both frequency and duration (Table 6.2). Current smoking was much more prevalent in cases than in controls (89% and 52% respectively), and there were also more ex-smokers in the controls than the cases (27% and 11% respectively). Alcohol (including heavy) consumption was not found to be significantly associated with head and neck cancer – although there was some evidence of an increased risk, and alcohol drinking prevalence was almost ubiquitous in the study population (83% cases, 84% controls). Modest consumption of fruit and vegetables (1 portion per week) were each associated with a protective association with head and neck cancer (Table 6.2).

Table 6.1 Associations of head and neck cancer with socioeconomic factors

	Cases	Controls	Age and sex adjusted‡	Age, Sex, smoking and alcohol adjusted‡
	n=103	(n=91)	OR (95% CI)	OR (95% CI)
Explanatory variable	*numbers (%)*			
Area-based SES				
SIMD quintiles				
1 (least deprived)	9 (8.9)	19 (20.9)	1.00	1.00
2	16 (15.8)	17 (18.7)	1.84 (0.64, 5.33)	1.67 (0.48, 5.80)
3	15 (14.9)	19 (20.9)	1.70 (0.59, 4.89)	1.44 (0.41, 5.01)
4	27 (26.7)	17 (18.7)	3.28 (1.18, 9.12) *	2.21 (0.66, 7.38)
5 (most deprived)	34 (33.7)	19 (20.9)	3.71 (1.35, 9.71) **	1.90 (0.59, 6.09)
	2 missing			
Carstairs quintiles				
1 (least deprived)	9 (8.7)	19 (20.9)	1.00	1.00
2	23 (22.3)	18 (19.8)	2.69 (0.96, 7.53)	3.07 (0.86, 10.95)
3	7 (6.8)	18 (19.8)	0.80 (0.24, 2.62)	0.45 (0.11, 1.96)
4	18 (17.5)	16 (17.6)	2.50 (0.87, 7.16)	1.20 (0.31, 4.58)
5 (most deprived)	46 (44.7)	20 (22.0)	4.66 (1.79, 12.18) **	2.08 (0.61, 7.07)
Individual SES				
Education				
Level				
Secondary school	75 (72.8)	54 (59.3)	1.00	1.00
Further education	24 (23.3)	25 (27.5)	0.59 (0.30, 1.17)	0.64 (0.29, 1.44)
Higher education	4 (3.9)	12 (13.2)	0.17 (0.05, 0.58) **	0.27 (0.06, 1.20)
Years				
≤10 years	60 (58.3)	48 (52.7)	1.00	1.00
>10 years	43 (41.7)	43 (47.3)	0.67 (0.36, 1.24)	0.95 (0.45, 2.02)
RGSC				
First occupation				
Manual	71 (69.6)	53 (58.9)	1.00	1.00
Non-manual	31 (30.4)	37 (41.1)	0.63 (0.33, 1.21)	0.81 (0.37, 1.79)
	2 missing			
Last occupation				
Manual	73 (71.6)	53 (58.9)	1.00	1.00
Non-manual	29 (28.4)	37 (41.1)	0.57 (0.30, 1.09)	1.12 (0.50, 2.50)
	2 missing			

Table 6.1 (continued)

	Cases	Controls	Age and sex adjusted‡	Age, Sex, smoking and alcohol adjusted‡
	(n=103)	(n=91)	OR (95% CI)	OR (95% CI)
Explanatory variable	*numbers (%)*			
Longest occupation				
Manual	67 (65.7)	49 (54.4)	1.00	1.00
Non-manual	35 (34.3)	41 (45.6)	0.70 (0.37, 1.30)	0.93 (0.44, 1.99)
	2 missing			
Ever manual				
Yes	51 (49.5)	56 (61.5)	1.00	1.00
No	52 (50.5)	35 (38.5)	0.63 (0.33, 1.17)	0.79 (0.37, 1.68)
Social mobility				
Stable manual	58 (56.9)	41 (45.6)	1.00	1.00
Stable non-manual	20 (19.6)	29 (32.2)	0.48 (0.22, 1.04)	0.83 (0.32, 2.18)
Downward	14 (13.7)	10 (11.1)	1.04 (0.41, 2.62)	0.63 (0.21, 1.89)
Upward	10 (9.8)	10 (11.1)	0.77 (0.29, 2.07)	1.42 (0.44, 4.62)
	2 missing			
Period of unemployment				
Never	50 (48.5)	25 (27.5)	1.00	1.00
Ever	53 (51.5)	66 (72.5)	2.27 (1.21, 4.26) **	1.74 (0.83, 3.62)
SEG				
First occupation				
Low	68 (66.7)	51 (56.7)	1.00	1.00
High	34 (33.3)	39 (43.3)	0.67 (0.35, 1.27)	0.70 (0.32, 1.51)
	2 missing			
Last occupation				
Low	72 (70.6)	51 (56.7)	1.00	1.00
High	30 (29.4)	39 (43.3)	0.56 (0.29, 1.05)	1.11 (0.50, 2.48)
	2 missing			
Longest occupation				
Low	66 (64.7)	46 (51.1)	1.00	1.00
High	36 (35.3)	44 (48.9)	0.63 (0.34, 1.16)	0.89 (0.42, 1.90)
	2 missing			
Ever low SEG				
Yes	56 (54.4)	58 (63.7)	1.00	1.00
No	47 (45.6)	33 (36.3)	0.72 (0.38, 1.35)	0.82 (0.39, 1.74)

‡ Unconditional logistic regression.
OR – Odds Ratio; CI – Confidence Interval
*** p < 0.05;**
**** p < 0.01**

Table 6.2 Associations of head and neck cancer with behavioural factors.

	Cases	Controls	Age and sex adjusted‡
	(n=103)	(n=91)	OR (95% CI)
Explanatory variable	*numbers (%)*		
Alcohol consumption			
Drinking status			
Current	86 (83.5)	76 (83.5)	1.00
Ex- / never	17 (16.5)	15 (16.5)	0.87 (0.40, 1.92)
Lifetime duration (years)			
<25	14 (14.0)	20 (22.0)	1.00
25-35	29 (29.0)	15 (16.48)	2.56 (0.98, 6.69)
35-45	36 (36.0)	33 (36.26)	1.68 (0.65, 4.38)
>45	21 (21.0)	23 (25.27)	2.04 (0.62, 6.66)
	3 missing		
Average weekly alcohol consumption over lifetime (units/week)			
<1.00	9 (9.4)	18 (20.0)	1.00
1.00-2.25	9 (9.4)	18 (20.0)	0.97 (0.30, 3.10)
2.25-4.70	30 (31.3)	18 (20.0)	2.94 (1.02, 8.50) *
4.70-8.60	26 (27.1)	18 (20.0)	2.45 (0.77, 7.76)
>8.60	22 (22.9)	18 (20.0)	1.93 (0.54, 6.85)
	8 missing		
Smoking			
Smoking status			
Never	11 (10.8)	44 (48.3)	1.00
Current	80 (78.4)	22 (24.2)	15.05 (6.45, 35.11) **
Ex-	11 (10.8)	25 (27.5)	1.72 (0.65, 4.55)
	1 missing		
Duration (years)			
0	13 (12.6)	46 (50.5)	1.00
0≤20	29 (28.2)	16 (17.6)	5.41 (2.22, 13.18) **
21-40	35 (34.0)	17 (18.7)	6.85 (2.90, 16.17) **
>40	26 (25.2)	12 (13.2)	8.55 (3.33, 21.96) **
Pack-years			
0	13 (12.6)	46 (50.5)	1.00
≤60	46 (44.7)	23 (25.3)	6.46 (2.89 14.42) **
>60	44 (42.7)	22 (24.2)	7.10 (3.16, 15.96) **

Table 6.2 (continued)

Explanatory variable	Cases (n=103) *numbers (%)*	Controls (n=91)	Age and sex adjusted‡ OR (95% CI)
Diet			
Vegetables / week			
≤2	22 (21.4)	9 (9.9)	1.00
>2-5	29 (28.2)	22 (24.2)	0.55 (0.21, 1.44)
>5-7	47 (46.1)	50 (54.9)	0.40 (0.17, 0.97) *
>7	4 (3.9)	10 (11.0)	0.19 (0.05, 0.78) *
	1 missing		
Fruits / week			
≤1	27 (26.2)	9 (9.9)	1.00
>1-2	28 (27.2)	11 (12.1)	0.86 (0.31, 2.43)
>2-7	43 (41.7)	55 (60.4)	0.27 (0.11, 0.63) **
>7	4 (3.9)	16 (17.6)	0.09 (0.02, 0.33) **
	1 missing		

‡ Unconditional logistic regression.
OR – Odds Ratio; CI – Confidence Interval
*** p < 0.05;**
**** p < 0.01**

Table 6.3 P-values for interactions between area and individual measures of SES

	Carstairs	SIMD
Unemployment	0.60	0.35
Education level	0.74	0.64

6.4.4 Fully adjusted explanatory models

To explore whether the socioeconomic factors could be individually and independently explained by the behavioural risk factors, all the socioeconomic factors, were evaluated firstly by adjusting for smoking and alcohol consumption. In this analysis, none of the socioeconomic factors were associated with head and neck cancer, although the consistent trend to increased risk with worsening deprivation, lower education, low occupational social classification, and experience of unemployment was observed (Table 6.1).

The combined effect of smoking and alcohol was also evaluated. No evidence for a synergistic interaction was found (p=0.51). Nor could any significant interactions between the significant (from the age and sex adjusted analysis – Table 6.1) area-based SES indicators and individual SES measures be detected (Table 6.3).

Finally, in the multivariate analysis, only smoking was found to be independently associated with head and neck cancer, with all other factors being completely dominated by the risks associated with smoking observed (OR 15.5; 95%CI 5.4, 45.0) (Table 6.4).

6.5 Discussion

6.5.1 Key points

This case-control study confirms the well known association of smoking with head and neck cancer risk. This relationship was so strong as to over-ride a detailed exploration of the socioeconomic components for the disease, which was also compounded by low study power. Nevertheless, an analytical framework which can be employed in future analysis was developed – particularly one suitable for analysis of the full European ARCAGE dataset.

Table 6.4 Odds ratios for the association of head and neck cancer with SES and behavioural risk factors

Explanatory variable	OR (95% CI)§
Age †	0.79 (0.52, 1.20)
Sex	
Female	1.00
Male	1.21 (0.44, 3.31)
Vegetables / week	
≤2	1.00
>2-5	1.52 (0.35, 6.52)
>5-7	1.39 (0.35, 5.51)
>7	0.53 (0.08, 3.69)
Fruits / week	
≤1	1.00
>1-2	1.27 (0.30, 5.32)
>2-7	0.63 (0.17, 2.29)
>7	0.43 (0.07, 2.68)
Average lifetime alcohol units / week	
<1.00	1.00
1.00-2.25	0.50 (0.10, 2.39)
2.25-4.70	1.39 (0.35, 5.56)
4.70-8.60	0.53 (0.10, 2.72)
>8.60	0.42 (0.07, 2.58)
Smoking status	
Never	1.00
Current	15.53 (5.36, 44.99) **
Ex-	1.55 (0.47, 5.03)
Education level	
Secondary school	1.00
Further education	0.41 (0.15, 1.15)
Higher education	0.23 (0.04, 1.36)
RGSC last occupation	
Non-manual	1.00
Manual	1.85 (0.66, 5.21)
Unemployment	
Never	1.00
Ever	1.75 (0.69, 4.42)
Carstairs †	1.02 (0.53, 1.97)

§ Multivariate unconditional logistic regression
OR – Odds Ratio; CI – Confidence Interval;
*** p < 0.05;**
**** p < 0.01**
† **Ordinal variables were modeled as single continuous variables**
P- values from unconditional age and sex adjusted logistic regression

6.5.2 Limitations

The limitations of the study design include issues common to all interview case-control studies (Breslow and Day, 1980). The unclear findings with regard to socioeconomic factors could be a result of the low power of the study due to the small numbers of cases and controls, which was primarily a factor of the low response. A particularly low response rate (35% for both cases and controls) was obtained in comparison to the only other recently published Scottish cancer epidemiological case-control study which employed similar methods (to the present study) to investigate oesophageal cancer and reported response rates of 62% for cases and 65% for controls (Sharp *et al.*, 2001). The main reason for non-participation was 'non-contactable' and the ethical committee did not permit more than one approach.

Following this worryingly low response rate, selection and participation bias is of particular concern. A formal evaluation of the study selection and participation bias was conducted (see Chapter 4). In summary, the overall control sample from GP practices did not represent the general population of Glasgow having 'over selected' from more deprived areas. However, individuals from more affluent backgrounds were more likely to participate. Thus the control sample selection biased in one direction was offset by participation bias in the opposite direction – fortuitously providing a control sample socioeconomically representative of the study-base (Glasgow) population. It is impossible to quantify the effect on our case-control analysis of this potentially biased participation, although it is possible that it masked the socioeconomic risk effects associated with head and neck cancer.

The low numbers also limited the ability to examine by subgroups including: anatomical subsite, age, or sex, although investigating the cancers grouped as head and neck cancers is common practice in other social epidemiological analysis (Elwood *et al.*, 1984; Ferraroni *et al.*, 1989). Further subgroup analyses would have reduced the power even further.

A further broader limitation is the controversy over an analytical approach which attempts to analyse, disentangle or treat independently individual and area measures of SES. Analysing individual social class, controlled for area SES effects, has been criticised as potentially ignoring the role that the social and physical environment might play in influencing people's health. Conversely, analysing area SES effects controlled for individual social class has also the potential to ignore the role of political and economic factors in determining what areas people are likely to live in and how society's resources

are distributed to different places through the people who live there (Macintyre and Ellaway, 2000).

6.5.3 Strengths

There are a number of strengths to this study. This included the strict inclusion criteria which permitted only histologically confirmed incident cases (diagnosed within 6 months prior to interview). The use of population-based controls also had the advantage of avoiding the inherent selection bias associated with hospital-based controls (Breslow and Day, 1980). Methodological rigor was employed throughout including training and calibration of the interview process, coding and database validation, and analytical completeness.

These results are based on a dataset collected via a thorough face-to-face interview in the subject's home which explored extensively the subject's life history including details of occupations and behaviours. SES was uniquely measured in several different ways, both at the area and individual levels. Area measures of SES included: the Carstairs and SIMD scores. The scores were obtained from validated postcodes utilising look-up software (National Statistics, 2006; Royal Mail, 2006). The main criticism of such indicators is the potential for 'ecological fallacy' – where individuals are allocated an area SES based on the location of residence. However, it has been argued that people who live in the same area can share many of the socioeconomic circumstances not reflected by individual measures, in that the socioeconomic environment confers risk apart from or over and above that of their individual social class (Evans and Stoddart, 1990; Macintyre *et al.*, 1993; Berkman and Macintryre, 1997).

Individual SES was measured by education and occupational social classifications. Education is a readily obtainable measure of SES which is generally: fixed in early adulthood, stable across the life course, and potentially a marker of early socioeconomic circumstances (Macintyre *et al.,* 1993). The educational level attained was corroborated by the data on the number of years of full-time education. In the UK, occupations are traditionally used to measure SES when investigating inequalities in health. The RGSC occupational social classification was the major historic way of social stratification in the UK – conceptualised to indicate broad styles of life, although it is increasingly being replaced by the SEG – which replaces occupational skill and social standing with employment relations as its main determinant (Office of Population Censuses and Surveys, 1990). Both of these variables were manipulated into binary hierarchical strata as the size

of our study did not allow for more refinement, and we have to accept the considerable heterogeneity within these social strata that would be expected (Menvielle *et al.*, 2004).

The individual SES variables investigated were unlikely to be substantially influenced by differential recall bias between cases and controls. SES information has been shown to be reliably recalled from childhood and independent of social class (Krieger *et al.*, 1998). The reliability of job coding was checked via a validation exercise involving all European study centres in the ARCAGE study who all coded 156 jobs in 20 occupational histories. The level of agreement (with the other European centres) was 83% for job codes and 81% for industry codes – which is in line with other studies that have attempted to quantify the accuracy of occupational coding (McKinney *et al.*, 2003).

6.5.4 Comparison with other work

Few studies that have investigated the social factors associated with head and neck cancer have adequately controlled for the known behavioural risk factors, and have simply adjusted for age (Sharp *et al.*, 2001). As shown in Chapter 4 previous studies have identified independent effects of social factors associated with head and neck cancers, having adjusted for smoking and alcohol drinking (Elwood *et al.*, 1984; Ferraroni *et al.*, 1989), while others, like our study, find that the social effects are completely lost when adjusting for alcohol and smoking (Greenberg *et al.*, 1991) and one study found that the effects of low social class could be explained by co-existing occupational exposures (Menvielle *et al.*, 2004).

6.5.5 Potential explanations

In this study, experience of high levels of education provided a tendency for a protective effect reducing the risk of head and neck cancer, although this was lost after adjusting for smoking and alcohol consumption. While these findings lend some evidence to support the mechanism for the effect of education to be predominantly through its influence on risky behaviours, the full effects of education and its influence through the life course and on health and potentially cancer are interesting hypotheses which are yet to be fully ‘unbundled’ (Yen and Moss, 1999).

The relationship between unemployment and cancer has been explored in many studies (Lynge, 1997). Experience of unemployment seemed to be a relatively strong SES indicator in our preliminary analyses, which is similar to the finding in a cross-sectional

survey of patients being treated for head and neck cancer in the North East of England, where 66% had experienced long-term unemployment (Greenwood *et al.,* 2003). However, in these analyses, the effect was significantly confounded by smoking and alcohol behaviours.

The data on social mobility suggested a tendency towards a decreased risk for head and neck cancer associated with upward mobility – again explained through lifestyle behaviours, but this is contrary to the findings of two French studies: one which found higher risks of head and neck cancer in upwardly mobile men – albeit unadjusted for smoking and alcohol consumption (Marshall *et al.,* 1999); and the other which found no clear pattern with social mobility and head and neck cancers (Menvielle *et al.,* 2004).

The risks associated with area socioeconomic deprivation have previously been demonstrated in ecological descriptive epidemiological studies in Scotland (Chapter 3 – Conway *et al.,* 2007). While there was a tendency for increased risk in those living in the most deprived communities, this effect was lost when adjusting for smoking and alcohol behaviours. Previous studies, in other fields of research, have attempted to tease out independent effects of individual and area effects, although it remains a much debated area (van Jaarsveld *et al.,* 2007). There was insufficient power to fully explore this here, but interestingly there was no interactive effect between the two levels, which suggests that the individual and area socioeconomic effects – to the extent that they were observed – were operating independent of each other.

There is no doubt that smoking is a predominant risk factor for head and neck cancer, a 15-fold increased risk was observed (although the precision of the estimate was lacking due to the study size). This is higher, but generally in-keeping with many studies and reviews (Castellsagué *et al.*, 2004; IARC, 2004a; Hashibe *et al.*, 2007), but the very large effect associated with smoking was perhaps a function of the almost universal prevalence, and very heavy nature of smoking in the cases.

The relationship with alcohol was not so clear. Surprisingly, given the body of evidence (Macfarlane *et al.*, 1995; Bagnardi *et al.*, 2001a, 2001b; Corrao *et al.*, 2004), alcohol was not found to be either independently nor synergistically (with smoking) associated with increased head and neck cancer risk. This could be due to the almost ubiquitous alcohol consumption throughout both cases and controls limiting any substantial differentiation of this behaviour. It is perhaps also a reflection of the wider Glasgow and Scottish population's well recognised high alcohol consumption culture (Bromley *et al.*, 2005).

There was also a tendency for a protective effect association with head and neck cancer of diets relatively higher in consumption of fresh fruit and vegetables (even at the low levels reported), as already described (Pavia *et al.*, 2006), although this was also not found to be independent of smoking and alcohol consumption.

While these findings are not conclusive regarding the independent effects of socioeconomic factors on head and neck cancer risk, they do lend support to the 'cause of the cause' hypothesis, to quote Rose (Rose, 1992). Thus, the socioeconomic effects potentially operate via their well recognised influence on lifestyle behaviours which have often been reported as coping mechanisms for the stress associated with low SES or influenced by their location and ability to afford healthy lifestyle alternatives (Marmot 1997; Stead *et al.*, 2001; Wrigley 2002).

6.6 Conclusions

In conclusion, the analysis of socioeconomic factors from a detailed self-reported life history questionnaire, in this relatively small population-based case-control study, has failed to produce any strong evidence to link socioeconomic components with an increased risk of head and neck cancer, while smoking remained the predominant risk factor. However, these unclear findings with regard to the socioeconomic determinants do not exclude them from the complex aetiological pathway of head and neck cancer. More detailed research on larger numbers utilising our analytical framework into the nature of such associations is warranted, including analysis of the full European multicentre ARCAGE study.

7 Discussion

7.1 Introduction

This section is structured to address the following questions: (i) What was the basis for interest in this area of study? (ii) What was already known? (iii) What were the gaps in knowledge? (iv) Why was it important, and why did this area merit further study? (v) Has the thesis achieved what it set out to do? (vi) How original was the approach? (vii) How does this thesis confirm or challenge other research? and (viii) What does this thesis contribute to knowledge?

7.1.1 What was the basis for interest in this area of study?

Interest in, and research on how socioeconomic factors influence health, came from a concern that individual lifestyles and behaviours were inadequate to fully explain disease – and in this case oral cancer risk. This interest was spurred on and inspired by consistent and persistent reports in recent years of the social and economic factors leading to inequalities in health and disease, in life and death. As discussed in detail in Chapter 1, such inequalities in health came to prominence with the 'Black Report' in 1980 (Department of Health and Social Security, 1980), and were most starkly brought to my attention as an undergraduate by Dr Harry Burns, then Director of Public Health in Greater Glasgow Health Board. He described the shocking statistics from Glasgow – that the residents of the affluent area of Bearsden live ten years longer than their neighbours a mile away in the more deprived area of Drumchapel (BBC, 1995).

Beneath these headlines lay an emerging body of research in the form of social epidemiology, which had begun to set out a range of models to explain these inequalities, and the links between social factors and health. Evans and Stoddart's (1990) 'health and wellbeing' framework, and Macintryre *et al.*'s (1993) 'Places or People?' are two such models. Evans and Stoddart's (1990) wide definition of health, and wide consideration of the factors which influence health, galvanised thinking, in aetiological terms, to the concept and role of the social environment in health or disease outcomes. In parallel, Macintyre *et al.* (1993) set out a convincing argument for considering the importance of the socioeconomic factors related to both individuals and the areas where they live. Macintyre and Ellaway (2000) later expanded on this concept by introducing

'compositional' (the characteristics of the individuals who live in an area) and 'contextual' (the physical and social characteristics of an area) explanations for health.

These two models provided a theoretical basis for taking a more holistic view of disease aetiology, enabling the potential for the risks associated with social factors (both individual and area, local and global) to be embraced. Such thinking opened up the possibility of exploring the potential impact and influence of social factors on oral cancer. This thesis has attempted to do this via a range of social epidemiology approaches which investigate the risk of developing oral cancer. In doing so, it has sought to broaden the scope of oral cancer aetiological research, by looking at the problem through an 'inequality lens'.

7.1.2 What was already known?

At the outset of this research (across the UK) there was some descriptive epidemiological evidence to suggest that trends in oral cancer incidence were continuing to increase up to the mid-1990s (Macpherson *et al.*, 2000; Quinn *et al.*, 2001). Particular attention had also been given as to whether these increases were more significant in younger adults (Macfarlane *et al.*, 1992; Mackenzie *et al.*, 2000). Shortly after the research in this thesis began, Macfarlane and Robinson (2003) with data to the mid 1990s for Scotland, showed in an age-period-cohort model that incidence was continuing to increase overall and was greater in the cohort born from 1910 onwards (aged 35-64 years).

In addition, there was some information on the socioeconomic gradient in the distribution of oral cancer cases in Scotland – with those from the most deprived areas having the greatest incidence of oral cancer (Harris *et al.*, 1998; Macpherson *et al.*, 2000). There were also similar cross-sectional descriptive epidemiological findings from elsewhere in the UK (Quinn *et al.*, 2001). However, the global descriptive epidemiology picture was more equivocal, with no clear relationship between oral cancer incidence and socioeconomic factors being demonstrated (Faggiano *et al.*, 1997).

Further, the international picture from the limited ad-hoc narrative reviews, which considered the analytical literature on the socioeconomic risk factors for oral cancer were also described as being equivocal (Hashibe *et al.*, 2003). Another review of data from a series of analytical studies in Italy which specifically examined the relationship of increased risk of oral cancer in lower socioeconomic groups, showed that this once observed relationship had disappeared (Bosetti *et al.*, 2001).

It was also generally apparent that analytical epidemiology on oral cancer, and cancer in general, tended to have a limited focus on socioeconomic factors, mainly confining such factors as potential confounders and for statistical adjustment only (Kawachi and Kroenke, 2006). The main thrust of analytical epidemiology was and largely remains on individual behaviours, and increasingly on genetic risk factors (Pearce, 1997).

7.1.3 What were the gaps in knowledge?

The gaps in the literature relate mainly to the limits of what was already known. In terms of descriptive epidemiology, a UK-wide analysis of oral cancer incidence and trends had not previously been undertaken. Further exploration of trends by age and sex had not been examined in detail at the UK level. There was also a wide range of anatomical sites and combinations of sites in definitions of oral cancer. With an emerging acceptance of a definition, which included cancer of the oral cavity and orophayrnx being considered together (Macpherson *et al.*, 2000; Llewellyn *et al.*, 2001), and now by the WHO and IARC (Barnes *et al.*, 2005), it was also felt important to describe and investigate oral cancer from this definition as a starting point.

