# Investigations into opportunities for early detection of oral cancer

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# Abstract

**Background:**

Early detection strategies for oral cancer aim to decrease the mortality rates and improve outcomes of the disease through early diagnosis and treatment. Guidance and regulatory bodies have an expectation that general dental practitioners will be able to promptly detect and refer patients with suspected oral cancerous lesions. However, the opportunities for early detection of oral cancer in primary dental care settings (particularly considering the low overall volume of the disease, the potentially increasing incidence rates, and the possibility of certain communities exhibiting particularly high rates) have not yet been investigated. This thesis examines the feasibility of early detection of oral cancer in primary dental care services, and undertakes risk-stratification to identify "high-risk" communities that can be utilised to target future early detection efforts. It further explores potential or missed opportunities for early detection in dental and other healthcare settings (both primary and secondary care), and assesses the feasibility of exploring routes to diagnosis.

**Aim:**

The aim of this thesis was to investigate opportunities for the early detection of oral cancer in Scotland by measuring the current burden of the disease, examining the feasibility of early detection in a dental setting, and exploring the potential role of alternative health care settings in early detection efforts.

**Methods**

Descriptive epidemiological and data linkage cohort studies utilising national routine administrative health datasets were undertaken. The descriptive epidemiological analysis included all cases of head and neck

cancer diagnosed between 1975 and 2012 and registered on the Scottish cancer Registry and annual midterm population estimates. These data were used to examine the incidence trends between 1975 and 2012 and the projected burden up to 2025 by individual subsites (oral cavity cancer, oropharyngeal cancer, and laryngeal cancer), age, sex, health board region, and socioeconomic status.

The cohort study included all patients diagnosed with oral cancer between 2010 and 2012 and registered on the Scottish Cancer Registry. The individual patient data were linked to NHS dental service activity in the two years prior to diagnosis, and this linked cohort dataset and published NHS Scotland dental workforce and registration and participation statistics were used to examine dental attendance rates and the feasibility of early detection of oral cancer in the primary dental care setting.

The individual patient data from the cohort were also linked to the hospital outpatient, hospital inpatient/day case, primary dental care, and general practitioner prescription databases. These four healthcare services were selected based on data availability. The linked data were used to examine all healthcare service contacts made by the cohort in the two years prior to referral. Additionally, a preliminary exploration of the referral period (defined as the one-month period prior to diagnosis) was also undertaken.

**Results and conclusions**

The findings of this thesis showed that the incidence rates of head and neck cancer had increased in Scotland between 1975 and 2012, and this appeared to be largely driven by a dramatic rise in the rates of oropharyngeal cancer in recent decades. This burden was predicted to continue to rise up to 2025, with the rates of oropharyngeal cancer bypassing the rates of oral cavity cancer, which were expected to exhibit only a modest increase. Males, individuals above 60 years of age, and those from the most deprived areas of Scotland consistently exhibited the

highest rates of cancer, irrespective of subsite. Moreover, an almost dose-like effect was seen to exist, with the rates of cancer increasing with the level of deprivation. Therefore, contrary to previous reports that oropharyngeal cancer exhibited an inverse socioeconomic profile, Scotland country-level data showed that those from the most deprived areas consistently bore the greatest incidence burden of head and neck cancer.

Despite these increasing trends, the overall burden of oral cancer in Scotland was relatively low, and just over half of the cohort examined in this thesis had not contacted a general dental practitioner in the two years prior to diagnosis, thus automatically limiting opportunities for early detection. Dentists were estimated to potentially encounter one patient with oral cancer every 10 years, one patient with oral cavity cancer every 17 years, and one patient with oropharyngeal cancer every 25 years. Therefore, strategies for early detection must consider the rarity of oral cancer incidence and the poor dental attendance patterns of patients, and the expectations of dentists in these efforts must be tempered. These results also highlight the importance of improving access and uptake of dental services among those at the highest risk of developing oral cancer (i.e. those from the most deprived communities).