In addition, there was much interest in increases in oral cancer incidence in younger adults, but there was limited exploration as to whether such increases were significantly different from those in older age-groups. This was of concern as age-specific incidence rates consistently demonstrated that oral cancer was far more common in older adults (Harris *et al.*, 1998; Quinn *et al.*, 2001). Yet, the focus of research was moving away from older adults, in the pursuit of an understanding of the aetiology of oral cancer in younger adults, which was being considered a ‘distinct entity’, despite acknowledgement that there were only a very small number of cases in younger patients (Agula *et al.*, 1996; Oliver *et al.*, 2000).

Little attention was also being paid to the descriptive epidemiology of oral cancer in relation to socioeconomic factors in the UK and elsewhere. While the socioeconomic gradient in the UK was known, outstanding questions included: how and when this gradient emerged? whether it was changing over time? and did the socioeconomic distribution of oral cancer vary by sex and age?

Internationally, the notion that the relationship between socioeconomic factors and oral cancer incidence was equivocal seemed to be accepted. However, the wealth of analytical literature on oral cancer had not been fully explored and was untapped with regard to

investigating social factors. Furthermore, a systematic review had not been undertaken, nor a meta-analysis considered for investigating this issue.

Analytical epidemiology investigating oral cancer aetiology also seemed constrained by a medical model or clinical epidemiology approach which had given rise to an almost unchallengeable, wide acceptance that oral cancer was almost entirely related to smoking and alcohol consumption (Rothman, 1978). Social epidemiological methods and approaches had barely been considered in analytical or aetiological studies investigating risk factors for oral cancer. The few studies that had attempted to look at socioeconomic factors were somewhat historic (Elwood *et al.*, 1984; Ferraroni *et al.*, 1989; Greenberg *et al.*, 1991), and did not include both individual and area socioeconomic factors. Further analytical epidemiology has been underutilised to investigate head and neck or oral cancer in Scotland. There had only been one case-control study of oesphageal cancer (Sharp *et al.*, 2001), and no analytical studies of oral, pharyngeal, or laryngeal cancers. Moreover, the observational studies on oral cancer were limited to case-series studies (Llewelyn and Mitchell, 1994; Mackenzie *et al.*, 2000).

7.1.4 Why was it important, and why did this area merit further study?

Given the gaps in knowledge, and the limited utilisation of social epidemiology approaches in existing research on oral cancer (described above), the importance of taking forward this research became apparent. In addition, the policy context in Scotland, the UK, and increasingly internationally (reviewed in depth in Chapter 1), is dominated by health inequality priorities. However, there remains an apparent disconnect of inequalities from cancer policy. To support the realignment of cancer policy and also to ensure that the research agenda is consistent with policy developments in health inequalities, the merit in the direction of the thesis was reassured. Indeed, a concerted exploration of the epidemiology of oral cancer in relation to socioeconomic circumstances and inequalities was warranted.

The arguments for why health inequalities should be studies and tackled were discussed by Woodward and Kawachi (2000). Broadly, there is a strong ethical basis – health inequalities are unfair and unjust, particularly when the underlying social factors themselves are unjustly distributed (e.g. education opportunities, income distribution). There are societal reasons – health inequalities affect the whole population, not just those in deprivation (e.g. the effects of alcohol consumption). There are economical arguments –

health inequalities are costly on societies resources, and interventions to reduce them can be cost-effective although there is limited empirical research in this area. In addition, health inequalities are avoidable – in terms that they are the direct consequence of policy, therefore political and policy decisions can be taken to address them. Research into the nature of the problems and effects of health inequalities together with evaluation of interventions to reduce them are important in providing an evidence base for policy and decision making. Watt (2007) adds an additional reason of scientific integrity – which relates to the specific ethics around the imperative to research and respond to the evidence base which is emerging around health inequalities.

7.1.5 Has the thesis achieved what it set out to do?

This thesis set out on a journey initially to investigate the epidemiology of oral cancer in Scotland with regard to younger adults. It was decided to focus on incidence rather than mortality and survival, as the interest was more from an aetiological 'risk' perspective. To these ends an initial descriptive epidemiology study (Chapter 2) was undertaken which expanded in scope to include the whole of the UK. It comprehensively gauged the incidence rates and trends of oral cancer for the UK, by age-group, sex, and geographical region.

Following this initial piece of work, many more hypotheses were generated around the potential influences of socioeconomic factors in determining the differences in incidence. Thus the main focus for the whole thesis became centred on investigating the extent of the incidence burden of oral cancer related to socioeconomic circumstances, to assess inequalities in the distribution of oral cancer, and to begin to assess the components of the socioeconomic factors that are important. This latter aim included attempting to assess the mechanism of the relationship. Giving rise to the questions: (i) did socioeconomic factors increase risk for oral cancer independently – either directly or through intermediate pathways? and (ii) were these effect pathways via a socioeconomic effect on traditional behavioural risk factors, or on other potential intermediates as yet undetermined?

Chapter 1 explored the theoretical basis for many of these questions and approaches, but the narrative literature review approach to assessing the international analytical epidemiology literature, which assessed the relationship between oral cancer and socioeconomic factors, was proving less than satisfactory. A systematic review and meta-analysis approach was adopted to address this problem, which became Chapter 4. In addition, this empirical approach brought an international context and dimension to the

thesis. It gauged the extent of the risk effects of socioeconomic factors (through a range of individual socioeconomic indicators) in high and low-income countries, in different continents, by age, sex, and attempted to consider these effects independent of smoking and alcohol consumption.

Chapter 3 comprehensively assessed the inequalities over time in oral cancer incidence by age and sex, but had to narrow its focus to concentrate on Scottish data alone.

Chapter 6 (together with the methodological research of Chapter 5) was an attempt to utilise a local case-control study to analyse in detail the socioeconomic factors in relation to oral cancer. Due to the small numbers, a compromise had to be made to utilise the data on head and neck cancer. The small numbers of cases and controls also limited the power of fully teasing out the area and individual socioeconomic effects, and a full exploration of the contribution of socioeconomic factors across the life course. However, it did provide a socioeconomic analytical framework for future studies.

Therefore, the thesis achieved in many ways what it set out to do – although what it set out to do evolved over the time, with each study influencing and helping to shape the next. This process was partly enabled by its part-time (long term) time-scale (5 years). However, it must also be acknowledged that there is much still to do.

7.1.6 How original was the approach?

7.1.6.1 Overall

There is significant originality in the approaches undertaken within the thesis. However, respect and due cognisance is given to Davey Smith's (2001) comments on epidemiology that 'replication is the hallmark of science', but also that through 'criticism [we] advance knowledge'. Therefore, the limits to the originality within the thesis will be explored here, although the limitations of the methodologies within the thesis will be discussed in a subsequent section.

The quote of Alvarez-Dardet and Ashton (2005) could be applied to this research, when they described: 'News scoop—hold the front page: "poverty damages health"' in relation to a host of further research emerging on the relationship between deprivation and health. This thesis, while not a wholly new direction for public health research, has taken the

problem of oral cancer and examined it in detail for the first time in relation to socioeconomic inequalities and poverty.

From the historical review in Chapter 1, it could be seen that an approach, which brings together both descriptive and analytical studies to investigate oral cancer risk is not in itself new (Singer, 1911). However, recent convention dictates that descriptive and analytical approaches are distinct and separate entities (dos Santos Silva, 1999). Nevertheless, this thesis uses a range of methods to enable the same overarching problem of socioeconomic inequalities to be observed from different angles and levels.

Most of the theoretical explorations (discussed in Chapter 1) are not in themselves entirely original. What is unique perhaps is bringing together perspectives of epidemiology, social epidemiology, socioeconomic factors and inequalities, through a range of methodological considerations to focus on the problem of oral cancer incidence.

While there had been much development in social epidemiology with regard to examining inequalities for cancer in general (Kogevinas *et al.*, 1997; Singh *et al.*, 2003), there is limited research in this area with regard to oral cancer. This body of work, as far as the author is aware, is the first concerted attempt to consider the broader social epidemiology in relation to oral cancer from multiple angles. Rather than follow the traditional epidemiological concern of identifying specific risk factors, which determine why some individuals get oral cancer while others remain disease free, the thesis studies have attempted to begin to rise to the challenge set by Rose (1992), and taken on by Marmot (2005), of identifying the 'cause of the cause', and building up the wider societal picture and component of this disease of complex aetiology. The originality of each of the empirical research chapters will be discussed in turn.

7.1.6.2 Descriptive epidemiology

Descriptive epidemiology of oral cancer in the UK and Scotland is not itself an underexplored field (Harris *et al.*, 1998; Robinson and Macfarlane, 2003). The descriptive study in Chapter 2 is original in the sense that it brings together the epidemiology of oral cancer for the whole of the UK, for the most recent years available at the time (1990-1999). It concentrates only on incidence as the measure of burden, and assesses both the differences for the whole period and the time-trends by age, sex, and UK region. It also, originally, looks at incidence by two wide age-categories – younger (age 45 and under) and older (over 45 years). The analytical approaches included the utilisation of Poisson

regression modelling, which is not entirely new to the fields of cancer descriptive epidemiology in general (dos Santos Silva, 1999). It was, however, not in widespread use and had not been applied to oral cancer incidence data until now.

As described in Chapter 2, many descriptive studies, both internationally and nationally, have looked at the relationship between area socioeconomic factors and health e.g. mortality across Europe (Mackenbach *et al.*, 2003); self-reported health across the UK (Shaw *et al.*, 1999); and disease-specific mortality in Scotland (McLaren and Bain, 1998). Cancer, including oral cancer, had also received some attention looking at the socioeconomic distribution in England and Wales (Quinn *et al.*, 2001), and for Scotland (Harris *et al.*, 1998, Brewster *et al.*, 2000; Macpherson *et al.*, 2000).

In addition to these observed inequalities, the changing patterns of inequalities are important. In England, the *Independent Inquiry into Inequalities in Health* reviewed the evidence on socioeconomic inequalities and concluded that the gap in health and mortality between the affluent and deprived was widening (Acheson, 1998). Many studies have analysed changes in inequalities over time. They demonstrated widening inequalities between countries (Mackenbach *et al.*, 2003), between regions of the UK (Shaw *et al.*, 1999), and within single regions of the UK (Phillimore *et al.*, 1994). However, occasional studies have found no change in inequalities (Strong *et al.*, 2002).

In Scotland, more recently, widening socioeconomic inequalities in health have been observed. In St Andrews University, Boyle and co-workers observed widening socioeconomic inequalities in mortality between 1980 and 2001 (Boyle *et al.*, 2004b), while in the University of Glasgow, Leyland (2004) showed the premature mortality gap between 1978-98, to be increasing more in Scotland than in England and Wales. Prior to these studies, the changes in inequalities over time had received less attention, and there were still limited studies on time-trends of specific disease inequalities. However, shortly after this time, there were a number of studies looking at time trends for particular health inequalities in Scotland, including: suicide (Boyle *et al.*, 2005; Levin and Leyland, 2005), and cardiovascular disease (Levin and Leyland, 2006), although not yet in cancer. This time-series work has culminated recently in a time-trend analysis of cause-specific inequalities in mortality in Scotland over two decades (Leyland *et al.*, 2007). While socioeconomic trends in cancer had not received as much attention in Scotland, there have been sporadic examples from cancer registries across the world including gastro-intestinal cancer in Finland (Weiderpass and Pukkala, 2006). However, no such investigation of trends in oral cancer had been undertaken until now.

7.1.6.3 Systematic review and meta-analysis

Meta-analyses of observational studies, as outlined in Chapter 1, while being controversial, are not new, and are increasingly accepted. Nor was it new to utilise meta-analysis to examine the effects of socioeconomic factors. However, the author believes that this was the first systematic review and meta-analysis of the socioeconomic factors associated with oral cancer.

Meta-analyses of observational studies have been undertaken in many areas, although, unlike the area of interventional studies, there is limited agreed guidance. Methods therefore had to be developed to some degree. Looking to previous examples in the literature, the methods were adapted from studies by: Petticrew *et al.* (1999) in their review of adverse life-events in relation to breast cancer; Bagnardi *et al.*'s (2001a, 2001b) meta-analysis of alcohol and cancer risk; and Parikh *et al.* (2003) who undertook a meta-analyses of socioeconomic inequalities in cervical cancer. While looking to these studies, the methods developed also followed systematic review guidelines of Cochrane (Sutton *et al.*, 1998; Higgins and Green, 2006) and the University of York's Centre for Reviews and Dissemination (2001). Both of these guidelines are for reviews of intervention studies rather than observational studies. They were used because it was felt that they reflected the latest thinking on the general approach to systematic reviews and meta-analyses. These guidelines also provided a ready framework for each of the stages of the review, and aided the development of methods including shaping: the study questions, the search strategy, study method quality assessment, and analytical methods including subgroup and sensitivity analyses. There are no methodological guidelines specifically for undertaking systematic review and meta-analyses of observational study (and this in itself is a gap in the literature). There are, however, the reporting guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (Stroup *et al.*, 2000), which were also considered in the development of the methods as well as reporting.

Originality in the methods included the development of a tool for assessing methodological quality, widening the scope of the search and managing to include unpublished data in the analyses, and undertaking a thorough meta-analysis to consider a wide range of sub-group and sensitivity analysis to support the validity of the findings.

7.1.6.4 Analytical epidemiology

Analytical epidemiology studies have been used in social epidemiology approaches to investigate many conditions, although they have been used sparingly in the investigation of head and neck or oral cancer (Menvielle *et al.*, 2004). Methods to investigate the components of the socioeconomic risk for head and neck cancer (Chapter 6) were adapted: from multi-level approaches, which include consideration of area and individual socioeconomic measures (Berkman and Kawachi, 2000; Krieger *et al.*, 2002); and also from life course approaches (Kuh and Ben-Shlomo, 2004) – utilising education as a marker of early SES, and occupational life history for adulthood SES, in addition to area-based SES measures at the time of diagnosis. Further, the measurement of social mobility from the occupational history was adapted from Menvielle and colleagues (2004) examination of occupation factors related to laryngeal cancer in France, while inclusion of unemployment experience followed consideration of the review on the topic by Lynge (1997).

The constraints on the methodology were due to the previously designed ARCAGE study, with its main focus on behaviours and genetics (and collecting socioeconomic factors primarily to adjust for potential confounding effects). However, additional area-based measures of socioeconomic circumstances were obtained from linking postcodes of residence to area-based socioeconomic deprivation indices. The originality of the approach was to flip the traditional case-control analysis logic on its head and to set *a priori* hypotheses focused on the socioeconomic factors as the main factors, and to control or adjust for behaviours as far as possible. Furthermore, the development of the analysis specification and framework utilising a wide-range of data, particularly occupational history (which was primarily collected to investigate the effect of occupational hazardous exposures), and area-based measures (including the new Scottish Index of Multiple Deprivation SIMD) (Scottish Executive, 2004c) was also unique.

There was also a thorough investigation of the methodological challenges associated with selection and participation in case-control study designs (Chapter 5). While this was somewhat of a deviation from the main thrust of the thesis, this too was investigated from the perspective of the socioeconomic aspects, which affect participation and selection. This was important, not only from a methodological point of view, but also in justifying the approaches taken in the subsequent case-control analysis (Chapter 6). There have been similar analyses undertaken on case-control studies in England (Law *et al.*, 2002; Smith *et*

al., 2004a). However, no such study had been undertaken in Scotland, nor had utilised the SIMD, until now.

7.1.7 How did the work confirm or challenge other research?

The descriptive epidemiology suggested that oral cancer was increasing across the UK and in Scotland in particular, which corroborated previous findings when considered together (Macpherson *et al.*, 2000; Quinn *et al.*, 2001; Robinson and Macfarlane, 2003). It did challenge, however, the perception that oral cancer was increasing more rapidly in younger adults than other groups in the population. While there is no doubt that oral cancer is increasing in younger age-groups, these increases are not significantly greater than for those in older age-groups. Further, when examined in detail for Scotland, those in older age-groups were at significantly higher risk, with the risk increasing with increasing age – ranging from a 12-fold elevated risk in those aged 45-49 years to a nearly 80-fold higher risk in those aged 85+ years compared to those under 45 years (Table 3.2). Similar general cancer findings were observed in the cancer incidence statistics published since the thesis study, which showed that for the period 2002-2004, Scotland continues to have the highest overall cancer incidence in the UK (National Statistics, 2007c).

Socioeconomic gradients observed in earlier studies were confirmed (Harris *et al.*, 1998; Macpherson *et al.*, 2000). Exploration of the changes over time in the socioeconomic distribution of oral cancer was uncharted territory, and the pattern of development of widening inequalities was discovered. Inequalities were demonstrated in younger and older population groups, and in men and women – although were most marked in older males.

The results from a systematic review and meta-analysis described in Chapter 4 challenge the internationally perceived wisdom that oral cancer incidence risk associated with socioeconomic factors is equivocal from analytical epidemiology (Bosetti *et al.*, 2001; Hashibe *et al.*, 2003), and reviews of the descriptive epidemiology (Faggiano *et al.*, 1997). The increased oral cancer risk associated with low SES was observed irrespective of the SES measure used, in high and lower income-countries, across the world, and remained when adjusting for potential behavioural confounders. The finding that suggested that while inequalities persist, but they have perhaps reduced between the 1970-80s and 1990s although not in the most recent decade, corroborates to some degree the reduction observed in the analysis in Italy, which found that inequalities had reduced (Bosetti *et al.*, 2001). However, the Italian study finding that inequalities had disappeared was not repeated. The

most stark findings were the overall risk effect estimates, which suggested that oral cancer risk associated with low SES is significant and comparable to lifestyle risk factors.

The case-control analysis of head and neck cancer proved to be inconclusive with regard to the independent effects of socioeconomic risk factors. Smoking was the major significant risk factor – which has been well recognised for many years (Rothman and Keller, 1972; Hashibe *et al.*, 2007). However, the unclear finding with regard to alcohol consumption was unexpected given the increasing evidence (Corrao *et al.*, 2004; Hashibe *et al.*, 2007). Furthermore, the familiar synergistic interaction between smoking and alcohol behaviours (Blot *et al.*, 1988) was not observed. The study failed to detect a clear independent relationship between socioeconomic factors and head and neck cancer as found in Chapter 4 and previously seen in similar detailed studies (Menvielle *et al.*, 2004). It is preferable to view the findings in relation to socioeconomic factors as unclear rather than null as there was upwards of a 2-fold significant effect associated with many socioeconomic measures (both individual- and area-based), even following age and sex adjustment. However, the enormous effect of smoking (over 15-fold increased risk) seemed to mask the effect of all other factors.

This work also needs to be viewed both in the context of, and as a contributor to, the stark health inequalities in Glasgow and Scotland. To quote the very recent interim report of the Commission on Social Determinants of Health (2007), which puts them into a global context: "…dramatic inequalities in health within countries are seen in rich as well as poorer countries. In the Scottish city of Glasgow, life expectancy of men in one of the most deprived areas was 54 years, compared with 82 years in the most affluent (Hanlon, Walsh & Whyte, 2006) [Hanlon *et al.*, 2006]. This means that the poorest men in Glasgow have lower life expectancy than the Indian average".

7.1.8 What did this thesis contribute to knowledge?

In addition to what has already been discussed, it is worthwhile reflecting on the contribution and potential contribution of these studies to the research base.

This thesis has made a contribution in several areas. The descriptive elements have gauged the 'recent' trends in oral cancer across the UK related to age, sex, and geographic region. In its published form (Conway *et al.*, 2006), the findings in Chapter 2 have already become a baseline reference for the recent burden of oral cancer in the UK. The socioeconomic analysis has improved the understanding of the nature, origins, and extent of

socioeconomic trends in oral cancer in Scotland, and it too has recently been published (Conway *et al.*, 2007).

The systematic review and meta-analysis, to some degree, addresses the international debate about the direction of the socioeconomic risk for oral cancer with those with lowest socioeconomic status having the greatest risk, and it suggests that this risk is not only independent of behavioural risk factors, but of comparable size. It confirms that socioeconomic factors have a significant role to play in the risk of developing oral cancer. The approaches developed contribute to the methodology in the area of systematic review and meta-analysis of observational studies, particularly with regard to examining the socioeconomic risks.

The analytical epidemiology was unable to tease out the components of the socioeconomic risk, and the interaction between individual- and area-socioeconomic factors and behavioural factors. It has proposed, however, a framework for analysis of socioeconomic risk factors. In addition it was also one of the first studies to compare the new SIMD with the traditional Carstairs deprivation index. Finally, it has made a contribution to understanding the nature of selection and participation bias in case-control study methodologies.

7.2 Limitations

It is important to review the thesis limitations. They relate to the limitations of epidemiology in general, social epidemiology, and the specific study designs employed in the empirical research. In drawing attention to the limitations it is envisaged that the strengths of the research approaches taken will also be highlighted. Further, reflections on such limitations bring forward ideas and suggest different approaches which could be improved if repeated. Such critical review has been described as the ‘engine’ that drives the development of epidemiology (Rothman, 2001). Thus, the major limitations which run through the empirical research of the thesis will be discussed in turn, namely: ecological fallacy, confounding, and bias. Then, in general terms, the limitations of the epidemiological approaches adopted: descriptive, systematic review and meta-analysis, and analytical will be discussed. Finally, the limitations of social epidemiology will be acknowledged. The limitations of the particular study designs themselves were considered in some detail in the discussion sections of each chapter – in fact the whole of Chapter 5 is concerned with the limitations in relation to the potential biases associated with selection methods and participation rates of the case-control study (described in Chapter 6).

7.2.1 Ecological fallacy

The first major potential limitation of the thesis, raised throughout the empirical research, was the problem of 'ecological fallacy' in the use of the area-based measures of socioeconomic circumstance. The ecological fallacy is whereby individual-level relationships are inferred from relationships observed at the area-level. This could be argued in relation to the use of area-based measures in the descriptive epidemiology of oral cancer (Chapters 2 and 3); and in the analytical epidemiology which investigated the socioeconomic effects on selection and participation, as well as the case-control analysis of the components of socioeconomic risk.

Piantadosi *et al.* (1988) was one of the first to argue strongly against the case for ecological analysis in epidemiology. In their critique, they concentrated on the underlying statistical basis against ecological data, however, they limit their scope to traditional (rather than social) epidemiological exposures – particularly the use of aggregated alcohol, smoking, and dietary data utilised at the aggregate level to infer individual-level exposures (Piantadosi *et al.*, 1988). More recently ecological studies are typically described as flawed and limited in usefulness 'to "hypotheses generation," leaving the more esteemed process of "hypothesis testing" to individual level data' (Schwartz, 1994).

Macintyre and Ellaway (2000) set out a commanding refutation of the ecological fallacy. Based on a discussion of the role of both the physical and social environment, they argue that the ecological fallacy is too readily used in criticism of social epidemiology, when in fact the fallacy can equally work the other way, whereby aggregated-level relationships are inferred from individual-level data. Further, they describe how it is valid to use aggregated or area-based measures of socioeconomic circumstances to infer aspects of the social environment which could not be captured by individual measures. They conclude by arguing that it is not the ecological measures themselves which are the problem – it is how they are used and interpreted. Therefore, it is inappropriate to use, for example, the area-based measures of Townsend (Townsend *et al.*, 1988) or Carstairs (Carstairs and Morris, 1991) indices to infer the individual socioeconomic status, as not everyone in an area with a particular deprivation score has the same socioeconomic characteristics. However, it is appropriate to infer the socioeconomic circumstances of the area in which they live from such indices. Throughout the thesis, careful language has been used and inferences made have been limited to those related to the social characteristics of the area.

Macintyre and Ellaway (2000), then go further in suggesting that differences in health between different areas can be explained in terms of the compositional make up of the individuals in an area (i.e. that the differences in characteristics between areas account for such differences) or in terms of the contextual social or physical surroundings of the areas where individuals live. This will be developed further in the explanation section of this discussion.

Therefore, in relation to the empirical research in the thesis, the studies acknowledged the potential limitation of the ecological fallacy. However, interpretation of ecological data was done carefully, and the limits of inference were acknowledged.

7.2.2 Confounding

The second major limitation was the problem of confounding, which was common to all the empirical research in the thesis. Confounding is a potential cause of spurious association – where one exposure factor that is not causally related to a disease outcome is associated with an exposure that does have a real effect on outcome. Thus, in this thesis, the main concern was the confounding effect on socioeconomic exposures of known behavioural risk factors for oral cancer such as smoking and alcohol consumption, where socioeconomic factors are also potentially associated with the behavioural factors.

It is an almost inescapable problem and criticism in epidemiological research, not only social epidemiology. Oakes and Church (2007) recently noted that it is impossible to guarantee that the findings of observational study epidemiology are unaffected by unmeasured confounding. They went on to review the increasing use of statistical techniques which attempt to model data on confounders, based on findings of other studies. However, they describe these techniques as not universally accepted, and unable to account for confounders where there is no data from which assumptions can be made.

In two articles in the *BMJ*, Davey Smith visits the issue of confounding in epidemiology. In the first paper, Davey Smith and Philips (1992) investigate how confounding factors are dealt with, and describe how the statistical techniques to adjust or control for confounders can ensure that the exposure – outcome relationship is ‘independent’ (of confounding factors). They argue that this is potentially inadequate, particularly when confounding effects are unmeasured (often described as ‘residual’). They conclude that ‘it is likely that many of the associations identified in epidemiological studies are due to confounding’. However, this is perhaps an over-emphasis of the problem, as it would mainly relate to

'weak associations'. This conclusion also does not take into account the relative strengths of the association between confounder and outcome, and confounder and exposure; and the prevalence of confounders in the study population – all of which would have an influence on the magnitude of the confounding bias. A decade later, Davey Smith with Ebrahim (2002) revisited the issue to see what can be done about confounding, related to socioeconomic circumstances. They suggest study replication in different settings as socioeconomic circumstances and mechanisms may operate in different ways in different populations. They also suggest further measures, including: improving the measurement of confounders (perhaps through more measurements on smaller numbers of participants), or undertaking sensitivity analysis to assess measurement error.