When examining the linked cohort data and undertaking a look-back analysis of their healthcare service contact history, just under half (45%) of the patients diagnosed with oral cancer were seen to have actually visited a primary care dental service clinic in the two years prior to the start of the referral period. However, the majority of the patients with oral cancer had contacted one of the four healthcare services examined (hospital outpatient, hospital inpatient/day-case, primary dental care, and general practitioner prescription) at least once over the same period, suggesting that there were potential or missed opportunities for the early detection of oral cancer in primary dental care and alternative healthcare settings. The proportions of patients contacting the four services increased closer to the start of the referral period, as did the mean number of contacts made with each service. Although not all of these instances would have

necessarily been associated with missed opportunities for early detection, it was highly likely that there were potential or missed opportunities amongst at least some of the patients with oral cancer.

The two most common services contacted most recently before the start of the referral period were general practitioner prescription and hospital outpatient, and there was a possibility that these services were the sources of referral. The hospital specialties contacted most frequently during the one-month referral period were ENT, oral surgery, oral and maxillofacial surgery, and general surgery, suggesting that these contacts were likely to have been associated with the signs and symptoms of oral cancer. While no significant opportunities for the early detection of oral cancer in hospital or secondary care settings were identified, these findings demonstrated considerable potential in other primary care settings, particularly general medical practices and community pharmacies.

In conclusion, this thesis identified several areas, particularly with regard to the subgroups of the population at the highest risk of developing cancer and alternative healthcare services, that early detection efforts can and should target. Future strategies should also aim to minimise delays in the diagnostic process and increase regular attendance rates by providing additional motivation and support to those who did not attend primary dental care clinics on a regular basis.

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# Author's Declaration

Parts of the research work included in this thesis have been presented in international and national conferences and have also been published or submitted with co-authors.

**National Conferences**

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Oral presentation title: Trends of oral cavity, oropharyngeal, and laryngeal cancer incidence in Scotland (2001- 2012).

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Oral presentation title: Opportunities for opportunistic oral cancer screening

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**Publications**

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**Chapter 3:** Purkayastha M, McMahon AD, Gibson J, & Conway DI (2017) Is detecting oral cancer in general dental practices a realistic expectation? - A population-based study using population linked data in Scotland. British Dental Journal (In Press).

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

Mitana Purkayastha

Glasgow, January 2018

# Abbreviations

| | |
|---|---|
| ACS: | American Cancer Society Cancer Facts and Figures Report |
| AJCC: | American Joint Committee on Cancer |
| ASR: | Age-standardised Rate |
| C.I: | Confidence Interval |
| CHI: | Community Health Index |
| CI5: | Cancer incidence in Five Continents |
| COE: | Conventional Oral Examination |
| CPD: | Continuing Professional Development |
| CRUK: | Cancer Research United Kingdom |
| EASR: | European age-standardised rates |
| eDRIS: | electronic Data Research and Innovation Service |
| GDC: | General Dental Council |
| GDP: | General Dental Practitioner |
| GDS: | General Dental Service |
| GP: | General Practitioner |
| HDI: | Human Development Index |
| HNC: | Head and Neck Cancer |
| IARC: | International Agency of Research on Cancer |
| ICER: | Incremental Cost-Effectiveness Ratios |
| INHANCE: | International Head and Neck Cancer Epidemiology Consortium |
| ISD: | Information Services Division |

| | |
|---|---|
| ISI: | International Statistical Institute |
| MIDAS: | Management Information and Dental Accounting System |
| NCD: | Non-Communicable Disease |
| NCI: | National Cancer Institute |
| NCIN: | National Cancer Intelligence Network. |
| NGO: | Non-Governmental Organisation |
| NHS: | National Health Service |
| NICE: | National Institute for Health and Care Excellence |
| NRS: | National Records Scotland |
| NSS: | National Services Scotland |
| OC: | Oral Cancer |
| OCC: | Oral Cavity Cancer |
| OHRA: | Oral Health Risk Assessment |
| OPC: | Oropharyngeal Cancer |
| OPMD: | Oral Potentially Malignant Disorder |
| OR: | Odd's Ratio |
| PBPP: | Public Benefit and Privacy Panel |
| PCT: | Primary Care Trust |
| PIS: | Prescribing Information System |
| PSD: | Practitioner Services Division |
| QALY: | Quality-Adjusted Life-Years |
| RR: | Rate Ratio |