In relation to the approaches in the thesis, the effect of confounding was a constant consideration. In the descriptive epidemiology, there was a lack of ability to control for the effects of potential confounding, which limited any hypotheses testing around the association between socioeconomic or other demographic determinants with oral cancer. However, it did permit the exploration of the data with a view to generating further hypothesis with regard to these factors.

Residual confounding is a major potential limitation of the systematic review and meta-analysis. Significant steps were taken to attempt to investigate confounding factors where they were available through a series of subgroup and sensitivity analysis. Following these procedures, the socioeconomic effects seemed to remain independent of potential behavioural confounders. Nevertheless, the potential for unmeasured behavioural confounding remained.

Finally, in the analytical epidemiology, this was the opportunity to tease out independent socioeconomic effects and adjust for confounders in the shape of behavioural risk factors. Such independent effects were not clearly observed, due to other limitations of the study, including study power. In thinking about the confounding issue in the analytical study, it is interesting to compare it with the work of Blakely *et al.* (2004). They demonstrated in a study on smoking and mortality related to socioeconomic factors that taking into account only one socioeconomic factor failed to capture the full range of socioeconomic potentially confounding effects. While the analytical study in Chapter 6 looked at the problem from the other perspective, utilising many socioeconomic measures, and adjusting for a range of behaviours, the socioeconomic effect was lost. However, it may also be worth considering that the socioeconomic effects were inadequately measured, and further that due to the

inter-relation of various socioeconomic factors they have the potential to confound each other.

Although there were limitations related to confounding throughout the empirical research in the thesis, the possibility of the findings being explained by confounding were considered, and the findings were presented more cautiously as a result.

7.2.3 Bias

The third major limitation of the thesis is the potential for bias. In epidemiological studies bias is defined as the result of defects in the design or implementation of the study. The main biases in epidemiological studies, according to Rothman and Greenland (1998), are: publication bias in systematic reviews and meta-analyses; and selection, participation, and measurement bias in observational studies.

Selection and participation bias: The fundamental questions with regard to selection and participation bias in case-control studies, according to dos Santos Silva (1999), are: Did the controls represent the population from which the cases arose? Was the identification and selection of cases and controls influenced by their exposure status? These questions were explored in depth in Chapter 5 with a particular focus on the socioeconomic aspects of these biases. In summary, the controls in the ARCAGE head and neck cancer case-control study were representative of the base-population in the sense that they came from areas with similar socioeconomic profiles, despite the participation bias. Further the selection of 'incident' (newly diagnosed) cases arising from a defined population, and using a population-based approach for selecting controls, minimised the risk of selecting cases influenced by their exposure status. However, the participation bias with more affluent cases and controls being more likely to participate and be interviewed was a significant issue. Nevertheless, despite these limitations, a population representative control group was recruited, and the analysis of the socioeconomic factors associated with head and neck cancer risk was valid.

Measurement bias is also a major source of bias in epidemiology. It can relate to both measurement and definition of outcomes and exposures. In relation to the descriptive epidemiology, measurement error will be discussed in the next section. For the analytical approaches, a series of steps were taken to ensure that measurement was as objective as possible. These included, in terms of outcome, setting strict inclusion and exclusion criteria – mainly focused on defining the case diagnosis, age limits, and geographical boundaries.

In the measurement of exposures, subjects were blind to the objectives of the study; however, given the nature of the condition, the interviewers were not blind to the case or control status of the subject. They were rigorously trained, and calibrated using standardised procedures for data collection and validated questionnaire tools.

Publication bias: The final potential source of bias in the thesis was that associated with publication bias – a major concern for systematic reviews and meta-analysis. As discussed in Chapter 1, publication bias is a consequence of the problem that some studies (often those with null findings) are not published. One way of addressing this is to seek out and include where possible data in the meta-analysis which were not published. Chapter 4 describes how the INHANCE consortium was utilised to obtain unpublished data. Further, the meta-analyses approach investigated the potential effect of publication bias in considerable detail and it was not a significant problem in the study, however, the power of the tests to detect publication bias may be low for some of the small meta-analyses so publication bias may still operate within this set of data.

Davey Smith (2001) notes that publication bias which favours the publication of positive results over null findings is a 'significant' problem. He notes the irony with the statistic that in examining 20 associations, chance will lead to one being significant at the $p<0.05$ level. It will be interesting to see if the case-control analysis (Chapter 6) of social factors is accepted for publication, as its findings – from purely a 'results' point of view are not entirely clear, even although methodologically there would be merit in publication.

7.2.4 Descriptive epidemiology

In addition to the issues of ecological fallacy and confounding discussed above, a main limitation of descriptive epidemiology studies relates to measurement errors of exposures and to the issue of the latent period. The issue of quality of measurement relates to the use of data on exposures collected for other reasons. Examples of such exposure data are smoking or alcohol data based on sales. However, as our exposure data were census derived postcode linked area-based measures of socioeconomic circumstances which we could link individually to the cancer registry cancer incidence data, the limitation in this regard were minimal. The measurement of cancer incidence is also subject to errors and quality issues as discussed in Chapters 2 and 3 and in Section 1.2.2.4.

Descriptive epidemiology has particular difficulties in contending with the nature of the timing of the measurement of the data on exposures and outcomes. These data are often

cross-sectional and are collected at one point in time – occasionally the same point in time for exposure and outcome. Preferably, there should be a time-lag between exposure and subsequent outcome. Kasl and Jones (2000) note this is a particular difficulty in determining this temporal sequence in terms of social factor exposures to outcomes, with importance of ensuring that the outcome did not lead to the exposure. In the thesis, the descriptive epidemiology in Chapter 3, investigating socioeconomic correlates to oral cancer trends, the socioeconomic indices were linked to the address postcode of residence of the subject at the time of diagnosis. While considerable efforts were made to ensure that the index used was most closely related to the date of diagnosis, the limitation of temporal association to some degree may remain and the potential explanation that having the disease oral cancer may lead to individuals living in more deprived socioeconomic circumstances is possible – see explanation Section 7.3.1.2 for full discussion.

Finally, a limitation of descriptive epidemiology is considered to be that it can only generate rather than test hypotheses. However, this is only a limitation if one sets out to test hypotheses on causality through descriptive epidemiology approaches. In this thesis, this limitation was known *a priori* and the objectives of the descriptive epidemiological sections were to explore the data, assess trends, with an expectation that this would generate further hypothesis. Therefore, in terms of the thesis, this can not be considered a limitation.

Furthermore, despite these limitations, descriptive epidemiology has an important and useful role in describing the burden of disease and beginning the process of signalling the presence of effects which warrant further investigation.

7.2.5 Systematic reviews and meta-analyses of observational studies

The debate on the validity of systematic review and meta-analyses of observational studies was extensively discussed in Section 1.2.4.7. In addition to the effects of confounding and publication bias noted above, particular consideration of the threat of false precision in the use of the techniques of meta-analysis, as described by Egger *et al.* (1998), is worth revisiting here. This relates to the fact that such meta-analyses produce a summary estimate from combining the effect sizes from several individual studies. The individual studies included may be distorted by bias and confounding (as discussed above), which may equally affect the summary estimate. Egger *et al.* (1998) caution against over-emphasis of the overall estimates and prefer a thorough exploration of the nature of heterogeneity

through sensitivity analyses. In the thesis study (Chapter 4), heterogeneity was observed, explored, and discussed extensively. It was felt, given the extensive subgroup and sensitivity analysis which included factoring issues of study method quality, that an overall effect estimate was merited.

7.2.6 Analytical epidemiology

A limitation of the thesis is that the analytical epidemiology was perhaps not fully up to the major challenge of investigating the components of the socioeconomic risk of oral cancer. This relates mainly to the design of the case-control study (Chapters 5 and 6), but perhaps relates to the wider limitations of analytical epidemiology.

The limitations of analytical epidemiology were discussed in a critique by Davey Smith (2001). This critique discussed several issues including: risk factor focus, 'black box' causality model, individual rather than social focus, and methodological limitations. Each of these will be discussed in turn in relation to the analytical research of the thesis.

Risk factor focus: The first limitation Davey Smith (2001) discusses is the over emphasis and focus of risk factors in epidemiology – which he described as 'risk factorology'. Here, in a given study, a large range of exposures are related to disease risk with those positively associated becoming risk factors (and negatively linked become protective factors). He identifies the paradox, whereby even although it is accepted that association does not mean causation, the main purpose of such studies is to search for 'causes.' Therefore, these associations are inevitably treated as causes and preventive messages are developed. It could be argued the approaches adopted in the thesis set up to look at the association of social factors, with the ultimate aim of assessing their role in the causality of oral cancer. However, at no point in the thesis is causality of social factors asserted, rather there is a concerted effort to explore their relationship with oral cancer, and then to go deeper to assess the components and potential pathways for the relationship. A detailed exploration of such potential explanations will be covered in Section 7.3.

Related to the focus on risk factors, Davey Smith and Ebrahim (2002) identify 'data dredging' as another limitation in analytical epidemiology. This is the process whereby large numbers of exposures are tested for significant associations in the same models. If statistically significant levels are set at the $p<0.05$ level, then as noted above, one out of 20 exposures could be related to chance and provide a false positive. They suggest that significant levels should be set at a higher level. In the thesis, the statistical analysis was

determined by *a priori* hypothesis and objective which informed an analysis specification, and significance was considered at $p<0.01$ and beyond.

‘Black box’ model: The second strand of Davey Smith’s (2001) critique was around the ‘black box’ model – the model whereby the pathways and particularly the biological mechanisms are either not understood, known, or crucially ‘biologically plausible’. While many may argue against the biological plausibility of social factors in relation to cancer development, there is an increasing body of evidence that has begun to identify potential biological pathways (Marmot and Feeney, 1997; Krieger 2005). This will be picked up in detail in the following explanations section.

‘Asocial science’: Davey Smith’s (2001) third major critique of analytical epidemiology is what he describes as its ‘asocial’ nature. He notes that much of epidemiology is focused on individuals and their lifestyles, out with the social economic context which they live. He goes on to suggests that methodological limitations of epidemiology relate not so much to the study designs as much as the focus of these studies – with a need to embrace complexity and the multilevels of social, economic, and political factors which affect individuals and populations, people and places. Both of these major limitations of epidemiology are exactly what this thesis has attempted to address with regard to the risk for developing oral cancer.

7.2.7 Social epidemiology

The final set of limitations relate to those of social epidemiology. It is interesting to note that there are limited critiques of social epidemiology in the literature – both in number and scope. The main early concerns were around the considered lack of a theoretical basis (Wainwright and Forbes, 2000) – a challenge, which the field has largely risen to (Berkman and Kawachi, 2000; Krieger, 2001b). Specific limitations remain, and relate to the tensions between the often conflicting drive to understand humans both from biological and social perspectives. This seems to be social epidemiology’s main problem – while trying to ensure the social perspective, the individual is ignored. The very nature of the criticism – but in reverse – which social epidemiologists have of ‘modern’ or clinical epidemiology which seems concerned only with the individual, the genetic, or the behavioural in isolation from the social context. Thus, throughout the thesis efforts have been made to build bridges between the social and individual in terms of understanding the socioeconomic risk. This has been done also in the context of awareness of the paradox – particularly relevant to cancer epidemiology – that cancer is a disease monitored and

understood (to a degree) at the population level, while occurrence and risk at the individual level is unpredictable.

Commentaries by Birch (2001) and Kaplan (2004) acknowledge the prevailing criticism of social epidemiology – that it confines itself largely to the identification and description of the problem of socioeconomic inequalities in the distribution of health and disease, but provides somewhat limited research on solutions to the problem.

Furthermore, Birch (2001) highlights the irony that social epidemiology may partly be to blame for pushing individual-centred behavioural policies forward in response to health inequalities. He illustrates the process through an example: (i) inequalities in a condition e.g. lung cancer are identified; (ii) lung cancer is known to be associated with smoking; (iii) initiatives are designed to target a subgroup of the population e.g. deprived people who smoke – who are subsequently considered a homogeonous group; (iv) the population-wide and societal perspectives are ignored. He notes a further example of this consequence in the UK government's *Independent Inquiry into Inequalities in Health*, which reviewed the evidence on inequalities through a model of health and wellbeing where there was no interconnectedness between the social and behavioural factors rather they seemed to be influencing health separately and independently (Acheson, 1998). In recognising these issues, the thesis research, while not providing a complete picture, attempts to investigate risk from both a social and behavioural perspective and crucially how these aspects related to each other. This will be further explored in the explanations section which follows, and due cognisance of these limitations will also be paid when formulating the conclusions and recommendations.

Social epidemiology is also open to many of the methodological weaknesses of traditional analytical epidemiology described above. However, key areas of debate related to the validity of social epidemiology, focus on: the utility of traditional analytical approaches to test causation associated with causal factors (Kaufman and Cooper, 1999); and further the nature of causation in relation to social factors (Susser and Schwartz, 2005). This will be discussed further when the explanations for the thesis findings are explored.

7.3 Explanations

The thesis now returns to the issue of the potential explanations of the risk of oral cancer associated with socioeconomic status, circumstances, and inequalities in relation to the empirical research findings.

Explanations of the association between oral cancer and socioeconomic status, circumstances, and inequalities are complex. This is further complicated by the multiple dimensions and layers through which the problem was observed. These include the challenge in explaining: (i) the burden of the disease falling greatest on those from deprived areas and communities together with the widening inequality trends over time which were identified in the descriptive epidemiology in Chapters 2 and 3; (ii) the oral cancer risk associated with the multiple individual measures of socioeconomic status, and global perspective considered in the systematic review and meta-analysis in Chapter 4; and (iii) the relationship between area- and individual-measures and the components of the pathways of socioeconomic risk associated with oral cancer which the case-control study in Chapters 5 and 6 began to explore. These findings will be threaded through the following discussion on potential explanations.

The Black Report proposed four main explanations: (i) artefact; (ii) natural and social selection; (iii) materialist or structuralist; and (iv) cultural and behavioural (Department of Health and Social Security, 1980). Bartley (2004) proposed an updated classification (i) material; (ii) cultural-behavioural; (iii) psycho-social; and (iv) life course. While considering each of these potential explanations in relation to oral cancer risk, the following general categories of explanations will be used here (i) artifactual and selection; (ii) behavioural and cultural; and (iii) socioeconomic. These explanations will take into account newly developed theories and interpretations; will also acknowledge the complexity of differing dimensions and interconnectedness of factors; as well as the fact that they are not mutually exclusive.

7.3.1 Artifactual and selection explanations

7.3.1.1 Artifactual

The ‘artifactual explanation’ states that the observed association between socioeconomic status and health is false. The basis for this explanation was concern that errors in the measurement of social phenomena, lead to spurious findings – which were then claimed to be of little causal significance. It was considered by the Black Report (Department of Health and Social Security, 1980) and dismissed on the basis that the census data from which these concerns arose were demonstrated to be misinterpreted. Whitehead (1992) later agreed that there were limitations with the measurement of socioeconomic status. However, she also dismissed the explanation through a description of the overwhelming evidence from a range of studies controlling for measurement error, and increasingly from

longitudinal and analytical epidemiology studies with individual level data, where measurement error was significantly less. Shaw *et al.* (1999) went further, in their review of the evidence, when they suggest that artefacts are more likely to lead to underestimation than overestimation of the extent of health inequalities. Bartley (2004) went even further by not considering or even mentioning it as a potential explanation in her authoritative text on health inequalities.

In both the descriptive and analytical studies of the thesis, the issue of measurement error has been explored in detail (Sections 7.2.3 and 7.2.4), and given the lengths taken to control for it, its effects were considered minimal.

7.3.1.2 Selection

The Black Report (Department of Health and Social Security, 1980) termed it the 'natural and social selection explanation', but it is also referred to as 'health selection' (Marmot and Feeney, 1997), 'reverse causation' (Goldman, 2001), and helpfully rounded up to simply the 'selection perspective' (Mackenbach, 2005). These terms all describe the process whereby people in poor health move down, or remain in lower socioeconomic strata. This social mobility has been defined as being either intergenerational (comparing an individual's SES with that of their parents) or intragenerational (comparing SES between earlier and later life) (Mackenbach, 2005). Unlike the artifactual explanation, the selection explanation accepts inequalities exist, but it does not accept that social factors influence health – rather it is the other way round.

The issue of time-lag between exposure and outcome was noted as a limitation in the thesis descriptive epidemiology (Section 7.2.4). While the descriptive epidemiology data were time-series, the linkage of postcode to deprivation index utilised the postcode of residence at the time of diagnosis. Therefore, from these data, selection could be a possible explanation as it was impossible to determine the socioeconomic circumstances prior to diagnosis. However, Mackenbach (2005) points out that most diseases arises in later life when social mobility has become rare, and this is true from the age distribution of oral cancer observed in the descriptive epidemiology. Therefore, the effect of downward social mobility would have had to have happened rapidly late on in life and followed the diagnosis of oral cancer.

The systematic review and meta-analysis utilised data from case-control studies, wherein individual measures of socioeconomic status were determined from historic information

prior to diagnosis. The findings from this study, particularly the education data, which can be used to reflect socioeconomic status in earlier life, do not support the health selection explanation. Nor is this explanation supported by the analytical epidemiology, which examined a range of socioeconomic factors in relation to oral cancer risk – all historical to the oral cancer diagnosis. It also attempted to explore the role of social mobility in the aetiology of head and neck cancer. While the study was not fully powered, there was minimal evidence to suggest that downward social mobility provided any greater risk than those who remained in lower occupational social classes. However, without longitudinal data from cohort studies, evidence for the selection hypothesis is going to be limited.

One area of the selection explanation receiving some interest is in the area of early life circumstances – such that poor health in childhood is associated with downward social mobility. Marmot and Feeney (1997) suggest there is some evidence to support this explanation, but considers the contribution to health inequalities overall to be minimal. The early life factors will be considered within the life course explanation (Section 7.3.3.6).

Another area is ‘indirect selection’ whereby rather than social mobility and position being influenced by health itself, it is factors which influence health i.e. personal attributes such as intelligence, personality, and mental health factors which may in turn influence educational attainment or occupational social class. Mackenbach (2005) highlights the few, albeit limited studies, beginning to show that this process may contribute to health inequalities.

There has also been renewed interest in what could be described as the ‘natural’ element of the Black Report’s original selection explanation – if genetics can be described as such. This will be considered in the next section.

7.3.1.3 Genetics

The evidence related to the role of genes in determining social class was considered by Holtzman (2002). On the question of whether natural selection explains social advantage, he found no evidence to suggest that genetic mutations would be sufficient to influence social standing. Further, he suggests that personal attributes, even if they were influenced by genes, would involve many independent and segregated alleles which could not be passed together between generations. He notes that the case for genetics is exaggerated at the expense of the role of the environment; and that attributes associated with social class are the result of socioeconomic inequalities not the cause. He concludes strongly with

'genetics should cease to be a subterfuge for explaining social differences'. There is wide consensus with the position that the role of genetics is limited in explaining health inequalities (Bartley, 2004). Nevertheless, there remains interest in this area as outlined by Mackenbach (2005). He describes the potential role of genes in indirect selection – whereby genetics exert their influence on inequalities through their role in certain attributes (such as intelligence, personality, and mental health), which in turn could influence intergenerational social mobility. However, the evidence in these areas remains weak and conflicting, with such attributes themselves being strongly socially patterned (Batty *et al.*, 2006).

However, the artifactual and selection hypotheses have largely given way to more direct 'causal explanations' which accept both the reality of health inequalities and the causal direction from social factors to health outcomes (Goldman, 2001). These will be taken up in the next section.

7.3.2 Behavioural and cultural explanations

A widely accepted explanation of health inequalities is the one related mainly to individual behaviours, but with recognition that these behaviours are culturally influenced (Bartley, 2004). The explanation follows that health damaging (and promoting) behaviours are related to socioeconomic status groups, such that smoking, alcohol, and diet are more prevalent in lower SES groups. It is also known that these behaviours are major factors in the aetiology of chronic diseases including cancer.

Doll and Peto (1981) first suggested that much of the cancer burden in the US could be attributed to 'modifiable behaviours' including smoking, diet, and alcohol. More recently, the Harvard Report on Cancer Prevention repeated this conclusion – that nearly two-thirds of cancer deaths in the US can be attributed to behaviours such as smoking, diet, and lack of exercise (Colditz *et al.*, 1996).

There is also limited doubt that behavioural factors are significant contributors to oral cancer risk – as the review of the aetiological factors in Chapter 1 demonstrated. However, important questions still arise from this in relation to oral cancer, particularly with regard to explaining the socioeconomic inequalities in oral cancer reported in this thesis. These questions, adapted from Marmot and Feeney (1997), include: (i) how much of the inequalities in oral cancer can be attributed to inequalities in behaviours?; (ii) and how and

why are behaviours related to socioeconomic factors and inequalities? The latter question originates from Rose's (1992) hypothesis – that social factors are the 'cause of the cause'.

The potential pathways and mechanisms of the association between socioeconomic effects and oral cancer risk will be explored, through a detailed examination of the relationship between socioeconomic status, circumstances, and inequalities with the behavioural risk factors associated with oral cancer.

7.3.2.1 Smoking

The overwhelming evidence associating tobacco smoking with oral cancer risk was extensively reviewed in Chapter 1. The relationship between smoking and socioeconomic factors is an important consideration in explaining the inequalities in oral cancer observed in this thesis.

Individual measures of SES: There is a large body of evidence associating smoking behaviours with low individual socioeconomic status through a range of measures, including: low income and poverty (Graham, 1987; Stronks *et al.*, 1997); housing tenure i.e. non-owner occupied housing (Stead *et al.*, 2001); low educational attainment (Stronks *et al.*, 1997; van Lenthe and Mackenbach, 2006); low occupational socioeconomic status (Jarvis and Wardle, 2006); and social phenomenon including lone parenthood (Jarvis and Wardle, 2006).

Laaksonen *et al.* (2005) recently attempted to disentangle these various individual-level socioeconomic dimensions related to smoking behaviour in a series of large cross-sectional surveys in Finland. They found that smoking behaviour was strongly related to low SES in structural (education and occupational social class), material (household income and tenure), and self-perceived (economic difficulties and satisfaction) dimensions. They found that no individual factor was significantly more important and concluded that smoking behaviour related to individual SES was a complex and multifaceted relationship.

Explanations: Smoking prevalence is determined by smoking uptake, nicotine addiction, and smoking cessation – with the first two consistently shown to be greater and the third lower in people of low socioeconomic status (Jarvis and Wardle, 2006). Proposed potential explanations for the association between low individual SES and smoking include: (i) psycho-social, (ii) mental health, (iii) structural or materialist, and (iv) cultural.

These will be discussed in turn: (i) Graham (1987) in her compelling qualitative work with women from deprived communities found that that smoking was described as a coping mechanism for the stresses associated with living on low income and caring for others. (ii) Jarvis and Wardle (2006) identify a direct potential mechanism via poor mental health and its association both with low socioeconomic status and with high smoking prevalence. (iii) Further pathways, described as structural and material, could also have direct effects such as the condition and type of housing (Macintyre *et al.*, 2003). (iv) The influence of cultural factors, in relation to the association of smoking behaviours with socioeconomic status is an important consideration (Stronks *et al.*, 1997), and will be discussed in more detail in Section 7.3.2.5.

In addition, Lawlor *et al.* (2003) describe 'lay epidemiology' around perceptions of life-expectancy, life-chances and risk interpretation as potentially influencing and rationalising smoking behaviours in disadvantaged members of society. This is an extension of the concept of 'locus of control' which refers to the aspect of an individual's belief system concerned with control over one's life. Thus, internal locus of control relates to beliefs that health can be influenced by, for example avoiding health-damaging behaviours such as smoking. This belief system has been shown to be more common among those from higher socioeconomic groups (Stronks *et al.*, 1997). Low educational attainment may also (although not exclusively in this way) relate to smoking through the awareness of health educational messages – which are also taken up more readily by more affluent and educated people (Schou and Wight, 1994). However, Jarvis and Wardle (2006) are keen to point out that there is no evidence to suggest more disadvantaged people are less motivated to give up, but lack resources (in the broadest sense) to do so.

Area-based socioeconomic measures: Stead *et al.* (2001) followed by van Lenthe and Mackenbach (2006) demonstrated that smoking prevalence is higher in more compared with less deprived communities and that this socioeconomic area-effect is associated with smoking, independently of individual SES. Recently, Gray (2007) undertook a comprehensive study utilising data from the Scottish Health Survey to compare behaviours and health outcomes with area- and individual SES measures between Glasgow and the rest of Scotland. She found that smoking was significantly higher among both men and women in Glasgow compared to the rest of Scotland and that most of the difference was explained by (area and individual) socioeconomic factors.

Explanations: In terms of the relationship between high smoking prevalence in disadvantaged communities, Stead *et al.* (2001) undertook qualitative research in Glasgow

to explore the potential explanations for this phenomenon. They found that those living in deprived areas had the double stress effect of coping on a low income and with disadvantaged neighbourhood circumstances. The area 'stresses' of the poor physical environment, high crime and fear of crime, limited opportunities for recreation, combined with cultural and community norms (which included people feeling they needed legitimate reasons such as asthma not to smoke) were reported to foster smoking behaviour and undermine cessation – encapsulated by feelings such as: "It's as if you're locked in". In Berkman and Glass's (2000) review of social networks, health damaging behaviours including smoking are described as increasing with social isolation.

Other area effects which seem to promote smoking in deprived areas have been found to include: the greater availability of tobacco, the greater number of convenience stores in deprived areas (van Lenthe and Mackenbach, 2006), in addition to the tobacco industry targeting deprived communities (Hackbarth *et al.*, 1995).