S.D: Standard Deviation

SDR: Statement of Dental Remuneration

SEER: Surveillance, Epidemiology and End Results Program

SES: Socioeconomic Status

SIMD: Scottish Index of Multiple Deprivation

SMR: Scottish Morbidity Records

SPIRE: Scottish Primary Care Information Resource

TNM: Tumour, Node, Metastasis

UICC: Union for International Cancer Control

UK: United Kingdom

UKNSC: United Kingdom National Screening Committee

UN: United Nations

UNDP: United Nations Development Program

USA: United States of America

WHO: World Health Organisation

# 1 Introduction

“It is hard to look at the tumour and not come away with the feeling that one has encountered a powerful monster in its infancy” (Mukherjee, 2010).

As Siddhartha Mukherjee, an Indian-born American physicist and oncologist very eloquently described in his Pulitzer prize winning book, *The Emperor of all Maladies,* cancer is a killer disease that has become one of the leading causes of mortality in the world, and this trend is only going to continue to grow (Mukherjee, 2010). In an interview with the New York Times, Mukherjee said that he found himself “thinking of cancer as this character that has lived for 4,000 years” and wondering “what was its birth, what is its mind, its personality, its psyche?” (McGrath, 2010). This line of thought ultimately led to the birth of a biography of the disease that weaved together his experiences as an oncologist and the history of cancer treatment and research (Mukherjee, 2010). The “power” of cancer was more lyrically described previously by the American poet, Jason Shinder, when he, rather nonchalantly, said to his friend “cancer is a tremendous opportunity to have your face pressed right up against the glass of your mortality” upon receiving a diagnosis of non-Hodgkin’s lymphoma and leukaemia, diseases which ultimately claimed his life (Thernstrom, 2008). Mukherjee (2010) later commented on these words, saying that “what patients see through the glass is not a world outside cancer, but a world taken over by it—cancer reflected endlessly around them like a hall of mirrors”, highlighting the sheer power and overwhelming nature of the disease. Cancer not only has major impacts on the individuals affected by it and their families, but also on communities and countries.

The World Health Organisation defined cancer as a “large group of diseases that are characterised by abnormal growth of cells beyond the limits of their usual boundaries, often accompanied by invasion into adjoining parts of the body and spread to other organs” (WHO, 2017a). The International Agency for Research on Cancer, in the 2014 *World Cancer Report*,

identified the global burden of cancer as one of the leading causes of mortality and morbidity, with over 14 million new patients and eight million cancer-related deaths occurring in 2012 alone (IARC, 2014). Approximately 60% of these new cancers and 70% of all cancer-related deaths occurred in Africa, Asia, and Central and South America. Vast global inequalities in the distribution of cancer between high and low-income countries were also observed, particularly by subsite, and such data were described by the WHO IARC as "key to an understanding of causation, and hence the development of preventive measures" (IARC, 2014). The total global annual economic cost of cancer was estimated to be approximately $US 1.16 trillion, thus posing a substantial threat to economies, families, and individuals (WHO, 2017a). The 70th World Health Assembly (2017) recently adopted a draft resolution, "C*ancer prevention and control in the context of an integrated approach",* that included 18 sponsors, 40 member states, and 11 non-governmental organisations (NGO) (WHO, 2016). The broad consensus of this resolution was that cancer was a growing public health concern and required prioritisation and funding. Moreover, it clarified that this more concerted approach to the prevention and management of cancer was necessary if governments aimed to achieve the Sustainable Development Goals by 2030, particularly the target to decrease premature mortality from non-communicable diseases (NCDs), such as cancer, by one third, and the target which endeavoured to achieve universal health coverage to improve cancer care and outcomes (WHO, 2017a).