Global dimension: Recent data on the relationship between smoking and disadvantage from low and middle income countries, particularly India, were reviewed by Jarvis and Wardle (2006) – where they noted that previous correlations of smoking with high SES (where smoking was associated with perceived Western sophistication and affluence) have been replaced with the association of smoking with socioeconomic disadvantage.

Trends in smoking and socioeconomic status: The relationship between smoking and socioeconomic status and widening inequalities in the distribution was demonstrated in Marmot *et al.*'s (1991) Whitehall studies of British civil servants. Between 1967-69 and 1985-88 smoking prevalence decreased in all social groups, however, it decreased more markedly in those from the higher occupational social classes.

Davy (2007) also recently undertook a pseudo-cohort analysis of data from the General Household Survey and noted evidence for long-running inequalities in smoking prevalence between manual and non-manual occupational classes in both men and women in Britain. This largely agreed with the analysis and review of the published smoking prevalence data which was undertaken as part of the descriptive epidemiology of the thesis (Section 3.5.3.1). However, in Davy's more detailed analysis of the primary data, there was some evidence of widening inequalities in some cohorts born after 1950 and more pronounced in men. These additional data do add support to the role of smoking in explaining to some extent the widening inequalities in oral cancer observed in the thesis. However, they add further complexity in the overall explanation of the trends in oral cancer, in that the oral

cancer incidence rates were continuing to rise in the face of falling smoking prevalence in all socioeconomic groups.

Smoking explanations in relation to the thesis findings: In addition to partly explaining the descriptive epidemiology trends in oral cancer inequalities observed, smoking may also be considered as a potential residual confounding factor in the studies included in the systematic review and meta-analysis. However, subgroup analyses including study estimates which had adjusted for smoking did not significantly reduce the SES effects by any measure, suggesting that other non-smoking factors may be involved in the aetiology of oral cancer.

Finally, in relation to the analytical epidemiology (Chapter 6), smoking was an overwhelmingly significant risk factor in the aetiology of head and neck cancer. The limitations of the case-control study in relation to the power of the study have already been fully discussed. However, the fact that almost all the cases in the study were smokers (or ex-smokers) speaks for itself. Smoking was confirmed as a major risk factor, although it was disappointing that the unclear findings in relation to socioeconomic factors made it impossible to fully assess the relationship between SES and behavioural risk factors. In a similar study by Menvielle and colleagues (2004), with greater numbers, socioeconomic factors were found to be independently significant of smoking and alcohol behaviours.

Therefore, smoking is obviously an important factor in the aetiology of oral cancer and is strongly related to socioeconomic status. Thus, socioeconomic factors may play a deeper role in the aetiology of oral cancer as a ‘cause of the cause’. However, in the same way that smoking alone is accepted as not being the sole aetiology factor for oral cancer, smoking can also be considered insufficient to account for the inequalities in oral cancer observed in this thesis.

7.3.2.2 Alcohol consumption

Given the strong evidence, reviewed in Chapter 1, that alcohol consumption is a major risk factor for oral cancer (both alone and in combination with smoking behaviours), its potential role as an intermediate in the pathway between socioceconomic circumstances and disease risk needs consideration.

Alcohol is a socioeconomic issue: in Scotland, in 2002/03, alcohol problems were estimated to cost over £1.1 billion (Scottish Executive, 2005c). Jarvis and Wardle (2006)

describe alcohol abuse as a marker of acute social breakdown. The aspects of alcohol consumption most strongly associated with low socioeconomic status and deprivation and most relevant to increased cancer risk were outlined by Møller and Tønnesen (1997). These relate mainly to heavy drinking, alcohol abuse, alcoholism or binge drinking.

Individual measures of SES: Marmot and Feeney (1997) described data from the UK Whitehall study which showed that there was very little difference by civil servant grade in the proportion of heavy drinkers for men. By contrast, for women, the proportion of heavy drinkers increased the higher they were in the occupational classification hierarchy. However, overall there was no clear trend in drinking behaviours between the grades. These figures do not support the idea that heavy drinking is greater in lower occupational social groups. However, it could be argued that even the lowest grade in the civil service would not be poor.

The above findings present an opposite picture to that generally observed from studies across Europe. Droomers *et al.* (1999) reported that prevalence of excessive drinking was consistently higher in men with lower educational attainment than in men with higher education, and they found a generally similar, although less clear, relationship for women.

Low income or increased poverty has also been observed to lead to increased alcohol use and problems – contradicting the widely held economic argument that poverty reduces drinking because of the prohibitive costs – although some studies do report high levels of abstention with low income (Khan *et al.*, 2002).

The evidence linking alcohol consumption to unemployment has been reported as equivocal in a review by Kasl and Jones (2000). However, this conclusion may be a factor of the vast range of definitions and studies in the area. More recent studies are trying to tease out some aspects of the relationship between unemployment and alcohol. Khan *et al.* (2002) found that recent unemployment decreases alcohol use, while longer unemployment increases it. They also note the emerging agreement that unemployment increases alcohol abuse among heavy drinkers, and moderate drinkers may decrease consumption.

Explanations: One possible explanation, particularly related to educational attainment, includes the suggestion that individuals from high socioeconomic groups may be more aware of the adverse consequences and may be more likely to make healthier choices around alcohol (Van Oers *et al.*, 1999).

However, as with smoking behaviour, there are potentially deeper explanations. Droomers *et al.* (1999) describe the 'tension reduction theory' of excessive alcohol consumption, whereby alcohol is consumed (heavily) to reduce stress, and the behaviour is particularly reinforced in a stressful environment. They also postulate that both the amount and nature of the stress, as well as the ability to cope with it are potential explanatory factors. They tested this theory in a longitudinal study in Holland, finding that the strong relationship between low educational attainment and excessive alcohol consumption was compounded by 'material stressors' such as financial problems.

A number of other studies which have investigated the 'stress' associated with a range of social factors have also shown that the stress reduction theory is a plausible explanation. These include the stress associated with unemployment, and from a lack of social support (Berkman and Glass, 2000). However, the stress-alcohol relationship is not consistently observed, and unhealthy behaviour such as alcohol consumption could also potentially lead to stress. Khan *et al.* (2002) believe that the difficulty in determining the direction of the relationship remains an issue – whether alcohol is an outcome of or contributor to low socioeconomic status.

Further, the role of socioeconomic adverse life events such as divorce, or severe financial difficulties in contributing to excessive alcohol consumption were described as 'not unequivocal' in a recent comprehensive critique of the literature (Veenstra *et al.*, 2006). Finally, Monden *et al.* (2006) attempted to assess whether childhood socioeconomic status explained alcohol behaviour but could find no correlation.

Area-based socioeconomic measures in relation to alcohol consumption have not been as well explored as for smoking. Ecob and Macintyre (2000) describe the literature on the role of area-effects in relation to alcohol (among other behaviours) as being inconsistent in relation to the context (the place effects), with most of the variance explained by the compositional (individual) aspects. This was repeated in the recent study by Monden *et al.* (2006). Gray (2007) recently reported that excessive alcohol consumption was significantly higher in Glasgow compared to the rest of Scotland, although there was no differences in consumption by levels of area socioeconomic deprivation.

However, alcohol advertising has been found to target deprived communities (Hackbarth *et al.*, 1995). Further, there is increasing attention being paid to the availability and affordability of cheap alcohol targeted to deprived communities, although availability and heavy consumption do not always correlate (Pollack *et al.*, 2005).

Global dimension: The data in the WHO's *Global Status Report on Cancer* (WHO, 2004a) suggest that globally there is a general trend for the levels of alcohol consumption of the global regions to be converging, with high income countries with high traditional consumption generally decreasing, while low income countries with low consumption increasing. Of course these regional data mask trends between and within individual countries.

Alcohol explanations in relation to the thesis findings: The relationship of the rising trends in oral cancer observed overall are in line with those for other alcohol-related disease markers such as liver cirrhosis (Leon and McCambridge, 2006) and with overall drinking behaviour patterns as explored in the discussion sections of Chapters 2 and 3. However, the widening inequalities observed in the trends of oral cancer do not seem to correlate particularly well with those in relation to alcohol. Socioeconomic inequalities in alcohol consumption are less clear – this is perhaps a function of the very high average consumption in the population such that inequalities are not as pronounced. As with the smoking behaviour explanation, the systematic review and meta-analysis controlled for alcohol consumption in the subgroup analysis which did not substantially alter the socioeconomic effects – however, residual confounding due to alcohol is always going to be a possibility. In relation to the analytical epidemiology, the relationship between alcohol and head and neck cancer risk was not clear – again this may be related to the high drinking rates in the controls.

The descriptive epidemiology was unable to compare the oral cancer trends with smoking and alcohol behaviours in combination, which is a recognised significant risk factor. The case-control study also could not demonstrate this synergistic relationship or an association with socioeconomic factors, although this could have been due to the small numbers.

7.3.2.3 Diet

From the literature review in Chapter 1, it is apparent that there is a growing body of evidence to support the role of diet, particularly fresh fruit and vegetable intake in preventing oral cancer. However, rather than diet simply being a lifestyle choice, Robertson *et al.* (2006) set out compelling evidence to support their argument that food is a political, social, and economic issue.

Individual measures of SES: De Irala-Estévez *et al.* (2000) undertook a systematic review of 11 studies from seven European countries (not including the UK) and found that in both

men and women, high educational attainment and high occupational social class were related to significantly and substantially higher fresh fruit and vegetable consumption than those from lower educational and occupational social groups.

Household income data from the UK, reviewed by Robertson *et al.* (2006), also consistently shows that those living on low incomes eat considerably less fresh fruit and vegetables than those on higher incomes. The relationship was found to be almost linear, with fresh fruit and vegetable consumption increasing with household income. A recent report from Glasgow demonstrated that both fruit and green vegetables were consumed at significantly lower levels in those from lower socioeconomic backgrounds in both Glasgow and the rest of Scotland. However, only consumption of green vegetables was lower in Glasgow compared with the rest of Scotland (Gray, 2007).

Area-based socioeconomic measures: Residential area deprivation has also been shown to predict fruit and vegetable intake independently of individual education level and occupational social class in a large (22,562 subjects) cross sectional study in the UK (Shohaimi *et al.*, 2004). These area effects were suggested to be related to the community characteristics including cultural norms of the area, access and affordability of healthy food, in addition to potential psychosocial factors.

However, in studies in Greater Glasgow, Cummins and Macintyre (2002a) found no differences in price or food availability between deprived and affluent areas. This led them to write an opinion piece arguing against the existence of 'food deserts' – defined as areas with limited access to affordable, healthy food (Cummins and Macintyre, 2002b). Their stance was criticised as it failed to highlight the inconclusive nature of the evidence in this area (Conway and Budewig, 2002). Moreover, around the same time, similar studies from elsewhere in the UK were demonstrating the existence and struggle associated with living in food deserts (Clarke *et al.*, 2002; Wrigley, 2002; Whelan *et al.*, 2002). In summary, these studies highlighted the issues involved in food poverty – defined as access to healthy, quality (and culturally acceptable) food on the basis of availability and cost. The concept of food deserts introduces both structural and material dimensions to the issue of food access, recognising that food retail also plays an important part. The debate has moved on from one focused on the existence of food deserts to a consensus around the realities of 'food poverty' (Lang *et al.*, 2001).

More recently, the focus on area-effects related to diet has also shifted from food deserts to the 'obesogenic environment'. This area of research, reviewed by White (2007), seeks to

understand aspects of the environment which inhibit physical activity, as well as the issues around availability and accessibility of healthy foods. He notes that one area of particular interest, but not providing consistent findings, is around the concentration of 'fast-food', 'take-away' or out-of-home food outlets in deprived areas. White (2007) points out the need to bring together research on individuals and their environment to gain insight into the socioeconomic and cultural factors involved in diet.

Diets with limited fresh fruit and vegetables are therefore more complicated than simply individual lifestyle choices. They are underpinned and influenced by a range of social, economic, and cultural factors, which include physical access to healthy and affordable food, and food culture in terms of food production, processing, selection and preparation. However, the pathways between social factors and diet are yet to be fully unpacked.

Global dimension: The WHO's Global *Strategy on Diet, Physical Activity and Health* (WHO, 2004b), warned that the future health burden will increasingly be 'diet-related' chronic diseases. It also reported that unhealthy diets, obesity and chronic disease are increasing in low and middle-income countries, even although malnutrition and infectious diseases dominate.

Diet explanations in relation to the thesis findings: The role of a poor diet – one limited in fresh fruit and vegetables – is linked to low individual and area SES, as well as to oral cancer risk. This may help explain the widening inequalities in oral cancer observed, although there were limited data on the trends over time of such diets related to deprivation. However, the emerging obesity epidemic, reported by White (2007), with its similar associations of socioeconomic deprivation and an unhealthy diet may suggest that dietary inequalities have played a role in increasing oral cancer and in widening inequalities. An arrow through this argument may be the finding that oral cancer is associated with malnourishment in the opposite direction. Such that, low body mass index (BMI) has been shown to increase oral cancer risk (e.g. Nieto *et al.*, 2003) – although the evidence is limited due to the difficulty in gauging this prior to diagnosis.

Dietary factors were not available for adjustment in the subgroup analysis within the systematic review and meta-analysis. This potentially could be considered a residual confounder contributing to the socioeconomic risk effects observed.

In the analytical epidemiology, there was very low consumption of fruit and vegetables overall, and low consumption levels (one portion per day) were shown to be protective in

the age and sex adjusted models. However, this effect was lost in the fully adjusted model, possibly related to the small numbers or the swamping of risk effect by that of smoking.

7.3.2.4 Other behavioural-related risk factors

Three other potential 'behavioural' (in its wide sense) factors which may explain the link between socioeconomic factors will be considered here. These are: HPV and sexual behaviour, occupation related factors, and factors associated with interaction with health services.

HPV and sexual behaviour: The complex relationship between socioeconomic factors and sexual behaviour was assessed by Johnson *et al.* (1994). The equally complex relationships between both sexual behaviour and HPV and oral cancer risk were examined in Chapter 1. Johnson *et al.* (1994) describe how rates of partner change seem to be higher in higher social classes, while other high risk sexual behaviour is more frequent in the most socially disadvantages. The recognised strong relationship of cervical cancer with both HPV and with lower socioeconomic circumstances also provides further evidence to draw from. HPV and sexual behaviour may help explain some of the inequalities in oral cancer observed in the thesis. However, collecting information on individual's sexual behaviour was beyond the scope of the ARCAGE study utilised in the thesis.

Occupational exposure risk factors in the form of toxic or harmful effects are a potential explanatory factor for the association of low occupational social class and oral cancer. This was found to explain inequalities in a French study of laryngeal cancer (Menvielle *et al.*, 2004). This remains a potential explanatory factor, however, examination of this was beyond the scope of the studies in this thesis.

Health services are always proposed as having a role in inequalities in health and internationally access to health services are very much socioeconomically determined (Marmot and Feeney, 1997). However, inequalities in health exist in the UK and Sweden with universal health care provision and also in the USA where nearly 20% are not covered by medical insurance (Marmot, 2006). In terms of inequalities in oral cancer, health services are more likely to have a role in the inequalities in mortality and survival rates, which are a function of treatment or access. The focus of this thesis is oral cancer incidence and it is unlikely that health services have a role. However, in terms of prevention, it may be argued that health services could have an influence on incidence rates – if an effectively developed screening programme which identifies and manages

potentially malignant lesions could be established. However, as discussed in Chapter 1, there is limited evidence across the whole spectrum of requirements for an effective screening programme.

Another potential role for health services is provision of health education and prevention advice. However, it is widely recognised that such approaches may contribute to increasing inequalities as the messages are taken up more readily by the highly educated and affluent (Schou and Wight, 1994).

Smoking cessation services are also considered as having a role to play in preventing oral cancer (Macpherson *et al.*, 2003; Watt *et al.*, 2003). However, Bauld *et al.* (2003) found that smoking cessation services were less effective in more deprived areas (albeit their data were self-reported four week quit outcomes). Therefore, there is a potential risk that smoking cessation services may also increase inequalities.

7.3.2.5 Cultural explanations

While cultural aspects were not explored directly in the analyses in this thesis, they are important to consider in terms of contextualising, understanding, interpreting, and potentially explaining the findings.

Hanlon *et al.* (2005) recently explored the possibility of what they described as a 'Scottish effect' to explain higher mortality rates in Scotland than in England and Wales between 1981 and 2001, when a decreasing influence of socioeconomic deprivation was observed in the data. While the 'Scottish effect' was not fully defined, one interesting possibility raised was the cultural explanation. This was described as arising from social factors and in particular deprivation, which potentially impact on the collective psyche, affecting health through behaviours and also more direct pathways.

Culture is not consistently defined in the social epidemiology literature although many common dimensions are described. Freeman (2004) provides a helpful definition of 'shared communication system; similarities in physical and social environment, common beliefs, values, traditions, and world view; and similarities in lifestyles, attitudes, and behaviour'. In Krieger's (2001b) glossary of social epidemiology, culture is encapsulated as meaning a 'particular way of life, whether of a people, a period, a group, or humanity in general'.

The role of ‘culture’ is not clearly explored in the literature – at least not under a ‘cultural’ heading. However, many of the components of what could be described as culture have in fact been investigated as potential explanatory factors for inequalities. Freeman (2004), describes culture as the key determinant of disease and argues that the effects of poverty act ‘through the prism of culture’ to increase cancer risk, although this approach seems to extract the economic dimension (poverty) from the social dimension.

The ‘collective lifestyles’ model of community behaviour is potentially a way of capturing the collective or cultural dimension of behaviours. Frohlich *et al.* (2001) described this as behaviours being integral to social practices and norms. They exemplify this concept through the example of smoking, demonstrating that smoking behaviour is related to cultural aspects including: the sale of cigarettes, the places where people smoke, which groups are smoking together, and the perception of smoking in the community.

Another cultural dimension to behaviours, is the tendency for behaviours to ‘cluster’ – such that individuals and communities participate in multiple health-damaging behaviours together (Sanders *et al.*, 2005). This further confirms the consistency of the effects of the social environment on behaviours.

Thus, the relationships of the components of culture with inequalities in oral cancer may help explain the thesis findings. Where culture has a role in socially patterning behaviours (or lifestyles) was explored in detail above. The role of beliefs, values, views, and attitudes from Freeman’s definition, was explored in relation to individuals’ smoking behaviour (Section 7.3.2.1). How these relate to common or social norms is part of the next question.

Bringing culture of a different nature to the discussion: as pointed out by the Advertising Executive character Adrian, in the movie *Bliss* (Carey and Lawrence, 1985): ‘The entire economy of the Western world is built on things that cause cancer’. He is somewhat cynically referring to the products advertised and consumed as behaviours outlined above. However, he could equally be referring to the structures of the physical and social environment in which we live. Eerily, this sentiment seems to also relate to Nobel Prize winning economist Paul A. Samuelson’s theory encapsulated by his quote: ‘Profits are the lifeblood of the economic system, the magic elixir upon which progress and all good things depend ultimately. But one man’s lifeblood is another man’s cancer’ (Tinnin, 1976). The role of the social dimensions and environment will be discussed in detail in the subsequent sections.

7.3.3 Socioeconomic explanations of oral cancer incidence

Building on Marmot and Feeney's (1997) general explanations for inequalities in health, a heady list of potential socioeconomic explanations is developing. From Berkman and Kawachi's (2000) social epidemiology text, these include: socioeconomic status, relative deprivation and area-effects, income inequality, discrimination, working conditions, job insecurity, unemployment, social integration, social networks, social support, mental health, early life experiences, culture, and behaviours.

In recent years, the study of social factors in relation to health has begun to be dominated by two explanatory models – (i) the eco-social and (ii) the life course perspective – which have received increasing attention. Before discussing the thesis findings in relation to these models, a number of more specific social explanations and issues will be explored.

7.3.3.1 Social factors and the causation debate

The potential limitation of the nature of causation inference from social factors was outlined in Section 7.2.7. Returning to this debate for a final time will help with an understanding of the role social factors themselves potentially have in explaining socioeconomic inequalities in oral cancer observed in the thesis.

Kaufman and Cooper (1999) raised questions about the validity of epidemiological study designs in analysing social factors. These were based on the arguments that: (i) social epidemiology violates the 'counterfactual requirement' – such that valid risk estimates need individuals to be identical except for the 'exposure' or 'non-exposure' status of the factor in question; (ii) prerequisite knowledge is needed – the complex mechanisms that lead from social factors to health inequality in order to analyse the independent causal effect of a single social factor are poorly understood; (iii) in addition, they note that the pathway between social factors and behaviours is too complex and multidimensional to be possible to assess; (iv) finally they suggest that social factors need new analytical epidemiology approaches, and suggest systems modelling and 'interunit dependency models' common in communicable disease epidemiology. However, they do disagree with a long-standing criticism placed on social epidemiology, that social factors are non-modifiable.

Krieger and Davey Smith (2000) refute these suggestions on several counts. In a detailed response outlining the flaws in the counterfactual argument, they describe how such a

problem is not unique to social factors, as a number of non-social exposures such as concentration of lead in drinking water would have similar comparability issues. They argue what is flawed is not having the 'imagination' to hypothesise and research the role and underlying explanations of social factors. As they put it – epidemiologists have a 'responsibility' to do so. Finally, they believe that the methodological limitations are partly related to the relatively limited funding and research which goes into investigating social factors – which have left the research still at high level comparisons rather than exploring the pathways of their effects.

Kaufman and Cooper (1999) seem to put social epidemiology in a catch-22 situation, for understanding the mechanism is the ultimate aim of social epidemiology. Krieger and Davey Smith (2000) note that this aim of elucidating the mechanisms from the social to the biological is a real challenge.

Greenland (2005) recently reasserted the counterfactual argument against social factors, and his reiteration of the old adage that investigation should only be focused on exposures which can be modifiable. Susser and Schwartz (2005) responded that there was no logical reason to treat social factors any differently from other factors, as many factors, even such as smoking, do not have an exact opposite counterfactual position – removing the exposure smoking from individuals would not necessarily leave them similar to non-smokers, as they may for example drink more alcohol or be more depressed to compensate for stopping smoking. On the issue of social factors not being modifiable, they point to the range of initiatives to increase education levels worldwide as evidence to demonstrate the possibility of improving social conditions.

Other terms in which epidemiologists frame causal factors for disease include: 'fundamental and proximal factors' (Link and Phelan, 1996), 'distal and proximal factors' (Diez Roux *et al.*, 2004), or 'upstream and downstream factors' (Susser and Susser, 1996b). Generally, in each of these, the former term refers to social factors, while the latter to the factors related to the disease at the individual level. However, a difficulty with these distinctions is that it excludes the possibility of social factors having a more direct effect on health and disease.

This thesis has attempted to develop an overarching approach which follows a more traditional epidemiological approach to risk factors, but at the same time focus on social factors and the multilevels at which they operate.

It could not be argued that causation has been established. However, consistent associations between low socioeconomic factors and increased oral cancer have been presented. It is intended to assess the plausible mechanisms for this association through this present exploration of the potential explanatory factors.

7.3.3.2 Socioeconomic status vs. socioeconomic circumstances

The question here is what is most important – individual socioeconomic status, or area-based socioeconomic circumstances in terms of oral cancer risk?

Individual socioeconomic status: The traditional individual measures of socioeconomic status employed in this thesis reflect the dominance of these indicators in social epidemiology. Despite their limited scope, they are evidently able to capture some elements of the way society is stratified – providing consistent and strong evidence that they are major factors in determining health. This importance is emphasised given the knowledge that the wider social determinants seemingly go beyond these traditional measures to include differentials in economic and political power, and social environmental factors – which are largely outside the radar of these measures (Lynch and Kaplan, 2000). Individual measures of socioeconomic status were identified as independent risk factors in the systematic review and meta-analysis. Education, occupational social class, and income were all found to be associated with increased risk of oral cancer, over and above known behavioural confounding factors. Rather than reiterate the potential explanations related to each measure from the discussion in Section 4.5.4, their role will be revisited within the life course perspective in Section 7.3.3.6.

Area-based socioeconomic measures are often incorrectly inferred or interpreted from epidemiology as individual SES (Macintyre and Ellaway, 2000). In this thesis, the area-based measures used have been interpreted from an ecological point of view – suggesting that there is something in the nature of the environment (physical and / or social) which is associated with increased risk. The potential explanations for the area-based inequalities in oral cancer identified initially in the descriptive epidemiology of the thesis will be discussed in detail in Section 7.3.3.6.

Multilevel analysis: It was the intention in the analytical epidemiology to bring both the individual and area socioeconomic measures together in a multilevel multivariate analysis. This would have permitted an examination of individual SES controlling for area socioeconomic circumstances; in addition to an analysis of area socioeconomic

circumstances while controlling for individual SES. Macintyre and Ellaway (2000) outline how this approach may help to tease out the contextual and compositional socioeconomic factors, and detail the many studies which have begun to use multivariate analysis in this way. However, it may also be an artificial distinction which does not account for their inter-connectedness – as controlling for area effects may lead to ignoring the role of the social and physical environment, while controlling for individual SES may lead to ignoring the role of the individual socioeconomic status and experience. Another difficulty in these adjustments lies from the fact that the (traditional) area-based measures of socioeconomic circumstances are derived from data on the people who live there – and socioeconomically deprived areas could be so defined because of a concentration of poor people rather than factors of the social or physical environment (Macintyre and Ellaway, 2000). However, the new indices of multiple deprivation characterise the area by factors beyond those related to individual's census data (Carr-Hill and Chalmers-Dixon, 2002).

In the analytical epidemiology, attempts were made to bring both the individual and area perspectives together. While significant individual and areas socioeconomic effects associated with increased oral cancer risk were found, significance was lost following adjustment for behavioural factors. Further, there were no significant interactions between the individual and area effects when examined separately, and no significant independent effects on oral cancer risk were observed when they were examined in a multivariate model. These unclear findings were perhaps related to the limitations of the analytical epidemiology discussed earlier.

7.3.3.3 The role of unemployment

The particular socioeconomic status of unemployment and its potential role in oral cancer risk is worthy of some attention. The role of unemployment has been reviewed in many contexts in relation to health inequalities: Lynge (1997) assessed its role in cancer inequalities, while Kasl and Jones (2000), Bartley (1994) and Bartley *et al.* (2006) looked at the impact on health in general. Recently, the UK Health Development Agency undertook a systematic review of the evidence on the causal relationship between worklessness and health (Mclean *et al.*, 2005). In addition, a systematic review and meta-analysis has also recently been published (McKee-Ryan *et al.*, 2005).

The first problem in this area of research is the wide variation in the definitions of unemployment (Bartley and Ferrie, 2001). Ideally the definition should be aged defined and include only those who were involuntarily out of work. A general definition which

includes all those of working age who are not in work will also include those who choose not to do so – their inclusion would underestimate the true effects of unemployment.

The vast majority of the literature focuses on the role of unemployment on mental health outcomes, with physical health outcomes mainly related to subjective measures (McKee-Ryan *et al.*, 2005; Mclean *et al.*, 2005). Mclean *et al.* (2005) are very cautious about the direction of causality in the unemployment-health relationship. However, McKee-Ryan *et al.* (2005) were compelled to draw stronger conclusions on causality, as they found such consistent and repeated evidence (particularly from longitudinal studies that show health negatively affected following job loss and positively affected following return to work). Irrespective, all reviews are in broad agreement that unemployed individuals have lower psychological and physical health and wellbeing than their employed counterparts.

In relation to cancer, there is limited evidence investigating the role of unemployment in cancer aetiology. A review of record linkage studies with individual level data on unemployment and cancer mortality from eight studies in five 'western' countries (including the UK) by Lynge (1997) found a general excess risk of cancer mortality in men (unemployment data were limited for females). This excess risk was particularly evident for lung cancer (UK excess risk was nearly 2-fold), and was found to persist when individual social class, smoking, alcohol intake, and previous sick leave were adjusted for. In addition, she investigated the relationship of smoking with unemployment and found that becoming unemployed did not increase smoking. However, she did find that smoking prevalence was higher among unemployed men than employed men although these patterns had been set prior to when unemployment started. Lynge (1997) also acknowledges the problem of the causality direction i.e. does unemployment lead to cancer or vice-versa. In a parallel study, Lynge and Andersen (1997) found an excess risk of nearly 25% for cancer incidence among unemployed men and women in Denmark, comparable to the excess all cause mortality of 20-30% identified by Kasl and Jones (2000).

Oral or head and neck cancer was not considered in the review by Lynge (1997). However, a recent case-series study from the north east of England found that over 60% of the cases of oral cancer had experienced long-term unemployment, although alcohol and smoking behaviours were highly correlated (Greenwood *et al.*, 2003).

Explanations: In addition to behavioural explanations discussed above and in Section 7.3.2.2 (in relation to alcohol consumption), a number of other potential mechanisms have been theorised through which unemployment can lead to poor health.

Bartley *et al.* (2006) identify four potential explanations for the relationship between unemployment and health: (i) selection – this is the reverse causality explanation explored in section 7.3.1.2 ; (ii) poverty – this relates to the acute financial difficulties brought about by unemployment, but which are not usually recognised in the literature; (iii) health behaviours – discussed in Section 7.3.2.1 in relation to smoking, and in Section 7.3.2.2 in relation to alcohol consumption; and (iv) unemployment as a stressful life-event – which is inconclusively related to health outcomes in the literature, and in cancer research has been limited thus far (inconclusively) to breast cancer risk (Petticrew *et al.*, 1999).

McKee-Ryan *et al.* (2005) plunge even deeper into the theoretical explanations, including: (i) 'work-role centrality' – which is around the importance of work to an individual's 'sense of self', which may have cultural or belief-system roots; (ii) 'coping resources' – which include personal (e.g. locus of control, or self esteem), social (e.g. social networks – families, friends), financial (e.g. adequate reserve or other sources of income), and 'time-structure' (ability to organise / use time) resources; (iii) 'cognitive appraisal' – which relates to self-perception or interpretation of the effects of unemployment; (iv) 'coping strategies' – which are in two general forms: 'problem/control' focused (e.g. job seeking, retraining, relocation) or 'emotional/symptom' focused (e.g. managing symptoms through seeking social support); and (v) 'human capital and demographics' – which are related to individual socioeconomic status (e.g. education, occupational social class), or demographic factors (e.g. age, sex, marital status). Other external factors to which McKee-Ryan *et al.* (2005) give attention are the length of unemployment, and the contextual unemployment rate, and welfare benefits arrangements. In addition, in their meta-analysis they find much empirical evidence to broadly support theories (i), (ii), (iii), and (iv), but not (v) particularly with regard to mental health. These effects were magnified with longer duration of unemployment and also in those who were school leavers rather than mature unemployed. Unemployment benefits were also not found to protect individuals from the adverse effects of unemployment.

There seems little doubt that unemployment is a highly stressful experience which impacts on those who lose their jobs in terms of their stress levels, mental health, behaviours, and physical health (including cancer risk). Unemployment was investigated in the analytical study in the thesis, at a relatively superficial level and experience of unemployment was

found to be a significant risk factor in the unadjusted analysis. There was no interaction observed with the area-based measures of socioeconomic circumstance, and the significant effect was lost when adjusted for smoking and alcohol behaviours and in the multivariate analysis. While this provides some limited evidence in support of a behavioural pathway, the study limitations inhibit strong conclusions to be drawn.

7.3.3.4 Socioeconomic position vs. socioeconomic inequality

The term socioeconomic position is used here to recognise the position on the hierarchy of both the individual socioeconomic status scale and the level of area socioeconomic circumstances or deprivation. This section will attempt to assess whether socioeconomic position or socioeconomic inequalities are potentially important in determining health – related to oral cancer risk.

The contemporary British philosopher, Alain de Botton (2004), wrote an eloquent thesis entitled ‘status anxiety’ drawing heavily on writing from the fields of philosophy, history and politics. The main thrust of his work focuses on how one’s relative socioeconomic status leads to ‘anxiety’ and ‘sorrow’. He quotes Adam Smith, the pioneering Scottish economist of the 18th century, to outline his argument: ‘The rich man glories in his riches because he feels that they naturally draw upon him the attention of the world. The poor man on the contrary is ashamed of his poverty’. Anxiety, de Botton argues, comes mainly from the inherency and magnitude of the relativeness of the status of an individual in relation to others in the community, rather than his or hers absolute position. Further, de Botton notes, the nature of the anxiety resulting from status is out of ‘lovelessness, snobbery, expectation, meritocracy, and dependence’ – with broad brush ‘solutions’ such as: ‘philosophy, art, politics, Christianity and bohemia’. However, there is a prevailing theme that the ‘anxiety’ he refers to is an individually self-induced response related to ‘envy’, and that it will always be so unless society is organised in non-hierarchical strata. While he focuses on the symptom of anxiety, rather than the wider outcomes of health or wellbeing – although he could just as easily have been – many parallels exist with health inequalities research. In fact, in describing health inequalities resulting from socioeconomic status Marmot (2006) has used the term ‘status syndrome’, while Wilkinson earlier had written an overview entitled ‘health, hierarchy, and social anxiety’ (Wilkinson, 1999).

Examples of this are highlighted in the text of Brunner and Marmot (2006) which draws comparisons between the health impacts of the social hierarchies in observational animal

studies on baboons (and experimentally manipulated social status of macaque monkeys) with that other group of primates, humans – in the Whitehall civil servant studies. Similarities in terms of common psycho-social responses to stress are observed in those of similar relative social status between the species.

Picking up the quote from Adam Smith (above) which relates to relative incomes, the majority of the research on how inequalities impacts on health is in relation to income inequalities, however, this has thus far been at the country or area-level (Kawachi, 2000). Wilkinson (1992, 2005) has led the way in this through his pioneering work comparing inter-country distribution of wealth with life-expectancy. He has consistently argued that it is in the distribution of the income rather than the material deprivation per se which is the source of health inequalities – with the more unequal the society the lower the life expectancy. However, this position is not without its detractors (Judge, 1995; Lynch *et al.*, 2000). The main hypothesis Wilkinson (2005, 2006) uses to explain how income inequalities translates to life-expectancy and health outcomes is through social capital, which will be discussed in Section 7.3.3.7.

Within-country income inequality in relation to health has received less attention. Kawachi (2000) described the Robin-Hood Index – as being the proportion of income that must be redistributed to attain perfect equality of incomes – in a comparison of inter-state mortality rates in the US. A minor increase (1%) in the Robin Hood Index was associated with an excess mortality of 21.7 per 100,000 deaths per year. More recently, economic analyses have attempted to look at the effect of absolute or relative income on health outcomes at both area and individual levels. This will be picked up in the following section on income.

In the UK, the Whitehall studies, described by Brunner and Marmot (2006), provide strong evidence of health inequalities related to individual socioeconomic status. Occupational social class was found to be strongly related to premature heart disease, over and above classic risk factors (such as smoking, cholesterol, and blood pressure) – the risk increasing with every step down the social hierarchy. These studies focus on health outcomes at different positions rather than the extent of social inequality in relation to the health outcome. However, in the potential explanations for the differences it is in the relative nature of the positions where they propose the answers lie. Those higher up the hierarchy potentially have: more control of their environment, have feelings of supremacy and dominance, and are better able to cope with stress than counterparts in lower strata.

This thesis did not assess the effect of the gap in socioeconomic inequality on oral cancer – although investigating this in relation to health outcomes beyond that of mortality has been identified elsewhere as a gap in research (Kawachi, 2000). However, through examination of the effect of the position (particularly low position) on both the individual and area-based socioeconomic measures with their hierarchical scales, identification of inequalities in the risk of oral cancer has been possible.

Finally, in this section, turning to the qualitative work on perceptions of inequalities introduced in Section 1.3.1.6, it seems that people are becoming more perceptive of socioeconomic inequalities and their role in health and disease. To these ends, Adler and Ostrove's (1999) promising work on developing direct individual measures of subjective social standing may help capture this. 'Awareness' of relative socioeconomic inequalities, rather than act as an explanation for health inequalities (an extension of de Botton's argument), seems to be more of an outcome itself. While the public seem to be increasingly aware of the socioeconomic factors related to health, the next step in the logic is awareness of the structural, economic and perhaps exploitative causes of these socioeconomic inequalities. However, as Wainwright and Forbes (2000), after Marx, pointed out 'such insight was the stuff of revolution'.

7.3.3.5 Economic resources

Jones and Wildman (2004), from a health economics perspective, described the nature of the relationship between income and health to be poorly understood. They defined two broad areas of potential impact: (i) individual income effects; and (ii) aggregate income effects (including relative deprivation, and income inequality). They described the first as having a direct link and the latter an indirect.

Following on from the previous section, the role of income in health provides an opportunity to explore the nature of relative and absolute socioeconomic effects, at both the individual and area levels.

Lynch *et al.*'s (2004) comprehensive systematic review found limited evidence from examining both area and multilevel (area and individual) studies to support the hypothesis that income inequality is a direct determinant of population health. However, they found abundant evidence that at the individual level lower levels of income adversely affect health. They concluded that income inequality is a function of a socioeconomic system, whereas income per se is characteristic of the individual; and related this to Rose's (1985)

earlier hypothesis that the 'cause of the cause' at the individual level may be different from that at the population level.

More recent studies are in broad agreement with Lynch *et al.* (2004). However, Jones and Wildman (2004) and Lorgelly and Lindley (2007), analysing data from the British Household Panel Survey, find no evidence to support the effect of relative income (or income inequalities) on health outcome – rather it is the absolute level that seems to be most important.

However, Wilkinson (2006) recently presented further evidence to show that the vast majority (80%) of studies at the area-level investigating found worse health inequalities where wider income distribution inequalities were present.

Wagstaff and van Doorslaer (2000), expanded by Lynch *et al.* (2004) – but combined here – set out the following hypotheses (which are yet to be fully tested) through which income affects health as: (i) absolute income or deprivation (poverty); and (ii) relative income or income inequality. The potential explanations for the former hypothesis include the recognition that individual income is related to occupation, which in turn is related to education and training (Lynch and Kaplan, 2000). Income also has the potential to 'directly' affect health through a range of factors, such as the ability to buy healthy food and products, access exercise opportunities, transport, and quality of housing. The explanations for the latter hypothesis potentially lie in two social theories – the psychosocial which will be covered in Section 7.3.3.8, and the neo-materialist which will be discussed here.

Lynch *et al.* (2000) adopted 'neomaterialist' theory as a potential explanation for health inequalities, giving the materialist explanation a 'new' label in the acknowledgement that economic circumstances have changed over time. In the present era, in relation to epidemiology, the diseases of concern are mainly chronic diseases, distinct from the 'materialist conditions' of the 19th century associated with infectious diseases. Neomaterialism also acknowledges that in addition to individual income resources, there are a number of other economic and social infrastructural factors that can affect health including the availability of healthy food, recreational facilities, transport, housing stock, education, and health services.

Therefore, it seems income can potentially affect health in many ways at both individual and population (aggregated or area) levels. In relation to oral cancer risk, widening

inequalities in the distribution of oral cancer observed at the area level may be related to the income associated with the deprivation or poverty levels in the areas or rather the individuals living in these areas. The infrastructural resources of the areas may also be a factor. As observed from the data in Chapter 4, at the individual level low income measures in a few studies from around the world (although mainly the Americas) demonstrated a significant increased risk with low income relative to high income in the study populations. In the analytical epidemiology of this thesis, individual income was not a variable collected, although the area-based socioeconomic measure (SIMD) which contains an income domain was used in the analysis. Residence in the most deprived area (by SIMD score) was significantly associated with increased risk for oral cancer, however, this risk was lost when behavioural factors were considered.

7.3.3.6 Social explanations

The following social theories will briefly be explored as potential explanations for the inequalities in oral cancer observed: (i) social production of disease; (ii) psychosocial, (iii) social capital; (iv) eco-social; and (v) life course.

Social production of disease: The secular trends in social, economic, and cultural factors may play a role in explaining the trends observed in oral cancer in this thesis. The social and economic factors were reviewed in Section 1.3.2, and the trends in the behavioural and cultural factors were explored above.

While not necessarily causal, they provide an additional contextual explanation to explain the trends observed. The trends in inequalities observed in oral cancer in this thesis, are also similar to a range of health outcomes in Leyland *et al.*'s (2007) recent work on cause-specific mortality rates.

To the author's knowledge, this was one of the first health inequalities study to propose that the theories of Scottish social and political historian, Tom Devine (2006), could be a potential explanatory factor. Devine's thesis details the post-industrial decline and emergence of deprivation and the social and economic divide in Scotland. These trends mirror the emergence of the widening inequalities in oral cancer observed. Recent work in Scotland has attempted to examine impacts of policy on addressing health inequalities (Blamey *et al.*, 2002), while Davey Smith and Lynch (2004a) examined historic trends in mortality in Britain related to major political, social and economic change.

This form of explanation is coming towards what Krieger (2001b) described as the 'social production of disease' model. A model focused on the fundamental social and economic causes of disease (Link and Phelan, 1996). While honourable, Krieger (2001b) argues, such an approach is limited in theory, and is almost too far focused 'upstream' (to use the key metaphor of the proponents of this theory) to be helpful in understanding the mechanisms of inequalities and formulating policy which goes beyond structural and societal change around living standards and equity. She argues that such research can only be limited to comparative descriptive epidemiology. However, this seems to somewhat miss the point, identifying the problem in the first place, as shown in this thesis is an essential first step. Not only does this gauge the extent of the problem, but it also generates hypotheses which can be explored in more detailed research to understand the pathways.

Psychosocial: In response to Lynch *et al.*'s (2000) neomaterialist explanation of health inequalities – where they argue against the importance of relative income inequalities and more in terms of absolute poverty as having the key role – Marmot and Wilkinson (2001), set out the arguments as the main advocates of the psychosocial explanation. The centre of their thesis is that psychosocial pathways arise from relative disadvantage over and above direct material disadvantage. As they put it: 'Social dominance, inequality, autonomy, and the quality of social relations have an impact on psychosocial wellbeing and are among the most powerful explanations for the pattern of population health in rich countries'.

Marmot with colleagues have led the research in the area of the psychosocial mechanisms, through which inequality gets (as they put it) 'under the skin' (Marmot and Wilkinson, 2006). Their research focuses on investigating the biologically plausible pathways between inequality through loss of social capital (see Section below) and the resulting 'stresses' it brings. In turn, neuroendocrine responses, including the chronic secretion of stress-response hormones, and in particular the inability to cope or recover from this, may have an impact on the immune system, especially in relation to the cardiovascular system. Most of the evidence on this is in relation to cardiovascular disease (and also depressive illness), and it has been less applied to cancer aetiology research. However, it is possible to see a potential read-across in that the immune system, and a chronic inflammation in particular, have been implicated in the aetiology of cancer (O'Byrne and Dalgleish, 2001).

A further potential strand to the psychosocial explanation comes from the work by Everson and colleagues (1996). In their Finnish longitudinal study they found that men with high self-rated feelings of 'hopelessness' – which correlated with low socioeconomic status – were at increased cardiovascular and cancer risk. This suggests a possible association with

mental health related conditions. However, an elevated cancer risk associated with depressive disorders was not found in the review by Lynge (1997).

In relation to the thesis findings – the psychosocial pathway may help explain the pathway from individual socioeconomic status to oral cancer risk consistently observed over and above the behaviour effects in the systematic review and meta-analysis. Specifically, the results in relation to the oral cancer risk associated with low occupational social class may have some explanation in Marmot *et al.*'s (2006) research on the psychosocial impacts of work stress (which can range from job insecurity, to job control and demands, to effort and reward imbalance) – although as yet there is only empirical evidence in relation to coronary heart disease, musculoskeletal disorders, and mental illness.

In addition to the potential 'direct' effects from psychosocial factors, they may also exert an indirect effect through influencing behaviours (see Section 7.3.2).

Social capital was defined by Szreter and Woolcock (2004), in a recent comprehensive review forming part of a debate on the topic in the *International Journal of Epidemiology*. They defined social capital as incorporating a range of overlapping social concepts including: social cohesion, social support, social integration, civic society, and social networks. They also interestingly point out that the theories of social capital are central to both the neomaterialist and psychosocial explanations for the links between socioeconomic inequalities and health.

In the same debate, the 'father of social capital', Robert Putnam (2004), recently argued that their was some evidence starting to suggest that relationship between social capital and income inequalities could operate the other way – such that increasing social capital could lead to more egalitarian policies which reduce income inequalities.

There have been many mechanisms through which social capital is proposed to connect with health – both theoretically and empirically (Berkman and Glass, 2000). In summary, these relate to the psychosocial aspects of social support, social influence, social engagement, person-to-person contact, and access to resources and material goods. The pathways through which these psychosocial mechanisms operate have been proposed as: behavioural (e.g. smoking, alcohol, diet), psychological (e.g. self-esteem, coping effectiveness, mental health, boosting feelings of safety and trust), and physiological (e.g. neuroendocrinal, allostatic load, immune system function – see Section 7.3.3.7 for discussion of biological mechanisms).

As noted above, Wilkinson is the big proponent of the argument that increased income inequalities leads to loss of social capital, quoting Plato to simplify the concept 'equality leads to friendship' (Wilkinson, 1999), and from reduced social capital arise health inequalities. The evidence of correlation between income inequality and health inequality seems broadly consistent and robust (Wilkinson, 2006). However, a range of qualitative and quantitative evidence relating social capital and health was recently reviewed as part of the Scottish Community-led Supporting and Developing Healthy Communities Task Group and was found to be somewhat conflicting – with significant links shown in larger compared with smaller area studies (Mackinnon, *et al.*, 2006). Wilkinson (2006) seems to concede that there is weaker evidence from studies of smaller areas, although he feels that much of the research into both inequalities and social capital controls for a number of variables which may mediate the effects (such as poverty, individual income, welfare, education, behaviours, urbanisation, etc.).

There were no direct measurements of social capital within the thesis, however, it is an interesting pathway through which health inequalities (including those observed for oral cancer incidence) could arise although more empirical evidence is required.

Eco-social: First termed by Krieger (1994), the eco-social model was reasserted by Krieger (2001b) as the key theory to explain health inequalities. It has echoes of Macintyre and Ellaway's (2000) call to refocus on the physical and social environment – the people and the places. It also attempts to capture the range of social environmental factors outlined by (among others) Evans and Stoddart (1990). It aims to encapsulate the interconnectedness of the 'macro' (wider environment) with the 'micro' (individual perspective), and also explicitly acknowledges social, economic, and political factors. The eco-social explanation attempts to bring together the elements of the social explanations (social production of disease, psychosocial, and social capital theories) with the biomedical explanations (behavioural theories) – through a renewed emphasis on environments.

The area-based socioeconomic circumstances per se are an interesting possibility to consider with the findings in the thesis. While area measures have previously been criticised as 'ecological fallacy' – as individuals are allocated an area socioeconomic status based on their residence – this may in fact help with an explanation. As Pearce (2000) put it 'the ecological fallacy strikes back'. Pearce (2000) and Macintyre and Ellaway (2000) set out the convincing case that the ecological perspective (and the way it is measured in terms of socioeconomic level) can provide important insights. They also argue that people who live in the same area can share many of the socioeconomic circumstances not

reflected by individual measures, in that the socioeconomic environment affects health and wellbeing apart from or over and above that of the individual. Macintyre and Ellaway's (2000) distinction between contextual (place related) and compositional (people related) are the key elements in a multi-level perspective.

Thus, the eco-social model may permit the breakdown of the explanation of inequalities in oral cancer observed to discrete, but interlinked potential pathways at multilevels, but with an area focus. These could include: (i) economic and social deprivation related to the physical environment (e.g. healthy food access, availability of low cost alcohol, poor housing, environmental pollution, transport, recreational facilities); (ii) economic and social deprivation related to the social environment (including 'social trauma' from e.g. fear of crime, social isolation, discrimination; and 'physical trauma' from e.g. alcohol, smoking culture); (iii) targeted marketing of harmful products to deprived area; (iv) inadequate area-services (e.g. education, health, transport, recreation).

As Krieger (2001b) points out, this attempts to consider the problem by 'more than simply adding 'biology' to 'social' analyses, or 'social factors' to 'biological' analyses. The ecosocial framework begins to envision a more systematic integrated approach capable of generating new hypotheses, rather than simply reinterpreting factors identified by one approach (e.g. biological) in terms of another (e.g. social)'. However, it also suggests that much research is needed as few of the potential pathways have been studied in detail.

In the thesis, both area-socioeconomic circumstances in the descriptive epidemiology and individual socioeconomic status in the systematic review and meta-analysis were found to be associated with increased oral cancer risk. However, the analytical study which brought them together was insufficient to disentangle their effects.

Life course: Receiving a lot of attention in recent years, the final potential explanation of social factors impacting on health, is the life course approach (Kuh and Ben-Shlomo, 2004). This model suggests that adult health and disease is determined by socioeconomic factors earlier in life – particularly early or childhood life. One of the first studies to examine the impact of timing and duration of socioeconomic status on health was the 'Midspan' series of large cohort studies in the West of Scotland which looked at (among many other things) life-time occupational social class, in addition to father's occupational social class and found that those with fathers in manual social classes and who remained in manual social classes for their lives had the greatest mortality risk from all causes, including cancer (Davey Smith *et al.*, 1997b). Increasingly, a number of studies have

repeated these findings and begun to show independent effects of childhood socioeconomic status (SES), controlled for adult SES (Kuh *et al.*, 2004). There are two main, but overlapping, socioeconomic pathways outlined by Kuh *et al.* (2004) between child and adult health: (i) parental socioeconomic status and circumstances influence childhood socioeconomic prospects including social and economic resources particularly educational attainment which affects adult socioeconomic status and circumstances (– the effects of which have been explored extensively above); and (ii) the second explanation is that socioeconomic factors impact directly on biological processes involved in development from gestation through to adulthood. The latter explanation is receiving a lot of attention including relating birth weight and size to long term health outcomes with an increasing focus on social factors (Kuh *et al.*, 2004). Most of the empirical evidence is related to cardiovascular disease (Davey Smith and Lynch, 2004b), but while oral cancer has not been considered through a life course approach, emerging research into breast, prostate, and testicular cancer suggests that childhood environment may have a role in the aetiology (Kuh and Ben-Shlomo, 2004).

In relation to the thesis findings of inequalities in relation to oral cancer, there were no data available related to assessing the second explanation (although it is hypothetical). There were data through which the first explanation could be explored. Father's occupational social class is the most frequently used measure of childhood socioeconomic status (Galobardes *et al.*, 2006a). However, this information was not available within the thesis datasets. Individual's educational attainment was available (in the systematic review and meta-analysis and in the analytical epidemiology) and this is able to capture elements of childhood socioeconomic status (Galobardes *et al.*, 2006a). In addition, life-time occupational social class histories were available in the analytical epidemiological analysis.

Low educational attainment was found to be associated with an almost 2-fold increased risk in the systematic review and meta-analysis. This association remained even when smoking and alcohol drinking behaviours were taken into account. Similar findings were found in the initial age and sex analysis in the case-control study, with an almost 2-fold protective affect associated with high educational attainment. However, significance was lost when behavioural factors were adjusted for.