In 2012, head and neck cancers (comprising oral, pharyngeal and laryngeal cancers) were the seventh most common cancer in terms of incidence and ninth most common in terms of mortality globally (Ferlay et al., 2015). The majority (more than 60%) of these cancers are diagnosed at a late stage when the prognosis is considerably poorer and the treatment options are more expensive (CRUK, 2017b; Howlader et al., 2017). This thesis focuses on early detection efforts for oral cancer, and considers its relationship with the burden of the disease. This first chapter sets out the background

and context to the thesis and includes a literature review highlighting the various gaps and debates.

Section 1.1– provides a broad background to the thesis, focusing mainly on the debates, both in the literature and clinically, in relation to the definitions of oral and head and neck cancer.

Section 1.2 – reviews the descriptive epidemiological literature on oral cancer globally, and particularly in the United Kingdom.

Section 1.3 – discusses the various concepts of early detection of oral cancer and the factors contributing to them, reviews the role of dental and alternative healthcare services in early detection efforts, and considers some of the evidence on missed opportunities for the early detection of cancer.

Section 1.4 – provides a brief summary of the various debates in the literature and lists some of the gaps identified.

Section 1.5 – sets out the hypotheses generated and the aims and objectives of this thesis.

## 1.1 Cancer classification and definitions

### 1.1.1 Early classification of diseases

Nosology or the science of classification of diseases, if Albert Einstein's definition of science as "an attempt to make the chaotic diversity of our sense experience correspond to a logically uniform system of thought" is to be adopted, has been a subject of research for a long time (McKusick, 1969). The development of disease classification arose from a need to produce "comparable cause-of-death statistics", and it allowed standardisation of groupings and the display of information collected during death registration (Moriyama et al., 2011). This work could be considered as the precursor of the discipline of descriptive epidemiology.

Moriyama et al. (2011) produced a detailed history of the classification of diseases. In summary, the first evidence of attempts to classify diseases (Jean Fernel's *Universa Medicini* published in 1554 and Thomas Sydenham's *Opera Omnia* published in 1685) were largely founded on humoral theories of disease and were of little use in terms of understanding the disease process. This approach underwent a radical change in the 18th century when various scientists such as Erasmus Darwin and F. Boissier de la Croix de Sauvages developed an interest in diseases. The latter published *Nosologia Methodica*, a treatise containing ten classes that were mainly symptoms subdivided into 300 orders and further genera. By the middle of this century, the ability of diseases to affect certain organs was recognised, and this led to the development of a morphological classification. Alibert's *Nosologie Naturelle*, published in 1817, represented the last use of the "botanical" systems of disease classification, and was replaced by John Mason Good's *A Physiological System of Nosology*, also published in 1817, which was included in future medical books and was used as a basis for disease nomenclature (Moriyama et al., 2011).

William Farr, after examining all the existing nosologies, concluded that Sauvage's work was the first of its kind to make any innovative contributions to the field. In 1839, he went on to publish the *First Annual Report of the Registrar General of Births, Deaths, and Marriages* in England (Felling, 1978; Eyler, 1979), where he divided the causes of death into three main categories: first were diseases that occurred on an epidemic or endemic basis or "communicable diseases"; second were diseases that appeared sporadically, which he further subdivided anatomically; and the third group was for death by violence. Although Farr campaigned the use of his system of classification extensively, it failed to gain popularity and was critiqued on various matters such as his decision to classify diseases anatomically and his notion of communicable diseases (Moriyama et al., 2011). Interestingly, William Farr, the nineteenth century British epidemiologist regarded as one of the founders of medical

statistics, also lends his name to the Farr Institute, a multicentre collaboration in the United Kingdom that provides infrastructure for big data and data linkage analysis (Farr Institute, 2017).