In addition to the behavioural explanations of the relationship between education and health, a number of possible pathways have been proposed. Kuh *et al.* (2004) acknowledge that the pathways for the relationship between education and health are not fully

understood, but propose two main explanations. Education: (i) reflects family background (parents' education, socioeconomic status, and area-socioeconomic circumstances); and (ii) predicts adult occupation and income. Kuh *et al.* (2004) expand on these from a life course perspective, reporting the evidence that parental education had an effect over and above an individual's educational attainment. They suggest that other factors related to parental education, such as motivation, direction, and speech, in addition to financial support and social contacts, powerfully influence adult socioeconomic status.

The other hypothesised pathways were discussed in Chapter 4 and noted by Berkman and Macintyre (1997), and Yen and Moss (1999). They focus on the role of education in reflecting access to health care and health information. However, they go beyond knowledge about risky health behaviours, to outline how education may help determine values for the future, cognitive ability and decision making, and locus of control. All of which could have an impact not only on behaviour, but also in terms of coping with psychosocial influences, and building social networks and capital. A final point worth noting is that education, as described in the systematic review and meta-analysis, is place and time dependent and the context is therefore important to the interpretation.

Occupational social class was found to be a more important predictor of mortality risk than educational status in the Midspan studies (Davey Smith *et al.*, 1998). This suggests that, in a UK setting, adult socioeconomic status and exposures may either have a more powerful impact on health, or better capture socioeconomic status. The occupational social class related to occupations across adulthood, in the thesis analytical epidemiology enabled the possibility of exploring the impact of social mobility, although the results were unclear. Due to the small numbers the occupational histories could not be analysed using a comprehensive life course analytical model which could take into account the timing and duration of 'exposure' to each social factor – in addition to relating this (occupational) life course grid to the behavioural exposures.

Lastly, in relation to the life course explanation, but also not collected in the thesis studies, an additional element of the socioeconomic pathway between child and adulthood is the role of health behaviours in childhood and adolescences on potential impacts on health behaviours in adulthood (– the effects of adult behaviours have been discussed above) (Kuh *et al.*, 2004).

7.3.3.7 Biological pathways

The pathway from social factors to biological change in the aetiology of cancer is not entirely clear.

While this thesis has focused on the social factors related to oral cancer, it is important to realise that integral to the translation of aetiological factors to pathogenesis of the condition are physiological and biological processes. Clearly, from the explanations explored above, there is much potential for this change to occur via behavioural factors leading to carcinogenic exposures, but also, in terms of the social factors the main potential explanation is related to stress. However, in cancer aetiology this very much remains a hypothesis.

The basis for the stress hypothesis is the bringing together of three strands of theory and empirical evidence: (i) health and disease are socially patterned (as has been demonstrated in this thesis in relation to oral cancer); (ii) both stress and the response to stress are similarly socially patterned (as discussed in Section 7.3.3.6; and Marmot and Wilkinson, 2006); and (iii) such stress and the response contribute to the aetiology of chronic diseases, such as oral cancer (although the evidence is stronger for cardiovascular disease at present).

Biological processes also underpin the life course approach – including 'Barker's hypothesis' of 'biological programming' in fetal and early life (Barker *et al.*, 1992). This hypothesis relates to their finding of the relationship between low birth weight (suggesting inhibited intra-uterine development) and subsequent adult cardiovascular disease. While this specific relationship has been questioned by more recent larger studies and systematic reviews, Perry and Lumey (2004) have broadened the hypothesis to include consideration of: fetal and maternal genotype; maternal nutrition and behavioural factors; and maternal social and physical environment – related through physiological and biological factors important for fetal growth, but also including early infant environment and development.

The biological pathways between socioeconomic stresses and cancer development are not entirely clear, but emerging hypotheses include the 'biological ageing' effects resulting from poor socioeconomic circumstances (Adams and White, 2004). The biological ageing hypothesis basically proposes that poor people age faster due to the social and physical environments to which they are exposed – such that poor people die younger, but from the same conditions as their richer counterparts.

Adams *et al.* (2005b) followed up the biological ageing hypothesis with an interesting cross sectional analysis of cancer registry data in the north east of England. Modelling the interaction of age at diagnosis with socioeconomic deprivation for the major cancer sites (lung, colorectal, prostate, and breast), they found that age at onset of all (apart from breast) cancer was younger with increasing deprivation. However, the biological processes of ageing remain poorly understood in relation to both age and cancer genesis.

There may also be a genetic role within this socioeconomic – biological ageing – cancer aetiological pathway, perhaps mediated (or (bio-)marked by) shortened telomeres as discussed in Section 1.4.5.16 (Cawthon *et al.*, 2003; Adams and White, 2004; Epel *et al.*, 2004). However, more recent evidence emerging is conflicting on the relationship between socioeconomic factors and telomere shortening. One large US female-twins study found a marginally significant relationship with low socioeconomic status and shortened telomeres, after adjusting for potential confounders including behaviours (Cherkas *et al.*, 2006). However, Adams *et al.* (2007) failed to find a relationship in a smaller, albeit more homogenous (in terms of the major determinant of age), study group in the north east of England – although the participation rate (under 30%) was very low.

7.3.3.8 Explanations for poverty and inequality themselves

In the same way as this thesis has urged one to think of the role of socioeconomic factors either directly or as causes of the causes in relation to oral cancer, it would be remiss to ignore the causes of the socioeconomic factors and circumstances themselves.

Mooney (2003) outlines the main sociological explanations of poverty and inequality: (i) the ‘cultures of poverty’; (ii) the ‘underclass; (iii) Marxist or structural explanations; and (iv) the ‘cycle of deprivation’.

Culture (in this case meaning system of values, beliefs, and norms regarded as normal for a group of people) as an explanation for poverty, according to Mooney (2003), focus on: attitudes, lifestyles, habits, and the structures within family life of the poor. Debate remains about the existence of a culture of poverty and whether it is in fact a response to conditions of poverty not as cause. This approach has also been criticised as ignoring wider structural issues and inequalities in society that marginalise the poor. Responses to this explanation are seen as victim blaming – which have parallels in the lifestyle focus of behaviour change health promotion responses to health inequalities.

Buckingham (1999) set out the debate on the existence of the 'underclass' in Britain, and reviews the competing theories and evidence. These include: the behavioural approach relating to work (which focuses on opting out of work and reliance on benefits); labour market approach (which relates to the collapse in demand for semi- or unskilled work); and the critical approach (which argues against its existence). Buckingham finds some evidence for its existence from the British National Childhood Development Study cohort, with the underclass being defined as being distinct in family structure, work commitment, and political allegiance. Novak (2001) is a key critic of this underclass discourse – arguing that the notion of the 'underclass' has echoes of the 'disreputable poor' definition of poverty (discussed in Section 1.3.1.4). Further, he notes the underclass argument describes not so much a lack of resources (or indeed of structural issues which are rejected) more that it is to do with lifestyle choice, behaviour and values – including a rejection of the work ethic. He also points out that a primary difficulty with the idea of an underclass remains the lack of evidence for its existence and indeed for a homogenous, subgroup who meet a pre-existing set of objective criteria for inclusion in such a class. Therefore, he argues, it seems likely that 'the underclass' is a pejorative explanation of a 'middle class' set of values and explanations of what is defined as anti-social and what is poverty – but again largely excludes the role of society and structures in the cause of poverty and inequality.

The main thrust of the original Marxist explanation, according to Novak (1995), is to view poverty in the context of the struggle between classes and the inequalities as a result of the organisation of a capitalist society – with the argument that if the goal is the accumulation of wealth, then accumulation of poverty has to be acknowledged as a consequence. Mooney (2003) notes that this perspective is alone in viewing poverty not in isolation from wider societal structural influences. From a Marxist perspective, poverty is always viewed in terms of inequality between an affluent controlling powerful minority over a repressed majority of ordinary workers – and the spectrum of inequality lies therein (Novak, 1995). Novak (1995) points to several paradoxes – (i) poverty is essential (rather than a by product) for wealth to exist; (ii) even where absolute poverty of hunger is largely gone, the pursuit of consumerism has divided society and stretched inequalities and saddled many in debt; and (iii) the paradox of the ever-growing middle class – on one side the owners of capital and on the other the poor: dependent on wages, protected economically to a degree, but at the same time with issues of job insecurity, forced redundancy and the consequences of deprivation.

Finally, the cycle of deprivation has been evoked as an explanation both from the cultural or behavioural perspective (Mooney, 2003) and from the structural, Marxist perspective to help explain poverty and inequality (Novak, 1995). Mooney (2003) discusses 'intergenerational poverty' in terms of the potential for behavioural, family, work culture to persist and be reproduced across generations. Novak (1995) argues that it is the economic cycle that produces at the same time wealth and poverty.

Lastly, the explanation of the problem of poverty and inequalities may lie in the earlier writings of the now Prime Minister, Gordon Brown (1983), where he remarked 'what some people call the problem of poverty, others call the problem of the riches'.

7.3.3.9 Concluding remarks on the explanations

The relative importance of each explanation remains a debate in wider inequalities research. However, across much health inequalities research there is wide acceptance of the role of social factors over and above behavioural explanations, and the debate has progressed to focus on the relative importance of the material vs. psychosocial (Lynch *et al.*, 2000), or eco-social vs. life course (Monden et al., 2006) social explanations.

As noted as early as in the Black Report (Department of Health and Social Security, 1980), the explanations for health inequalities do not have to be mutually exclusive. Even in studies that have focused on one explanation, more than one potential pathway has been identified – explanations and pathways are also likely to overlap and be inter-related and not independent (Monden *et al.*, 2006).

However, it is likely that the explanations for the inequalities in oral cancer incidence, boil down to: (i) Rose's (1992) 'cause of the cause' hypothesis – with the behavioural risk factors being widely accepted causes for oral cancer; (ii) more 'direct' roots from social factors. The analytical epidemiology provided somewhat limited evidence that social factors were medicated through behaviours, or rather smoking behaviour. However, this was not the picture from the systematic review and meta-analysis of 41 similar (but generally bigger) case-control studies, which found socioeconomic risk effects associated with oral cancer independent from behavioural confounders. Therefore, there seems to be at least some unexplained socioeconomic effect.

Finally, in explanatory terms, one is attracted to Phil Hanlon's 'It all matters' hypothesis (Hanlon *et al.*, 2006) – which describes the emergence of health and health inequalities in a

population as being a ‘complex interplay between physical environment, social environment, individual response and behaviour, genetic endowment, and the provision of services’. This captures the complexity of health and equally disease aetiology.

7.4 Outstanding hypotheses and further research

7.4.1 Outstanding hypotheses

The very nature of epidemiological study is that it continually raises more questions than it answers. This is particularly true of the descriptive epidemiology of the thesis. Outstanding hypotheses resulting directly from the thesis research include:

The explanation of socioeconomic inequalities in oral cancer remains unanswered. This includes determining which components of socioeconomic status and circumstances are most important – individual or area factors.

The extent to which socioeconomic factors explain the burden of oral cancer in relation to behavioural factors is not clear – both in relation to their impact on behavioural factors and through other pathways.

How inequalities in oral cancer differ by country and region of the world remains open – this includes determining the effect of context of the country profile including its development status.

The potential pathways through which social factors translate to oral cancer risk have been identified, but the mechanisms, particularly with regard to the socio-biological pathway, remain unknown.

7.4.2 Further work

‘The bottom line, it almost always seems, is that “more research is needed” – a conclusion comforting to epidemiologists working in the field’ – Davey Smith (2001) somewhat cynically pointed out. He was suggesting this conclusion from epidemiology was a significant limitation of epidemiology, stemming from concern that both positive and negative findings seem to always warrant further investigation. However, the same conclusion could be drawn from almost all areas of research.

In relation to taking forward research to address these outstanding hypotheses and beyond, an exhaustive 'shopping list' of ideas and potential projects could be outlined. The following suggested further research will focus on the priorities for research, including the methods that could be adopted, the feasibility, and the potential benefits and implications of the work.

Descriptive epidemiology: In descriptive epidemiology terms, the burden of oral cancer in relation to socioeconomic circumstances of areas has not been fully determined. For Scotland, recently developed methods by Boyle *et al.* (2005), including creating consistent geographic areas over time, may be useful to tease out the area-deprivation effect in relation to geographic areas and assess clustering in distribution. In addition, descriptive epidemiology based on the SIMD (Scottish Executive, 2004c) for more recently available data may provide more insights. In consideration of the UK picture, it would be worthwhile assessing whether the Scottish deprivation pattern and trends were replicated elsewhere. Internationally, oral cancer incidence epidemiology has not been investigated recently in detail. This could be undertaken, incorporating ecological socioeconomic factors, to begin to get a picture of inequalities in oral cancer at the global level.

In general, future descriptive epidemiology may provide more insight if addition ecological modelling approaches were incorporated, including area-level indicators of behavioural factors (such as measures of per capita alcohol consumption, or smoking prevalence), adopting a similar approach, for example, to that of Petti and Scully (2005) in their international comparison of oral cancer mortality rates. Taking this further, international socioeconomic measures could be modelled into these comparisons, perhaps utilising the international indicators on income inequality adopted by Wilkinson (2005, 2006) among others. This could also build on the preliminary work of Hobdell *et al.*, (2003) on oral health and global inequalities.

Meta-analysis: This could follow on from the systematic review and meta-analysis (Chapter 4), which used the aggregated effect estimates from the INHANCE consortium (INHANCE, 2007). The consortium have granted access to the individual patient-level data to examine in detail the effects of socioeconomic factors on their large dataset of case-control studies (including over 14,000 cases and 16,000 controls from 15 case-control studies from around the world). Initial scoping work has already begun to ascertain the range of socioeconomic measures used in their studies. Individual patient data are acknowledged as permitting pooled estimates which enable analyses with greater

sophistication and ability to control for potential confounding factors to be undertaken (Clarke and Godwin, 1998).

Analytical epidemiology: The analytical epidemiology presented in this thesis is only the beginning. The author is taking the lead on the analysis of socioeconomic factors within the European-wide ARCAGE study (IARC, 2000). Building on the analytical framework developed in Chapter 6, the ARCAGE analysis will provide sufficient power (with over 2,000 cases and controls) to tease out the relative effects of individual socioeconomic factors in relation to behavioural factors, and to begin to examine the socioeconomic data from a life course perspective. It is unlikely that European-wide area measures will be available for consideration of area-effects, although this will be looked into in more detail. Following from the thesis, this is probably the study with the highest priority, as the European dataset is almost complete, and funding is available to undertake this.

Looking further into the future, analytical epidemiology work could also include: the application of analytical epidemiological approaches addressing the potential socioeconomic pathways to contribute a better understanding of the mechanisms involved. This may include the investigation of psychosocial factors, work stress, unemployment, and social support that are mediated through neuro-endocrine mechanisms. In addition, research could be considered to investigate the role of telomeres as biomarkers for socioeconomic factors, with due cognisance given to the difficulties of this (Aviv *et al.*, 2006). In addition a life course approach utilising 'life grid' methodology could also be explored as a means of capturing socioeconomic and behavioural data across the life history (Nicolau *et al.*, 2007)

Further into the future: Going beyond the present research focus on socioeconomic inequalities in relation to oral cancer incidence (and aetiology) there are a number of other areas of research on inequalities related to oral cancer. Krieger (2005) has developed a grid for defining and investigating what she describes as 'the continuum of cancer disparities'. Undertaking this approach in relation to oral cancer would help identify broader research gaps across the full 'cancer continuum' which she defines as: 'prevention, incidence, etiology, screening, diagnosis, access to clinical trials, treatment, survival, morbidity, mortality'. While the focus of the thesis was on incidence and aetiology, consideration of research in these other areas may be a useful first step in considering future directions.

In relation to survival, there may be potential to investigate this via the follow-up ARCAGE study which is currently being planned to look at factors related to survival

outcomes. The Scottish centre is part of follow-up grant applications to take this forward, and could lead again on the socioeconomic dimension.

There may also be merit in going deeper than the natural quantitative constraints of an epidemiological approach to begin to look at the perspective of the patients, and their 'journey' – focusing on their perceptions in relation to socioeconomic circumstances and status in relation to oral cancer risk, along the lines of the work of Rowa-Dewar *et al.* (2007) in relation to cancer in general. Such qualitative approaches may glean new insights into the relationship between socioeconomic factors and oral cancer.

Applying some of the research methods and approaches to health inequalities problems beyond the focus of this thesis – oral cancer – would also be important. This could include other cancers, and links with the Scottish Cancer Registry are already established to begin this process. Other oral health research, particularly dental caries in children, is also being pursued in the Dental Public Health Unit, University of Glasgow, partly informed by some of the approaches adopted in this thesis.

Epidemiology is all about developing new ways of looking at a problem; looking for insights; and applying the findings. However, there also comes a time when epidemiology needs to be converted into public health action – the implementation of such policy and action would also warrant evaluation and research.

Lastly, this thesis has renewed the examination of oral cancer from a socioeconomic inequalities and poverty perspective. At a time when research on oral cancer has a high focus on the molecular and genetic risks and continued focus on 'lifestyle' risk factors, this has been an opportunity to step back and view the bigger picture of the wider and social determinants. Ongoing research with this truly holistic perspective is essential.

8 Conclusions and recommendations

8.1 Conclusions

The burden of oral cancer in the UK is increasing, and remains higher in men than women, in older compared with younger groups, and in northern regions. Scotland has the highest rates of oral cancer, and over the past 30 years, widening socioeconomic inequalities in the distribution of oral cancer have been observed.

An almost 'dose-like' effect is seen, with oral cancer incidence increasing with increasing levels of socioeconomic deprivation. These trends are particularly strong for men emerging in the late 1970s, but are present also for women although less strong and appearing in the 1980s. From studies from around the world, low individual level socioeconomic status – via educational status, occupational social class, or income – is associated with around a 2-fold increased risk for oral cancer. The size of this elevated risk is comparable with that of behavioural risk factors, and is consistently demonstrated, in high and low income countries, across the world, and remains when adjusting for potential behavioural confounders. Inconclusive results are seen from the detailed analytical epidemiological investigation, with regard to the relative effects of area- and individual- socioeconomic measures, and of socioeconomic factors in relation to behavioural factors – although there is little doubt that smoking contributes a substantial weight on risk.

The truth of the explanation of the pathway through which socioeconomic factors impact on oral cancer is unknown. It was not possible to assess which of the range of potential explanations (set out in the Discussion Chapter), is most important. It is likely that the explanations for the inequalities in oral cancer incidence, lie in (i) Rose's (1992) 'cause of the cause' hypothesis – with the behavioural risk factors being widely accepted causes for oral cancer; and / or (ii) more 'direct' roots from social factors.

Nevertheless, it can no longer be satisfactory to consider oral cancer as simply being caused by behaviours such as smoking tobacco and drinking alcohol, in isolation from a social and cultural context. It is clear that the aetiology of oral cancer is complex, and that social factors have an integral explanatory role. That role, however, is yet to be fully defined.

The epidemiology of this thesis presents oral cancer as a significant and increasing public health problem, impacting most on the already most disadvantaged in society. There will be ever increasing resource implications for the health services if these trends continue; but the implications on communities, families, and individuals will be greatest of all.

8.2 Recommendations

8.2.1 Basis for recommendations

To again paraphrase Clemesson, one of the founders of the Danish Cancer Registry: the aim of every form of cancer epidemiology study is to prevent it (Clemmeson, 1965).

This section will first explore the potential overarching responses to the findings of the thesis, and then provide some more detailed recommendations (notwithstanding those related to further research described above).

The notion that cancer is preventable is compelling. Rather than suffering from the condition, enduring the severe treatment regimen, or succumbing to the hopeless survival prognosis, a ('primary') prevention approach is instinctively attractive. However, unfortunately, in public health terms, cancer prevention is not quite as simple as Snow's pioneering epidemiology work to control infectious diseases which culminated in the direct action of removing the water pump handle to cut off the source of cholera infected water (Ashton, 1994). Cancer prevention, however, is complicated in that it is a multifactorial aetiological process with an indeterminable latent period.

The prevailing biomedical model of oral cancer aetiology, exemplified by the Harvard Report on Cancer Prevention, thus far considers that as much as 75% of cancer mortality is related to behavioural risk factors (Colditz *et al.*, 1996). Added to this, the increased emphasis of understanding the genetic and molecular biology, it would seem that some are almost arguing that cancer is on the verge of being controlled via 'biobehavioural' approaches, and the role of social factors is given scant recognition (Hiatt and Rimer, 2006).

The near four decade 'war on cancer' (in the US) has made only modest progress (Rockhill and Weed, 2006) – with epidemiological evidence on lung cancer translating into smoking prevention approaches and interventions being a notable success in terms of generally reducing lung cancer incidence. However, partly resulting from these prevention

approaches, inequalities in both lung cancer and smoking remain seemingly more intractable problems (Pearce, 2007; Scottish Cancer Registry, 2007).

This thesis only adds to the complexity of both oral cancer aetiology and prevention approaches by bringing the role of social factors to the fore.

Responses to health inequalities in general and oral health inequalities in particular were outlined by Watt (2007) to include: behavioural approaches, population considerations, and 'upstream action'.

Behavioural response: The individual behavioural or lifestyle approach to health inequalities was described by Watt (2007) among others, as 'public health behaviourism'. He then outlines the major limitations of such an approach as: ineffective, 'victim blaming', over-simplifying the problem, lacking theory, not being cost-effective and diverting resources from more effective measures.

The effectiveness of behavioural approaches has long been questioned – with such interventions having been shown to potentially widen inequalities in health outcomes (e.g. Schou and Wight, 1994).

Behavioural risk factors for oral cancer, such as smoking, alcohol drinking, and poor diet – particularly when they are labelled 'lifestyle' factors are considered as involving a degree of personal choice, and are therefore often viewed outside of their socioeconomic and cultural context defined as individual responsibility. This leads to overly simplistic responses that are more 'victim blaming' than understanding, and usually completely ignores the cultural, never mind social factors. In addition, the view that behaviours are modifiable (with the implication that social factors are not) gives credence to interventions focused on behaviour change (Greenland, 2005). The lack of a theoretical basis for behavioural focused interventions, which ignore the wider social context, in contrast to developing social theories, was demonstrated in an earlier review by Watt (2002). An additional critique is economically based. There is limited research into the health economics related to the various approaches, but particularly the cost effectiveness of behavioural focused approaches (Macintyre *et al.*, 2001). Further, Watt (2007) highlights the potential opportunity cost in diverting resources from interventions that address the social factors.

Population approaches as opposed to individual approaches were originally defined by Rose (1992). The population approach, according to Rose, would prevent higher numbers of cases of disease than an individually targeted approach. This basic concept has subtly expanded to compare 'population' approaches to 'targeted' or 'high risk' group approaches. This can readily be conceptualised, with an example: Batchelor and Sheiham's (2002) analysis of dental caries distribution in the UK child population. While there is a smaller proportion with high levels of dental caries, potential interventions which target the whole population will shift not only those at the high end but the rest of the population towards lower decay levels. However, a layer of complexity, not always explicitly acknowledged, comes when 'the problem' is socioeconomic inequalities in the distribution of disease, whereby population approaches potentially may perpetuate or increase the unequal distribution of the disease (Joffe and Mindell, 2004), while the converse, i.e. a targeted approach, may bring those in most need who are most socioeconomically deprived to a level more comparable with the population and reduce the inequality. These are difficult ethical, economic resource allocation, and societal issues – one which policy has so far failed to fully address – leading to inconsistencies in the adoption of 'universal' and 'targeted' policies on a range of health issues, exemplified by the debate around the provision of health visiting services and the resulting report by Hall and Ellimen (2003) (known as the 'Hall 4 Report').

'Upstream action' is the thrust of Watt's (2007) challenge – to develop public health strategies and policies which address the underlying social causes of disease and particularly oral diseases. This follows on from the historical, but still relevant, WHO (1986) Ottawa Charter and renewed focus on social determinants in WHO strategy, culminating with the recent WHO *Commission on Social Determinants of Health* (2007) who plan to publish a final report in 2008, detailing comprehensive recommendations for action in relation to health inequalities.

Sheiham and Watt (2000) earlier argued for the importance of ensuring oral health and diseases are not considered separate to wider general health concerns, with the 'common risk factor approach' which seeks to highlight (mainly traditional) risk factors for oral diseases as being no different in many instances to those of other diseases. This was expanded by Watt (2005) to acknowledge the common social factors in disease aetiology.

Building further on this, Watt (2007) set out a series of guiding principles for developing oral health strategies to improve oral health and address health inequalities, including: empowering and engaging communities through participatory approaches, intersectoral,

partnership and multi-strategy working, drawing on evidence based practice and policy implemented with robust evaluation approaches.

The evidence base for policies directed at tackling socioeconomic inequalities from across the UK, the World, and Europe were reviewed respectively by Macintyre *et al.*, (2001), Crombie *et al.*, (2004) and Mackenbach (2006) – with the worrying conclusion in the latter paper, when summing up the general limited evidence base, noted: 'Whether it will actually be possible to substantially reduce socioeconomic inequalities in health remains an open question.'

8.2.2 Recommendations

This section attempts to apply the guiding principles set out above to recommendations for policy and practice in relation to addressing inequalities in oral cancer incidence; utilising two frameworks: (i) The Ottawa Charter (WHO, 1986) – which stresses the need to: build healthy public policy, encourage community action, develop personal skills, create supportive environments, and reorient health services in order to ensure effective public health actions. This remains a useful framework to ensure the comprehensive range and levels of action on addressing issues related to health inequalities. (ii) In addition, the 'PESTLE' management tool to analyse complexity adapted from the work of Boddy (2002) – may provide a different perspective through which to consider the range of dimensions related to addressing the health inequalities challenge: political, economic, social and cultural, technological, legislative, and environmental. Recommendations will be provided for policy, public health, and practice.