The Great Exhibition held in 1851 in the Crystal Palace in London (UK), which brought together statisticians from all over the world, ultimately triggered the first International Statistical Congress in 1853 where "Causes of Death" was identified as one of the measures suitable for international statistical comparison (Moriyama et al., 2011). Jacques Bertillon, Chief of Statistics for the City of Paris, chaired a committee that was commissioned to prepare a classification of the causes of death, which was to be presented at the next meeting of the International Statistical Institute (ISI) held in Chicago (USA) in 1893. This list defined diseases by their nature of transmission or frequency of occurrence and included the following 14 main headings: general diseases, diseases of the nervous system and sense organs, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the genitourinary system, puerperal diseases, diseases of the skin and annexes, diseases of the locomotor organs, malformations, diseases of early infancy, diseases of old age, the effects of external causes, and ill-defined diseases. This classification received general acceptance and marked the birth of the *International List of Causes of Death*. By the next ISI meeting in 1899, this list had already been widely accepted in many countries in North America, South America, and Europe. In 1898, the American Public Health Association passed a resolution that this list would be revised every ten years, and this responsibility would be attributed to "an international committee for which strict regulations were set out" (Moriyama et al., 2011). This was maintained up until the 6$^{th}$ revision when, following World War II and the demise of the League of Nations, this responsibility was handed over to the World Health Organisation who have been accountable for the revisions ever since (Moriyama et al., 2011).

### 1.1.2 International Classification of Diseases and Related Health Problems- 10th revision

The International Classification of Diseases, now in its 10th revision, is a standardised diagnostic tool that defines the universe of diseases in a comprehensive manner, and its main purpose is to "allow systematic recording, analysis, interpretation, and comparison of mortality and morbidity data" across different countries and areas (WHO, 2004). It is also used for all epidemiological and health management purposes, including monitoring of the incidence and prevalence of various diseases and their relation to the characteristics of the affected individual, managing health care resources, ensuring that safety and quality guidelines are adhered to, scrutinising reimbursements, and monitoring outcomes. The International Classification of Diseases for Oncology (ICD-O) is an extension of the second (neoplasm) chapter of the International Classification of Diseases, and was first published by the WHO (2017c). It is mainly intended for use by cancer registries, and has a coding system that records tumour topography and morphology.

The design of the ICD permits easy storage, retrieval, and analysis of health data to allow evidence based decision-making. It also permits easy exchange and comparison of data between various regions and hospital settings, as well as within the same region or hospital over different periods of time, and the principle users include nurses, health workers, physicians, health information managers, policy-makers, national health program managers, researchers, and epidemiologists (WHO, 2017c). However, this classification has also been described as having limited use when little or no information is available about the patient (Kurbasic et al., 2008). It is also considered unsuitable for indexing distinct clinical entities, and has some constraints in case of studies examining the financial aspects of diseases (WHO, 2004). Moreover, the definitive ICD coding of a disease can only be determined after several patient visits, and it is extremely rare for this to become apparent at the very first patient-health care worker interaction (Kurbasic et al., 2008). This is particularly

true for cancer where there is a need to triangulate clinical and pathological information before confirming the diagnosis.

Furthermore, although this system of classification of diseases is particularly good for the identification of individual precise anatomical sites (e.g. floor of the mouth), several debates begin to emerge when these sites are grouped into collective areas (e.g. oral cavity). This will be discussed in further detail later in this chapter.