Policy

- Policy needs to be directed toward tackling root causes of disadvantage. Crombie *et al.* (2004) set out a range of potential structural, social, and economic policies which could tackle the underlying inequalities. These include: taxation and tax credit measures, old-age pensions, sickness or rehabilitation benefits, maternity or child benefits, unemployment benefits, housing policies, labour market policy and developments, community developments, and care facility infrastructure.

- Legislative challenges include converting healthy public policy to law, but also to monitor all legislation, not only for health impact, but for impact on inequalities (– to apply the 'inequality lens' to all policy and legislation).

- Major efforts to change social and economic conditions are necessary to eliminate inequalities in health. A hypothetical analysis undertaken in the US, published earlier this year, found that giving everyone the health of the highly educated would save more lives than those of medical services by a ratio of 8:1 (Woolf *et al.*, 2007). Thus, education and opportunities for education are both integral and symptomatic of the wide social change advocated for.

- Globally, health policy also needs to continue to shift its direction toward tackling the root causes of poverty and inequalities, and the WHO *Commission on Social Determinants of Health* can be commended in driving this forward (Marmot, 2005).

- Cancer policy in Scotland needs to become more consistently aligned with health inequalities policy. Social factors need to be explicitly recognised as a significant risk factor and services orientated to meet this need.

Public health

- The thesis results and conclusions support a shift in public health, health promotion, and health service action from a narrow focus on behaviours and lifestyles to one that addresses wider social factors.

- The increasing incidence rates in oral cancer and widening inequalities in its distribution present a significant public health problem. While awareness of the association between oral cancer and socioeconomic factors has previously been known, little has been done to explicitly address this. A comprehensive public health preventive approach is warranted.

- Public health strategies should form the basis of the approach and detail the action required. They need to be developed with the aims of preventing and /or leading to early detection of oral cancer. The evidence base to support screening programmes is limited and further screening approaches need developed and evaluated (Speight *et al.*, 2006).

- It should be more explicitly recognised that public health strategies, need to be appropriately targeted and resources allocated to addressing the problem in low socioeconomic groups and deprived communities where the greatest risk and need lies. Public health activities and service developments need to be targeted to those living in

deprived areas and those with low socioeconomic status as the key 'priority risk group' – to date, 'high risk groups' have primarily been defined by their: sex, age-groups, smoking and alcohol behaviours (Speight *et al.*, 2006).

- Rather than target interventions *to* deprived communities, activities should be undertaken *with* communities as full participants, partners and even leaders. To these ends, all public health programmes in Scotland need to embrace the recommendations of the Community-led Supporting and Developing Healthy Communities Task Group (2006) including: engaging with, working in meaningful partnerships with, building the capacity of, and providing funding for the sustainability of the community and voluntary health sector within Scotland. This approach will foster social networks and social capital and help create supportive healthy environments in communities.

- There remains a need to continue to develop the evidence base in relation to reducing health inequalities.

Practice

- Health services do have a role to play in terms of ensuring access to all, irrespective of socioeconomic background, and also in relation to continuing to shift towards a preventive, anticipatory model of care. Further technological solutions could also be pursued in relation to preventing conditions such as oral cancer – *viz-á-viz* the recently announced Human Papillomavirus (HPV) vaccination for 12 year old girls for prevention of cervical cancer by the (UK) Joint Committee on Vaccination and Immunisation (2007).

- While continuing to develop approaches to address behavioural risk factors (such as continued smoking cessation and alcohol counselling services), these activities need to be undertaken with full appreciation and consideration of the underlying socioeconomic and cultural factors influencing these behaviours. However, efforts to reduce exposure to behavioural risk factors alone are unlikely to succeed unless they are supported by measures designed to improve socioeconomic circumstances and to reduce socioeconomic inequalities.

- One of the first goals is to create a mindset shift in clinical practice colleagues and public policy makers – described by Watt (2007) as shifting 'from victim blaming to upstream action'.

- Health professionals and policy makers need to consider advocating for socioeconomic change in addition to health behaviour and service change.

In summary, health inequalities, exemplified in this thesis by oral cancer incidence, is a complex challenge. It needs a concerted effort to meet the challenge – building bridges and meaningful partnerships between and with: (i) policy and practice, (ii) research and development, (iii) multiple sectors, agencies, and organisations, and (iv) all communities.

In addition, to take on the challenge of tackling inequalities, a fresh and enthusiastic approach is required, involving: passion and commitment, a willingness to take risks, and commitment to work with others – in short, a new 'can do' mindset.

To conclude, the following three quotes seem to capture in turn: the truth, the knowledge, and the challenge in tackling health inequalities:

'Massive poverty and obscene inequality are such terrible scourges of our times…that they have to rank alongside slavery and apartheid as social evils' (Nelson Mandela, 2005).

'The primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social' (Geoffrey Rose, 1992, p.129).

'Economic injustice will stop the moment we want it to stop and no sooner, and if we genuinely want it to stop the method adopted hardly matters' (George Orwell, 1937, p.139).

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Appendices

Appendix 1 UK cancer registries data collection form

For oral cancer defined as ICD-10 C00-C06, C09-C10, and C14.

Table 1 Numbers of **male** registrations, with crude and age-standardised incidence rates by sex, age and year

	Year of Diagnosis									
Age group	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Under5										
5-9										
10-14										
15-19										
20-24										
25-29										
30-34										
35-39										
40-44										
45-49										
50-54										
55-59										
60-64										
65-69										
70-74										
75-79										
80-84										
85+										
All ages										
Crude Rate										
EASR										

Table 2 Numbers of **female** registrations, with crude and age-standardised incidence rates by sex, age and year

	Year of Diagnosis									
Age group	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Under5										
5-9										
10-14										
15-19										
20-24										
25-29										
30-34										
35-39										
40-44										
45-49										
50-54										
55-59										
60-64										
65-69										
70-74										
75-79										
80-84										
85+										
All ages										
Crude Rate										
EASR										

Appendix 2 Caldicott Guardian approval request

Mr David I Conway
BDS, FDSRCS(Eng), MPH, FDS (DPH) RCS
Lecturer / SpR in Dental Public Health
Dental Public Health Unit
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E-mail: d.conway@dental.gla.ac.uk

UNIVERSITY of GLASGOW

Dr Rod Muir
CPHM / Caldicott Guardian
Information Services
NHS National Services Scotland
Gyle Square
1 South Gyle Cresent
Edinburgh EH12 9EB

18th May, 2005

Dear Dr Muir,

Re. Permission to access Scotland Cancer Registry data

I hereby write to request permission to use the Scottish Cancer Registry data as part of the descriptive analysis within my PhD on the epidemiology of oral cancer. I have attached a copy of my detailed data request letter to Dr David Brewster.

I can assure you that I will maintain confidentiality, and store the data in a secure manner as you advise.

It is likely that I will be seconded to ISD in the very near future and will keep you informed of the progress of this.

If you require any further information do not hesitate to contact me.

Kind regards,
Yours sincerely,

David Conway

cc. Roger Black, Head Scottish Cancer Intelligence Unit, ISD, NHS National Services Scotland
cc. David Brewster, Director of Cancer Registration, ISD NHS National Services Scotland
cc. Lorna Macpherson, Senior Lecturer in Dental Public Health, University of Glasgow Dental School (PhD Supervisor)

Appendix 3 Caldicott Guardian approval response

Information Services

1st Floor, Room 119
Gyle Square
1 South Gyle Crescent
EDINBURGH EH12 9EB

Telephone 0131 275 6000
Fax 0131 275 7606
www.isdscotland.org

NHS National Services Scotland

Mr David I Conway
Lecturer/SpR in Dental Public Health
Dental Public Health Unit
University of Glasgow Dental Hospital & School
378 Sauchiehall Street
GLASGOW
G2 3JZ

Date 8 June 2005
Your Ref
Our Ref

Enquiries to Rod Muir
Direct Line 0131 275 6613
Email rod.muir@isd.csa.scot.nhs.uk

Dear Mr Conway

Permission to access Scotland Cancer Registry data

Thank you for your letter dates 18th May 2005. I have now had a chance to discuss this with Dr Brewster and we agreed that since these data are anonymised there will be no problem with you having access to the data. However it would be preferable if you held the data in ISD for the purposes of analysis. Perhaps you could agree this with Dr Brewster.

Kind regards

Yours sincerely

Rod Muir
Consultant in Public Health Medicine

CC Dr Brewster

Appendix 4 Confidentiality statement

NHS National Services Scotland

Information Services
NHS National Services Scotland

Confidentiality statement

for users of NHS patient data

User Details	**Sponsor Details** [see over for appropriate sponsor]*
Name DAVID CONWAY	Name PROF JEREMY BAGG
Position LECTURER IN DENTAL PUBLIC HEALTH	Position HEAD OF DENTAL SCHOOL
Organisation UNIVERSITY OF GLASGOW DENTAL SCHOOL	Organisation UNIVERSITY OF GLASGOW
Address 378 SAUCHIEHALL ST. GLASGOW G2 3JZ	Address 378 SAUCHIEHALL STREET GLASGOW G2 3JZ
Tel. No. 0141 211 9802	Tel. No. 0141 211 9701
Data Protection Reg. No.	
Name(s) of any co-user(s) : —	

Data Requested: Head and neck cancer registry data 1968 -> present.

Intended use of data (include publications): . PhD and scientific publications related to INCAGE study papers.

User's Declaration :

I declare that I understand and undertake to abide by the rules for confidentiality, security and release of data received from Information Services, as specified in paras 1 - 7 on page 2 of this document.

Signature David Conway Date 1/6/2005

Sponsor's Declaration :

I declare that DAVID CONWAY (named above as the user of the data requested), is a bona fide worker engaged in a reputable project and that the data (s)he asks for can be entrusted to him/her in the knowledge that (s)he will conscientiously discharge his/her obligations in regard to confidentiality of the data, as stated in paras 1 - 7 on page 2 of this document. I am happy for him/her to receive these data.

Signature Jeremy Bagg Date 3.6.05

Appendix 5 Scottish Cancer Registry data request letter

Mr David I Conway
BDS, FDSRCS(Eng), MPH, FDS (DPH) RCS
Lecturer / SpR in Dental Public Health
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UNIVERSITY
of
GLASGOW

Dr David Brewster
Director of Cancer Registration
Information Services
NHS National Services Scotland
Gyle Square
1 South Gyle Cresent
Edinburgh EH12 9EB

18th May, 2005

Dear Dr Brewster,

Re. Oral Cancer – Scotland Cancer Registry data request.

Further to our brief meeting on Monday 16th May I would be grateful for your assistance with this request.

My PhD is investigating the epidemiology of oral cancer in Scotland. The analytical section includes the ARCAGE (Alcohol Related Cancers and Genetic Susceptibility in Europe) head and neck cancer study in Scotland. I am also keen to explore in detail the descriptive epidemiology of head and neck cancer in Scotland.

Therefore, could I please have access to the Cancer Registry data for Scotland from 1968 onwards. The data which I would like to investigate are for the oral cancer codes, as set out in Table 1 (attached).

The basic tumour information I would require include:

- Incidence year,
- Tumour site (ICD-9),
- Tumour Morphology (ICD-0),
- Tumour site (ICD-10),
- Tumour morphology (ICD-0(2))
- Histology Verification or Diagnosis indicator
- Death Certificate Only Indicator

The demographic variables I am interested in are:

- Age,
- Sex,
- Health board,
- Community Health Partnership Areas,

Appendix 5 continued

Carstairs Deprivation Category and Quintile,
Scottish Index of Multiple Deprivation,
Occupation where possible,

I can assure you that I will store the data in a secure manner and will take your advise on how best to do this. I will also be writing to Dr Rod Muir in his role as Caldicott Guardian for permission to access the data and will copy him this request.

It is likely that I will be seconded to ISD in the very near future and will keep you informed of the progress.

Many thanks again for your help with this.
Kind regards,
Yours sincerely,

David Conway

cc. Roger Black, Head Scottish Cancer Intelligence Unit, NHS National Services Scotland
cc. Rod Muir, Consultant in Public Health Medicine / Caldicott Guardian, ISD, NHS National Services Scotland.
cc. Lorna Macpherson, Senior Lecturer in Dental Public Health, University of Glasgow Dental School (PhD Supervisor)

Appendix 6 Search strategy for systematic review

Search terms: case control studies:

Subject Headings:
"Case-Control Studies" / or "Case Control Study"/
“Epidemiology” /
“Epidemiological Research" / or "Cancer Epidemiology" / or "Cancer Risk" / or "Risk Factors" / or "Relative Risk" / or "High Risk Population" /
relative risk.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm] /
epidemiological research. mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm] /
“cancer epidemiology”/
“Controlled study” (EMBASE)

or

Keywords:
case control$ or case-control$ or case referen$ or case-referen$
Epidemiological Research"/ or "Cancer Epidemiology"/ or "Cancer Risk"/ or "Risk Factors"/ or "Relative Risk"/ or "High Risk Population"/

AND

Search terms: oral cancer:

Subject Headings:
"head and neck neoplasms"/ or mouth neoplasms/ or gingival neoplasms/ or lip neoplasms/ or palatal neoplasms/ or tongue neoplasms/ or pharyngeal neoplasms/ or exp oropharyngeal neoplasms/
or
"head and neck tumor"/ or "head and neck cancer"/ or jaw cancer/ or mandible cancer/ or maxilla cancer/ or lip cancer/ or lip carcinoma/ or mouth cancer/ or mouth carcinoma/ or pharynx cancer/ or pharynx carcinoma/ or oropharynx cancer/ or oropharynx carcinoma/ or tongue cancer/ or tongue carcinoma/ or tonsil cancer/ or tonsil carcinoma/ or jaw tumor/ or mandible tumor/ or maxilla tumor/ or lip tumor/ or mouth tumor/ or pharynx tumor/ or oropharynx tumor/ or tongue tumor/ or tonsil tumor/

or

Keywords:
((cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$) adj5 (oral or intra-oral$ or intraoral$ or gingiva$ or oropharyn$ or oro-pharyn$ or mouth$ or tongue$ or cheek or cheeks or gum or gums or palate or palatal or maxilla$ or pharyn$ or tonsil$ or mandib$ or lip or lips or jaw or jaws))

Exclusions:
animal
oral contraceptive$
Exp "Breast Neoplasms"/
Exp "Ovarian Neoplasms"/
"Cervix Neoplasms"/
exp urogenital tract tumor/ or uterine cervix tumor/
Contraceptive Agent/
exp Contraceptives, Oral/

Appendix 7 Supplementary references for studies included in meta-analysis

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European Study of Cancers of the Head and Neck

Lifestyle and Quality of Life Questionnaire

Epidemiological Studies Team
Information & Statistics Division
Trinity Park House
South Trinity Road
Edinburgh
EH5 3SQ

NHS SCOTLAND

I would like to thank you for agreeing to participate in this study. Before we begin the interview, I need to read the following paragraph in order to be sure that everyone who takes part in the study has the same information.

We are conducting a study in the UK and in other countries to try to identify possible lifestyle factors which may lead to the development of certain diseases. For this study we need to interview both people with these diseases and those without the diseases

The information you give during the interview will be treated as strictly confidential and any results will be anonymised with no individual being identified in any published results.

Before we begin the interview, can I ask you to read and sign this form agreeing to the interview.

A7 Interviewer ☐☐

GENERAL INFORMATION

B1 Date of interview (day month year)

B2 Start time (according to 24hr clock) (hour min)

B3 Sex (1=male, 2=female)

B4 What is your date of birth? (day month year)

B5 What is your ethnic origin? (showcard 1a)

01 = White
02 = Asian – Bangladeshi
03 = Asian – Chinese
04 = Asian – Indian
05 = Asian – Pakistani
06 = Asian – Other
07 = Black – Caribbean
08 = Black - African
09 = Black - Other
10 = Mixed – White and Black Caribbean
11 = Mixed – White and Black African
12 = Mixed – White and Asian
13 = Mixed - Other
14 = Other _____(specify)

B6 In what town or district do you live? _____

B7 For how many years have you been living there?
(If less than a year code 00 and go to B8, If greater than a year go to B9)

B8 If you were living there for less than one year, where did you live one year ago? _____

B9 In what country were you born? _____

B10 In what town or district were you born? _____

B11 How many years of full time education did you complete?

B12 What is the highest educational level you obtained? (showcard 1b)

1 = Primary school
2 = Secondary school
3 = School or college sixth form
4 = College of Further Education
5 = Polytechnic or University
6 = Some other type of college_____ (specify)

We are now going to talk about smoking.

SMOKING HABITS

C1 Have you ever smoked cigarettes, cigars, a pipe, or any other tobacco products at least once a week for a year?

If other tobacco product , please specify _____

Would you say: 1 = Yes, I currently smoke, or have stopped smoking within the last 12 months
2 = I used to smoke, but stopped smoking over 12 months ago
3 = I have never smoked [Go to C10]

I am now going to ask you to describe the periods in your life during which you smoked.

Please ignore any changes that occurred for less than a year, and let me know only the significant changes of an increase or decrease in the amount you smoked of 50% or more.

CIGARETTE SMOKING

C2 Have you ever smoked at least one cigarette a week for at least 1 year?

1 = yes → (A)a)
2 = no → C3

First period:

(A)a) At what age or in what year did you first start smoking cigarettes?	**b) Which cigarette brand did you mainly smoke?**	**c) Which type of cigarettes did you mostly smoke?**	**d) How many cigarettes did you smoke?** (per day or per week)	**e) Did you continue to smoke in this way or did you stop or change your smoking habits substantially at anytime?**	**f) When was that?** *(Probing: At which age or in which year did you stop smoking or change your smoking habits ?)*	**g)** *(If stopped)* **Did you ever start smoking cigarettes again subsequently?**
(A) age or year or	brandname	1= manufactured with filter 2= manufactured without filter 3=hand-rolled	day or week	1 = no change ►C3 2 = stopped ►f 3 = changed ►f to **(B)b)**	age or year stopped or changed or	Yes ► **(B)a)** No ►C3

Subsequent periods:

(B)a) When did you begin smoking again or change to smoking a different amount or different product?	b) Which cigarette brand did you mainly smoke ?	c) Which type of cigarettes did you mostly smoke?	d) How many cigarettes did you smoke? (per day or per week)	e) Did you continue to smoke in this way or did you stop or change your smoking habits substantially at anytime?	f) When was that? *(Probing: At which age or in which year did you stop smoking or change your smoking habits?)*	g) *(If stopped)* Did you ever start smoking cigarettes again subsequently?
(Probing: at which age or in which year was that?)						
(B) age or year or	brandname	1= manufactured with filter 2= manufactured without filter 3=hand-rolled	day or week	1 = no change ►C3 2 = stopped ►f 3 = changed ►f to **(C)b)**	age or year stopped or changed or	Yes ► **(C)a)** No ►C3
(C) age or year or	brandname	1= manufactured with filter 2= manufactured without filter 3=hand-rolled	day or week	(1) no change ►C3 (2) stopped ►f (3) changed ►f to **(D)b)**	age or year stopped or changed or	Yes ► **(D)a)** No ►C3
(D) age or year or	brandname	1= manufactured with filter 2= manufactured without filter 3=hand-rolled	day or week	1 = no change ►C3 2 = stopped ►f 3 = changed ►f to **(E)b)**	age or year stopped or changed or	Yes ► **(E)a)** No ►C3
(E) age or year or	brandname	1= manufactured with filter 2= manufactured without filter 3=hand-rolled	day or week	1 = no change ►C3 2 = stopped ►f 3 = changed ►f to **(F)b)**	age or year stopped or changed or	Yes ► **(F)a)** No ►C3

(use additional sheets if more smoking periods are needed)

CIGAR/CIGARILLO SMOKING

C3 Have you ever smoked cigars or cigarillos at least once a week for at least 1 year? ☐

1 = yes → (A)a)
2 = no → C4

First period:

(A)a) At what age or in what year did you first start smoking cigars/ cigarillos?	b) Did you mainly smoke cigars or cigarillos?	c) Did you inhale the smoke?	d) How many cigars/cigarillos did you smoke? (per day or per week)	e) Did you continue to smoke in this way or did you change your smoking habits substantially at anytime?	f) When was that? *(Probing: At which age or in which year did you stop smoking or change your smoking habits?)*	g) *(If stopped:)* Did you ever start smoking cigars/cigarillo again subsequently?
(A) age or year or	1 = cigars 2 = cigarillos	1 = yes 2 = no	day or week	1 = no change ►C4 2 = stopped ►f 3 = changed ►f to **(B)b)**	age or year stopped or changed or	Yes ► **(B)a)** No ► C4

Subsequent periods

a) When did you begin smoking again or change to smoking a different amount or different product?	b) Did you smoke mainly cigars or cigarillos?	c) Did you inhale the smoke?	d) How many cigars/cigarillos did you smoke? (per day or per week)	e) Did you continue to smoke in this way or did you change your smoking habits substantially at anytime?	f) When was that? *(Probing: At which age or in which year did you stop smoking or change your smoking habits?)*	g) (if stopped:) Did you ever start smoking cigars/cigarillos again subsequently?
(B) age or year or	1 = cigars 2 = cigarillos	1 = yes 2 = no	day or week	1 = no change ►C4 2 = stopped ►f 3 = changed ►f to **(C)b)**	age or year stopped or changed or	Yes ► **(C)a)** No ► C4
(C) age or year or	1 = cigars 2 = cigarillos	1 = yes 2 = no	day or week	1 = no change ►C4 2 = stopped ►f 3 = changed ►f to **(D)b)**	age or year stopped or changed or	Yes ► **(D)a)** No ► C4

PIPE SMOKING

C4 Have you ever smoked a pipe at least once a week for at least 1 year? ☐

1 = yes ► (A)a)
2 = no ► C5

First period					
(A)a) At what age or in what year did you first start smoking a pipe?	**b) Did you inhale the smoke?**	**c) How many pipes did you smoke?** (per day or per week)	**d) Did you continue to smoke in this way or did you change your smoking habits substantially at anytime?**	**e) When was that?** *(Probing: At which age or in which year did you stop smoking or change your smoking habits?)*	**f)** *(If stopped:)* **Did you ever start smoking a pipe again subsequently?**
(A) age or year ☐☐ or ☐☐☐☐	1 = yes 2 = no ☐	☐☐ day or ☐☐ wk	1 = no change ►C5 2 = stopped ►e 3 = changed ►e B)b) ☐	age or year stopped or changed ☐☐ or ☐☐☐☐	Yes ► **(B)a)** No ►C5 ▒
Subsequent periods:					
(B)a)When did you begin smoking again or change to smoking a different amount or different product? *(Probing: ...at which age or in which year was that?)*	**b) Did you inhale the smoke?**	**c) How many pipes did you smoke?** (per day or per week)	**d) Did you continue to smoke in this way or did you change your smoking habits substantially at anytime?**	**e) When was that?** *(Probing: At which age or in which year did you stop smoking or change your smoking habits?)*	**f)** *(If stopped:)* **Did you ever start smoking a pipe again subsequently?**
(B) age or year ☐☐ or ☐☐☐☐	1 = yes 2 = no ☐	☐☐ day or ☐☐ wk	1 = no change ►C5 2 = stopped ►e 3 = changed ►e C)b) ☐	age or year stopped or changed ☐☐ or ☐☐☐☐	Yes ► **(C)a)** No ►C5 ▒
(C) age or year ☐☐ or ☐☐☐☐	1 = yes 2 = no ☐	☐☐ day or ☐☐ wk	1 = no change ►C5 2 = stopped ►e 3 = changed ►e D)b) ☐	age or year stopped or changed ☐☐ or ☐☐☐☐	Yes ► **(D)a)** No ►C5 ▒

(use additional sheets if more smoking periods are needed)

C5 **For current smokers**: How soon after you wake up do you smoke your first cigarette? ☐

For ex-smokers: How soon after waking up did you used to smoke your first cigarette? ☐

1 = Within 5 minutes
2 = Within 6-30 minutes
3 = Within 31-60 minutes
4 = After 60 minutes

1 = yes
2 = no

C6 **For current smokers**: Do you find it difficult to refrain from smoking in places where it is forbidden (e.g. cinema, aeroplanes, hospitals)? ☐

For ex-smokers: Did you find it difficult to refrain from smoking in places where it is forbidden (e.g. cinema, aeroplanes, hospitals)? ☐

C7 **For current smokers only** [EX-SMOKERS go to C8]: Have you ever tried to quit smoking? ☐
1 = Yes
2 = No [if no go to D1]

C8 **For current smokers**: How many times have you tried to quit smoking? ☐☐

For ex-smokers: Before quitting how many times did you try to quit smoking? ☐☐

C9 What was your longest period of abstinence from smoking? (excluding current period for ex-smokers). You can answer in 1 = days ☐
2 = months
3 = years

Specify number ☐☐

QUESTIONS C10-C14 ARE FOR NEVER-SMOKERS ONLY

C10 Have you ever lived with a smoker? ☐
1 = Yes
2 = No [if 'No' go to C13]

C11 Did this person ever smoke in your presence? ☐
1 =Yes
2 = No [if 'No' go to C13]

C12 Please describe the smoking habit of the person or people you have lived with. If there were changes in their smoking behaviour, or if you started living with someone else who also smoked, please describe this as a separate period (only record significant changes of at least a 50% increase or decrease in the number of hours you were exposed):

First period			
a) How old were you (or what year was it) when you first began living with a person or people who smoked?		b) How many hours per day were you exposed to smoke?	
from	to	weekdays	holidays/weekends
a age ☐☐ or year ☐☐☐☐	age ☐☐ or year ☐☐☐☐	☐☐	☐☐
Subsequent periods			
a) Did the person or people you were living with change their smoking habits or did you live with other people who smoked? : When was that?		b) How many hours per day were you exposed to smoke?	
from	to	weekdays	holidays/weekends
b age ☐☐ or year ☐☐☐☐	age ☐☐ or year ☐☐☐☐	☐☐	☐☐
c age ☐☐ or year ☐☐☐☐	age ☐☐ or year ☐☐☐☐	☐☐	☐☐
d age ☐☐ or year ☐☐☐☐	age ☐☐ or year ☐☐☐☐	☐☐	☐☐

C13 Have you ever worked in an indoor setting in which other people smoked? ☐
1 = Yes
2 = No [if 'No' go to D1]

C14 Please describe the periods during which you have been working with smokers, if there were changes in the number of hours you were exposed to other people smoking, or if you changed jobs and there were differences in terms of your exposure to smoke, please describe this as a separate period (only record significant changes of an increase or decrease in exposure to other people's tobacco smoke of 50% or more):

First Period				
a) How old were you (or what year was it) when you first began working with people who smoked in your presence?			b) How many hours per day on average were you exposed to tobacco smoke at work, including time spent at the canteen or during breaks?	c) Would you say that the place was usually: 1 = very smoky (you could see clouds of smoke in the air) 2 = fairly smoky (you could see some smoke in the air) 3 = a little smoky (you could only smell the smoke)?
from		to	hours per day	
a age ☐☐ or year ☐☐☐☐		age ☐☐ or year ☐☐☐☐	☐☐	☐
Subsequent periods				
a) How old were you (or what year was it) when your exposure to other peoples' smoke at work changed?			b) How many hours per day on average were you exposed to tobacco smoke at work, including time spent at the canteen or during breaks?	c) Would you say that the place was usually: 1 = very smoky (you could see clouds of smoke in the air) 2 = fairly smoky (you could see some smoke in the air) 3 = a little smoky (you could only smell the smoke)?
from		to	hours per day	
b age ☐☐ or year ☐☐☐☐		age ☐☐ or year ☐☐☐☐	☐☐	☐
c age ☐☐ or year ☐☐☐☐		age ☐☐ or year ☐☐☐☐	☐☐	☐
d age ☐☐ or year ☐☐☐☐		age ☐☐ or year ☐☐☐☐	☐☐	☐

Now we are moving on to talk about food.

DIETARY HABITS How often did you have the following foods and drinks. Can I just remind you we are talking about one year ago?

	Unit	Food item (showcard 2)	How many times per day, week, month, year? (mark one column only)				
			day	week	month	year	never
D1	1 portion	Beef					
D2	1 portion	Pork					
D3	1 portion	Poultry and game birds					
D4	1 portion	Lamb and other meat					
D5	1 portion	Fish and other seafood					
D6	1 portion	Bacon, sausages, burgers, sliced meat, paté etc					
D7	1 portion	Raw green vegetables and salads					
D8	1 portion	Cooked fresh or frozen green vegetables					
D9	1 portion	Carrots					
D10	1 portion	Fresh tomatoes					
D11	1 portion	Tinned or dried pulses (e.g. peas and beans)					
D12		As a summary, how often would you say that you ate any kind of vegetables (potatoes excluded)?					

Fresh Fruit

D13	1 portion	Fruit juice					
D14	1 portion	Apples or pears					
D15	1 portion	Citrus fruit (oranges, grapefruit, lemons)					
D16	1 portion	Bananas					
D17	1 portion	Berries (strawberries, raspberries, blackberries etc.)					
D18	1 portion	Plums, peaches, apricots					
D19	1 portion	Kiwi fruit					
D20	1 portion	As a summary, how often would you say that you ate any kind of fresh fruit (including fruit salads)?					
D21	1 cup	Tea					
D22	1 cup	Coffee					
D23		At what temperature did you usually drink your tea or coffee?	1 very hot		2 hot		3 warm
D24	1 portion	How often do you use olive oil:					
		For salads					
		For cooking					

DRINKING HABITS

E1 Have you ever drunk alcohol. How would you describe yourself? ☐

1 = I currently drink (including occasional drinking), or have stopped drinking within the last 12 months
2 = I used to drink (including occasional drinking), but stopped drinking over 12 months ago
3 = I have never drunk alcohol [Go to F1]

For those who have stopped drinking (ie those who answered 1 or 2 to question E1), questions E2, E3 and E4 refer to the period before they stopped consuming alcohol.

E2 How frequently did you drink alcohol one year ago? (showcard 3a) ☐

1 = Every day
2 = Most days but not every day
3 = 1 to 3 times per week
4 = Less than once per week & more than once per month
5 = Less than once per month
6 = Never

E3 Regarding your normal drinking habits one year ago, when did you normally drink? ☐

1 = With meals
2 = Not with meals
3 = Both
4 = Didn't drink one year ago

E4 How often would you consume alcohol before noon? (showcard 3a) ☐

1 = Every day
2 = Most days but not every day
3 = 1 to 3 times per week
4 = Less than once per week & more than once per month
5 = Less than once per month
6 = Never

E5 Have you ever in your lifetime drunk large amounts of alcohol in a short period of time, ☐

(eg more than 10 drinks in a couple of hours) ? (1 = Yes, 2 = No)

If yes how often did you do this? (showcard 3b) ☐

1 = Every day
2 = Most days but not every day
3 = 1 to 3 times per week
4 = Less than once per week & more than once per month
5 = Less than once per month
6 = Only on one occasion

From what age did you do this? from (age) ☐☐

to (age) ☐☐

I am now going to ask you to describe the different types and amounts of drinks that you have had throughout your life. I will ask in turn about beer, wine, before-dinner drinks, spirits and any other type of alcohol. Please could you describe the times in your life during which you consumed each of these types of drink. Please summarise the important changes in your life regarding each drink and ignore any changes that occurred for less than a year. Let me know only the significant changes of an increase or decrease in the amount you drank of 50% or more

E6 Beer

Have you ever drunk beer, lager, stout, cider or shandy? ☐

1 = Yes ►(A)a)
2 = No ► E7

First period:

(A)a) At what age (or in what year) did you begin drinking beer?	b)i) How often did you drink beer?	c) Did you drink pints, bottles, or any other measure? (showcard 5) (specify)	d) On those days that you drank beer, how many pints/ bottles/ (other measure) did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently? Stop drinking beer ► E7 Stop drinking and then start again ► (B)a) Change to a different amount of beer ► (B)a)
Aa) age or year ☐☐ or ☐☐☐☐	b)i) days / week or days / month ☐☐ days/week or ☐☐ days/mth	Pints / bottles / other _____ (specify)	measures ☐☐☐	e) age or year ☐☐ or ☐☐☐☐	
	b)ii) What type of beer did you drink? _____	c) If bottles or cans, what size was it from the chart? How many mls was this? ☐☐☐☐	d) How many units in total did the interviewee drink per day? ☐☐☐		

Subsequent periods:

When did you begin drinking beer again or change the amount of beer that you drank?	b)i) How often did you drink beer?	c) Did you drink pints, bottles, or any other measure?	d) On those days that you drank beer, how many pints/ bottles/ (other measure) did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
(B) age or year ☐☐ or ☐☐☐☐	days / week or days / month ☐☐ days/week or ☐☐ days/mth	pints / bottles / other _____ (specify)	measures ☐☐☐	age or year ☐☐ or ☐☐☐☐	Stop drinking beer ► E7 Stop drinking and then start again ► (C)a) Change to a different amount of beer ► (C)a)
	b)ii) What type of beer did you drink? _____	If bottles or cans, what size was it from the chart? How many mls was this? ☐☐☐☐	How many units in total did the interviewee drink per day? ☐☐☐		
(C) age or year ☐☐ or ☐☐☐☐	days / week or days / month ☐☐ days/week or ☐☐ days/mth	pints / bottles / other _____ (specify)	measures ☐☐☐	age or year ☐☐ or ☐☐☐☐	Stop drinking beer ► E7 Stop drinking and then start again ► (D)a) Change to a different amount of beer ► (D)a)
	b)ii) What type of beer did you drink? _____	If bottles or cans, what size was it from the chart? How many mls was this? ☐☐☐☐	How many units in total did the interviewee drink per day? ☐☐☐		
(D) age or year ☐☐ or ☐☐☐☐	days / week or days / month ☐☐ days/week or ☐☐ days/mth	pints / bottles / other _____ (specify)	measures ☐☐☐	age or year ☐☐ or ☐☐☐☐	Stop drinking beer ► E7 Stop drinking and then start again ► (E)a) Change to a different amount of beer ► (E)a)
	b)ii) What type of beer did you drink? _____	If bottles or cans, what size was it from the chart? How many mls was this? ☐☐☐☐	How many units in total did the interviewee drink per day? ☐☐☐		

E7 Wine

Have you ever drunk wine, (including Babycham, Champagne and Cava)?

1 = Yes ►(A)a)
2 = No ► E8

First Period:					
(A)a) At what age (or in what year) did you begin drinking wine?	b) How often did you drink wine?	c)) Did you drink a small glasses / large glasses / bottles?	d) d) On those days when you drank wine, how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently? Stop drinking wine ► E8 Stop drinking and then start again ► (B)a) Change to a different amount of wine ► (B)a)
Aa) age or year or	b) days / week or days / month days/week or days/mth	Specify which here:	How many units in total did the interviewee drink per day?	e) age or year or	
Subsequent Periods:					
(B)a) When did you start drinking wine again or begin drinking a different amount of wine?	**b) How often did you drink wine?**	**c) Did you drink a small glasses / large glasses / bottles?**	**d)** On those days when you drank wine, how much per day did you drink?	**e) Until when did you continue to drink this amount?**	**f) Did you subsequently?**
Ba) age or year or	b) days / week or days / month days/week or days/mth	Specify which here:	How many units in total did the interviewee drink per day?	e) age or year or	Stop drinking wine ► E8 Stop drinking and then start again ► (C)a) Change to a different amount of wine ► (C)a)

E8 Pre-dinner drinks (Aperitifs)

Have you ever had a pre-dinner drink?

1 = Yes ►(A)a)
2 = No ► E9

First Period:					
(A)a) How old were you (or in what year was it) when you first started having a drink before your meals?	bi) How often did you have a pre-dinner drink?	c) Did you drink a small glass / large glass/ measure?	d) On those days when you had a pre-dinner drink, how much per day you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently? Stop drinking before dinner ► E9 Stop drinking and then start again ► (B)a) Change to a different amount ► (B)a)
a) age or year or	bi) days / week or days / month days/week or days/mth b)ii) What drink did you usually have?	specify which here:	How many units in total did the interviewee drink per day?	e) age or year or	
Subsequent Periods:					
Ba) When did you begin having a pre-dinner drink again or drink a different amount?	bii) How often did you have a pre-dinner drink?	c) Did you drink a small glass / large glass/ measure?	d) On those days when you had a pre-dinner drink how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
Ba) age or year or	bi) days / week or days / month days/week or days/mth b)ii) What drink did you usually have?	Specify which here:	How many units in total did the interviewee drink per day?	e) age or year or	Stop drinking before dinner ► E9 Stop drinking and then start again ► (C)a) Change to drinking a different amount ► (C)a)

E9 Spirits

Have you ever drunk spirits such as gin, whisky, brandy, rum, etc?

1 = Yes ►(A)a)
2 = No ► E10

First Period:

(A)a) At what age (or in what year was it) when you first began drinking spirits?	bi) How often did you drink spirits?	c) Did you drink a small glass, small measure / large glass, large measure?	d) On those days when you drank spirits, how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
a) age or year	bi) days / week or days / month	Specify which here:		e) age or year	Stop drinking spirits ► E10
or	days/week or days/mth			or	Stop drinking and then start again ► (B)a)
	b)ii) What drink did you usually have?		How many units in total did the interviewee drink per day?		Change to a different amount ► (B)a)

Subsequent Periods:

(B)a) When did you begin drinking spirits again, or change to a different amount?	bi) How often did you drink spirits?	c) Did you drink a small glass, small measure / large glass, large measure?	d) On those days when you drank spirits, how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
B)a) age or year	bi) days / week or days / month	Specify which here:		e) age or year	Stop drinking spirits ► E10
or	days/week or Days/mth			or	Stop drinking and then start again ► (C)a)
	b)ii) What drink did you usually have?		How many units in total did the interviewee drink per day?		Change to drinking a different amountt ► (C)a)

E10 Other drinks

Have you ever drunk any other type of drinks that I have not mentioned previously, such as fortified wines, tonic wines, alco pops or any other?

1 = Yes ►(A)a)
2 = No ►F1

First Period:

(A)a) At what age (or in what year was it) when you first started drinking?	bi) How often did you drink?	c) Did you drink a small glass, small measure / large glass, large measure?	d) On those days when you had a drink, how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
a) age or year	bi) days / week or days / month	Specify which here:		e) age or year	Stop drinking ► F1
or	days/week or days/mth			or	Stop drinking and then start again ► (B)a)
	b)ii) What drink did you usually have?		How many units in total did the interviewee drink per day?		Change to a different amount ► (B)a)

Subsequent Periods:

(B)a) When did you begin drinking a different drink, or change to a different amount?	b) How often did you drink?	c) Did you drink a small glass, small measure / large glass, large measure?	d) On those days when you had a drink, how much per day did you drink?	e) Until when did you continue to drink this amount?	f) Did you subsequently?
B)a) age or year	bi) days / week or days / month	Specify which here:		age or year	Stop drinking ► F1
or	days/week or days/mth			or	Stop drinking and then start again ► (C)a)
	b)ii) What drink did you usually have?		How many units in total did the interviewee drink per day?		Change to drinking a different amount ► (C)a)

HISTORY OF VARIOUS DISEASES

F1 Throughout your life, excluding the last year, have you ever had skin warts/ veruccae? ☐

1 = Yes
2 = No *[if 'No' go to F6]*
9 = Don't know
1=yes 2=no

Was it on your: F2 Hands ☐

F3 Feet ☐

F4 Head & Neck ☐

F5 Other including genitals (specify) _____ ☐

F6 Throughout your life, excluding the last year, have you ever had Candida Albicans/thrush? ☐

1 = Yes
2 = No *[if 'No' go to F10]*
9 = Don't know
1=yes 2=no

Was it on your: F7 Genitals ☐

F8 Mouth ☐

F9 Other (specify) _____ ☐

F10 Throughout your life, excluding the last year, have you ever had herpetic lesions (cold sores)? ☐

1 = Yes
2 = No *[if 'No' go to F14]*
9 = Don't know
1=yes 2=no

Was it on your: F11 Lip ☐

F12 Genitals ☐

F13 Other (specify) _____ ☐

F14 Throughout your life, excluding the last year, have you ever had heartburn? ☐

1 = Yes
2 = No *[if 'No' go to F17]*

If Yes, how frequently? (showcard 4a) ☐

1 = At least once a day
2 = 2 to 6 times per week
3 = Once per week
4 = Less than once per week

F15 At what age did you first begin suffering from heartburn? ☐☐

F16 Did you take medication for heartburn? ☐

1 = Yes
2 = No

Which (specify) _____

F17 Throughout your life, excluding the last year, have you ever suffered from regurgitation? ☐

1 = Yes
2 = No *[if 'No' go to F20]*

If Yes, how frequently? (showcard 4a) ☐

1 = At least once a day
2 = 2 to 6 times per week
3 = Once per week
4 = Less than once per week

F18 At what age did you first begin suffering from regurgitation? ☐☐

F19 Did you take medication for regurgitation? ☐

1 = Yes
2 = No

Which (specify) _____

F20 Throughout your life, excluding the last year, have you ever taken aspirin regularly (at least once a week for a year)? ☐

1 = Yes from ☐☐ to ☐☐
2 = No *[if 'No' go to G1]*

ORAL CAVITY HEALTH

Can I remind you that the following questions relate to one year ago.

G1 Did you wear a denture? ☐

1 = Yes
2 = No *[if 'No' go to G5]*

G2 In the upper jaw did you wear? ☐

1 = full denture
2 = partial denture
3 = no denture

G3 In the lower jaw did you wear? ☐

1 = full denture
2 = partial denture
3 = no denture

G4 At which age did you start wearing dentures? ☐☐

If subject wore full dentures in upper and lower jaw go to question G11.

G5 How often did you clean your teeth? (showcard 4b) ☐

0 = Never
1 = Less than once a week
2 = 1 to 2 times a week
3 = every other day
4 = once a day
5 = 2 times a day
6 = 3 times a day
7 = more than 3 times a day

G6-9 Which of the following did you use to clean your teeth? (These may not be mutually exclusive)

1=yes
2=no

G6 Toothbrush ☐

G7 Dental floss ☐

G8 Toothpaste ☐

G9 Other (specify) _____ ☐

G10 Did your gums bleed when you cleaned your teeth? ☐

1 = No
2 = Sometimes
3 = Always or almost always

G11 How often did you use mouthwashes? (showcard 4b) ☐

0 = never
1 = less than once a week
2 = 1 to 2 times a week
3 = every other day
4 = once a day
5 = 2 times a day
6 = 3 times a day
7 = more than 3 times a day

G12 During the last 20 years, how often did you go to see a dentist? ☐

0 = at least every year
1 = every 2 to 5 years
2 = less than every 5 years
3 = never

OCCUPATIONAL HISTORY FORM

Let's now talk about your work. We are interested in the kind of work you have done and where you have worked. Please treat significant changes of job title as separate jobs, even if they occurred within the same company. Please also indicate times during which you were not employed, e.g. you were a housewife, unemployed, student, undergoing professional training etc.

H1 a) I want to go through those jobs one after another.

Let's start with the time after you finished school. When did you start your first job? When did you finish this job?

date age

from

to

b) b) What was your job title?

c) What did this company / organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

H2 a) Let's proceed to your next job activity.

When did you start and when did you finish this job?

date age

from

to

b) b) What was your job title?

c) What did this company / this organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

H3 a) Let's proceed to your next job activity.

When did you start and when did you finish this job?

date age

from

to

b) b) What was your job title?

c) What did this company / this organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

H4 a) Let's proceed to your next job activity.

When did you start and when did you finish this job?

date age

from

to

b) b) What was your job title?

c) What did this company / this organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

H5 a) Let's proceed to your next job activity.
When did you start and when did you finish this job?

date age
from
to

b) b) What was your job title?

c) What did this company / this organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

H6 a) Let's proceed to your next job activity.
When did you start and when did you finish this job?

date age
from
to

b) b) What was your job title?

c) What did this company / this organisation mostly do?
Activity of the company / production:

d) Please describe what kind of work you mainly did and how you did it?
main activity:

EXAMINATION BY INTERVIEWER

Anthropometric measures

I2 Can you tell me what was your weight one year ago?
stones pounds
or kg

I3 If you remember, can you tell me what was your weight at age 30?
(leave blank if subject is less than 30)
stones pounds
or kg

I4 Can you tell me how tall you are?
feet inches
or cm

Measurement was obtained from: 3
1 = direct measurement
2 = medical notes
3 = participant

I5 Finish time (according to 24hr clock) – end of lifestyle questionnaire
hours mins

I6 Interviewee's comments (controls only).
That is the end of the interview. Do you have any comments you would like me to record at this time?

I7 Interviewer comments

Place of interview

Other people present at interview

Quality of Life Questionnaire

J0 Start time of Quality of Life Questionnaire (according to 24hr clock) hour min

Have you had any of the following treatments for your current illness?

Surgery	1 = yes 2 = no	If yes: date of surgery	
Chemotherapy	1 = yes 2 = no	If yes: start date	
		finish date	
Radiotherapy	1 = yes 2 = no	If yes: start date	
		finish date	

Patients' concerns: **In these questions you will be asked about your concerns. We will, for all the concerns listed, indicate how bothered you have been by ticking the answer (box) which applies to you at this time.**

Have you been concerned during the last week by:

		no concern	slight concern	moderate concern	major concern
J1	Job	☐	☐	☐	☐
J2	Current illness	☐	☐	☐	☐
J3	Relationship with others	☐	☐	☐	☐
J4	Inability to do things	☐	☐	☐	☐
J5	Treatment	☐	☐	☐	☐
J6	Fear of recurrence	☐	☐	☐	☐
J7	Sexuality	☐	☐	☐	☐
J8	Physical symptoms	☐	☐	☐	☐
J9	Feeling different	☐	☐	☐	☐
J10	Amount of support	☐	☐	☐	☐
J11	Finances	☐	☐	☐	☐
J12	Feeling upset	☐	☐	☐	☐
J13	Future	☐	☐	☐	☐

Below is a list of comments made by people after a diagnosis of cancer.

We will tick each item to show how frequently these comments are **true** for you **during the last week**.

If they did **not** occur during that time, we will tick the 'never' column.

		Never	Rarely	Some times	Often
K1	*" I avoid getting upset about the possibility of the cancer coming back"*	☐	☐	☐	☐
K2	*" I think about the cancer returning when I didn't mean to"*	☐	☐	☐	☐
K3	*" I **try** not to talk about my cancer recurring"*	☐	☐	☐	☐
K4	*" Other things keep making me think about recurrence"*	☐	☐	☐	☐
K5	*"I prevent myself from thinking about recurrence"*	☐	☐	☐	☐
K6	*"I picture myself being told that the cancer has returned"*	☐	☐	☐	☐
K7	*"I just try to ignore feelings about the cancer returning"*	☐	☐	☐	☐
K8	*"I get waves of strong feelings about the cancer coming back"*	☐	☐	☐	☐

Please turn over

L8 I feel as if I am slowed down:
- Nearly all of the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

L9 I get a sort of frightened feeling like butterflies in my stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

L10 I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

L11 I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

L12 I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

L13 I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

L14 I can enjoy a good book or radio or television programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Please turn over

Here are some questions about your attitudes and worries about cancer.

A few people have told us that they feel worried not only about having cancer but also whether it might return after treatment.

- **For each question, I will ring the number to give your answer.**
- **Please refer to** the past week only.
- **(If applicable) If you have had your diagnosis for less than a week, please would you refer** to the time since you were told about your diagnosis.

M1 What do you think are the chances that you will get a recurrence (that is, the cancer will come back after treatment) of your cancer?

0	1	2	3	4	5	6	7	8	9	10
Definitely will not		Probably will not			50 – 50			Probably will		Definitely will

M2 To what extent does worry about cancer spill over or intrude into your other thoughts and activities?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A great deal

M3 How emotionally upset or distressed are you about the possibility of cancer returning?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A great deal

M4 How often have you worried about the possibility that cancer might come back after treatment?

0	1	2	3	4
None of the time	Rarely	Occasionally	Often	All the time

Please turn over

This questionnaire asks about your health and quality of life **over the past week.** Please answer all of the questions by indicating one response for each question.

N1 **Pain** (tick one box)

- I have no pain
- There is mild pain not needing medication
- I have moderate pain - requires regular medication (codeine or painkiller)
- I have severe pain controlled only by painkillers
- I have severe pain, not controlled by medication

N2 **Appearance** (tick one box)

- There is no change in my appearance
- The change in my appearance is minor
- My appearance bothers me but I remain active
- I feel significantly disfigured and limit my activities due to my appearance
- I cannot be with people due to my appearance

N3 **Activity** (tick one box)

- I am as active as I have ever been
- There are times when I can't keep up my old pace, but not often
- I am often tired and have slowed down my activities although still get out
- I don't go out because I don't have the strength
- I am usually in bed or chair and don't leave home

N4 **Recreation** (tick one box)

- There are no limitations to recreation at home or away from home
- There are a few things I can't do but I still get out and enjoy life
- There are many times when I wish I could get out more, but I'm not up to it
- There are several limitations to what I can do, mostly I stay at home and watch TV
- I can't do anything enjoyable

N5 **Swallowing** (tick one box)

- I can swallow as well as ever
- I cannot swallow certain solid foods
- I can only swallow liquid foods
- I cannot swallow because "it goes down the wrong way" and chokes me

N6 **Chewing** (tick one box)

- I can chew as well as ever
- I can eat soft solids but cannot chew some foods
- I cannot even chew soft solids

N7 **Speech** (tick one box)

- My speech is the same as always
- I have difficulty saying some words but I can be understood over the phone
- Only my family and friends can understand me
- I cannot be understood

N8 **Shoulder** (tick one box)

- I have no problem with my shoulder
- My shoulder is stiff but is has not affected my activity or strength
- Pain or weakness in my shoulder has caused me to change my work
- I cannot work due to problems with my shoulder

N9 **Taste** (tick one box)

- I can taste food normally
- I can taste most foods normally
- I can taste some foods
- I cannot taste any foods

N10 **Saliva** (tick one box)

- My saliva is of normal consistency
- I have less saliva than normal, but it is enough
- I have too little saliva
- I have no saliva

N11 **Mood** (tick one box)

- My spirits are excellent, and my mood is unaffected by my cancer
- I am generally in good spirits
- I am neither in good spirits nor depressed about my cancer
- I generally feel down about my cancer
- I am extremely depressed about my cancer

N12 **Anxiety** (tick one box)

- I don't worry too much about my cancer
- I worry a little bit about my cancer
- I worry quite a lot about my cancer
- I worry almost all the time about my cancer

N13 Which issues have been the most important to you during the past 7 days? (tick up to 3 boxes)

Pain	Activity	Shoulder
Swallowing	Speech	Anxiety
Taste	Mood	Recreation
Appearance	Saliva	Chewing

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life (tick one box)

- Much better ☐
- Somewhat better ☐
- About the same ☐
- Somewhat worse ☐
- Much worse ☐

In general, would you say that your health related quality of life during the **past week** has been. (tick one box)

- Outstanding ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐
- Very poor ☐

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life.

Considering everything in your life that contributes to your personal well-being, rate your overall quality of life during the past 7 days. (tick one box)

- Outstanding ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐
- Very poor ☐

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions.

Please say if there are any other issues you would like to mention which I can note down here that you feel have been missed in this interview and that are important for you.

THANK YOU VERY MUCH FOR ALL YOUR HELP.

Finish time (according to 24hr clock) – end of interview ☐☐:☐☐ (hour mins)