### 1.1.3 Definitions of head and neck cancer

Head and neck cancer is defined by the World Health Organisation International Agency for Research on Cancer (WHO IARC) to broadly include all cancerous lesions of the lip, tongue, palate, floor of the mouth, gums, salivary glands, tonsils, oropharynx, nasopharynx, hypopharynx, and larynx (Barnes, 2005). However, various sources of literature often differ in their definitions of head and neck cancer, oral cavity cancer, and oropharyngeal cancer, particularly with regard to the subsites that are included within each of these groupings. The GLOBOCAN project, coordinated by IARC, provides a global perspective of the incidence, mortality, and survival of all cancers. This project addressed the “components” of head and neck cancer as individual subsites to show that incidence and mortality rates differed considerably based on the anatomical locations included, and made the data available via an interactive website (IARC, 2017a). However, they combined the lip (including external lip) and oral cavity as one subsite, and did not permit separation and examination of the rates of oropharyngeal cancer and oral cavity cancer individually.

The National Cancer Institute (NCI), a subdivision of the US National Institute of Health, defined head and neck cancer as “cancer that arises in the head or neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx [voice box])” (NCI, 2014). However, the fact sheets generated by the Surveillance, Epidemiology and End Results (SEER) program of the NCI used a different definition of head and neck cancer

wherein the oesophagus, eye and orbit, larynx, oral cavity and pharynx (with reporting for the sub-site of tongue), and thyroid were also included (Radosevich, 2013). Moreover, their main reports combined oropharynx and hypopharynx as one subsite, and the "Oral cavity and Pharynx" section of the SEER Cancer Statistics Review 1975-2014 focused on a combination of the anatomical locations and addressed the individual subsites only very briefly (Howlader et al., 2017).

Another important and accessible source of cancer statistics in the United Kingdom is Cancer Research UK (CRUK), a cancer charity that promotes and funds research campaigns for better cancer prevention and management. They defined head and neck cancer as including approximately thirty different organs and tissues including the "eye, nasal and paranasal sinus (cancers in the nasal cavity and in the sinuses around the nose), nasopharynx (the area that connects the back of the nose to the back of the mouth), mouth and oropharynx (cancers of the tongue, the gums, cheeks, lip and floor and roof of the mouth), larynx or laryngeal cancer (cancer of the voice box), and oesophagus (cancer of the food pipe or gullet)" (CRUK, 2017a). In contrast, the National Head and Neck Cancer Audit, 2014, conducted in England and Wales, defined head and neck cancer as "neoplasms arising principally from the mouth (oral cavity), voice box (larynx), throat / upper gullet (pharynx), salivary glands, nose and sinuses, and primary bone tumours of the jaw", and did not appear to include tumours involving the oesophagus (NHS, 2014). Similarly, the Scottish Cancer Registry defined head and neck cancer as including malignant neoplasms of the lip, oral cavity, pharynx, nasal cavity, middle ear, accessory sinuses, and the larynx (ICD-10 codes C00-C14 and C30-C32), and also did not include tumours of the oesophagus (ISD Scotland, 2017a).

### 1.1.4 Definitions of oral cancer

A review of the literature on the definitions of oral cancer revealed a lack of consensus in the terminology used, with common variations including cancer of the mouth and pharynx, cancer of the oral cavity, intraoral

cancer, oral cavity cancer, oral malignant tumours etc (Tapia and Goldberg, 2011). This not only complicated search strategies but also hindered the identification of all relevant and appropriate studies. Although no systematic review was undertaken here, a thorough literature search identified a short list of the various terms in use (Table 1-1).

This was further complicated by a lack of consensus in the method of definition employed, with two main schools of thought becoming apparent. The first was an *anatomical* method of definition which took the boundaries of the various subsites into consideration, while the second was an *aetiological* method of definition largely focused on risk factors (particularly the relatively newly recognised risk factor, the human papilloma virus) (D'Souza, 2007).

**Table 1-1: Different terminologies used for "oral cancer" [adapted from (Tapia and Goldberg, 2011)]**

| |
|---|
| Cancer of the tongue and oral cavity and pharynx (Møller, 1989) |
| Cancer of the oral cavity/oropharynx (Merletti et al., 1989) |
| Tongue and mouth cancer (Franceschi et al., 1990) |
| Malignant oral tumours (Östman et al., 1995) |
| Mouth cancer (Moore et al., 2000a) |
| Oral cavity and pharynx cancer (Canto and Devesa, 2002) |
| Cancer of the oral cavity (Carvalho et al., 2004) |
| Oral and pharyngeal cancer (Tarvainen et al., 2004) |
| Intraoral cancer (Chandran et al., 2005) |
| Oral cavity and oropharyngeal cancers (Gillison, 2007) |
| Oral cavity and pharynx-throat cancer (Rodu and Cole, 2007) |
| Cancer of mouth and pharynx (Tarvainen et al., 2008) |
| Oral and oropharyngeal cancer (Warnakulasuriya, 2009a) |
| Cancer of oral cavity and pharynx (Goldstein et al., 2010) |
| Oral cancer (Zini et al., 2010) |
| Oral cavity cancer (de Camargo Cancela et al., 2010) |
| Oral malignant tumours (Rojas Alcayaga et al., 2010) |

#### 1.1.4.1 Anatomical definitions of oral cancer

Unlike other parts of the body, the boundaries of the oral cavity, that is, where the "mouth" ends and the "throat" begins, cannot always be clearly demarcated, resulting in variations in the way in which "oral cancer" is defined in published literature, as reviewed by Tapia and Goldberg (2011). Gray's Anatomy defined the mouth or oral cavity as extending from the internal mucosal surface of the lips to the palatoglossal fold antero-posteriorly, and from the floor of the mouth and tongue to the hard palate infero-superiorly (Bannister et al., 1999). The buccal mucosa lined the cheek from the commissure of the lips to the palatoglossal fold, and the gingiva outlined the teeth. All of these soft tissues were lined by squamous epithelium, and different areas of the mouth exhibited different levels of keratinisation (Bannister et al., 1999). The oropharynx was the region lying behind the oral cavity, anatomically defined superiorly by the posterior section of the soft palate and inferiorly by the superior border of the epiglottis. Anterio-posteriorly, Gray's stated that it extended from the posterior third of the tongue and the isthmus of Fauces to the oropharyngeal wall. The palatopharyngeal arches and tonsils were found laterally (Bannister et al., 1999).

Although these are the broadly accepted boundaries, other anatomical texts seemed to vary in their descriptions of the boundaries (Cunningham, 1818; Bannister et al., 1999; Rosse and Gaddum-Rosse, 1997), particularly with regard to the interface between the oral cavity and oropharynx. De Camargo Cancela et al. (2010) defined oral cancer as including only the areas within the vermillion border of the lip and the junction between the soft and hard palates, while others included the oropharynx (Warnakulasuriya, 2009a), nasopharynx and hypopharynx (Rodu and Cole, 2007).

Smith et al. (2010) stated that currently there existed an "uncontrolled explosion of different ways of describing information", and this not only complicated epidemiological research but also made it difficult to identify

relevant literature with ease (Tapia and Goldberg, 2011). Grouping various anatomical sites under one definition had certain advantages such as reducing the risk of issues with classification and increasing the number of eligible cases in wider diagnostic categories, as concluded by Moore et al. (2000b). Moreover, according to Boyle et al. (1990), it also eliminated the need for accurate estimation of the primary site of the tumour, as classifying neoplasms into sub-groups of oral cancer often reduced the need for clinicians to assign a precise location to tumours that extended over multiple anatomical sites. However, this type of grouping also had some documented disadvantages including loss of information and masking or misrepresentation of the true rates of cancer, particularly when the anatomical subsites differed with regard to aetiology and pathogenesis and, in case of large populations, exhibited high incidence rates of any one of the subsites (Smith, 1989; Junor et al., 2010).

#### 1.1.4.2 Aetiological definition of oral cancer

Evidence from case-control and descriptive epidemiological studies have suggested that oral cavity and oropharyngeal cancers may differ in terms of their risk factors (Chaturvedi et al., 2008). The most important advancements in understanding these risk factors were made under the auspices of the International Head and Neck Cancer Consortium (INHANCE). This collaboration pooled together individual participant data from 35 large case-control studies, and now contains a total of 25,500 patients with head and neck cancer and 37,100 controls (INHANCE, 2004). Winn et al. (2015) summarised the results of the INHANCE analyses and reported that the key risk factors of oral cavity cancer were tobacco and alcohol consumption, with increased risk of developing cancer being observed upon smoking even a few cigarettes a day and considerable benefits being associated with quitting tobacco consumption. Other risk factors identified by them included socioeconomic factors such as low education and income, lean body weight, family history of head and neck cancer, and short height. Dietary factors such as increased intake of fruits and vegetables

and foods high in antioxidants, on the other hand, were reported to have a protective effect and reduce the risk of developing cancer.

However, in relation to differences in aetiological factors by subsite, D'Souza et al. (2007), in their case-control study examining 100 patients diagnosed with oropharyngeal cancer and 200 controls, first reported an association between the human papillomavirus (HPV) infection and oropharyngeal cancer. This was corroborated by several other studies that reported an association between HPV infections and the individual subsites typically included under oropharyngeal cancer (El-Mofty and Lu, 2003; Herrero et al., 2003; Gillison, 2004; Dahlstrand and Dalianis, 2005; Furniss et al., 2007). In contrast, HPV infections did not appear to affect the oral cavity and other subsites in the head and neck region to the same degree, although the evidence on this was relatively unclear (Hübbers and Akgül, 2015).

This critical difference in the aetiology of oral cavity cancer and oropharyngeal cancer has resulted in many epidemiological studies opting to examine incidence trends by HPV-associated groups instead of the more traditional subsites (oral cavity and oropharynx) (Chaturvedi et al., 2008; Chaturvedi et al., 2011; Chaturvedi, 2012). This has also given rise to another method of definition wherein subsites exhibiting an association with HPV (such as the base of the tongue and tonsil) are included under oropharyngeal cancer (Gillison, 2000; Dahlstrand and Dalianis, 2005), and the remaining are classified under oral cavity cancer. In order to better understand these differences, the main global cancer epidemiology and surveillance agencies as well as a few known local groups were selected and their definitions of oral cavity and oropharyngeal cancers were assessed. Tables 1-2 and 1-3 show the variations in the subsites included under the definitions of "oral cavity cancer" and "oropharyngeal cancer" between some of these databases. The major differences appeared to lie in the grouping of the lingual tonsil, soft palate, uvula, and the base of the tongue, with some databases opting to include them under oral cavity

cancer (possibly anatomical method of definition) and others including them under oropharyngeal cancer (HPV-associated method of definition).

**Table 1-2: Inconsistencies in subsites included under "oral cavity cancer" in various descriptive databases**

| Oral Cavity Cancer | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subsite** | **INHANCE** | **SEER** | **ACS** | **IARC GLOBOCAN** | **C15** | **Gillison group** | **NCIN** | **Scottish Cancer Registry** |
| External lip | | X | X | X | | | | |
| Lip | X | X | X | X | | | | |
| Base of tongue, NOS | | X | X | X | X | | | X |
| Dorsal surface of tongue, NOS | X | X | X | X | X | X | X | X |
| Lingual tonsil | | X | | X | X | | X | X |
| Overlapping lesion of tongue, or tongue NOS | | X | X | X | X | X | X | X |
| Upper gum | X | X | X | X | X | X | X | X |
| Soft palate, Uvula | | X | X | X | X | X | | X |
| Overlapping lesion of palate or palate NOS | | X | X | X | X | X | | X |
| Cheek mucosa | X | X | X | X | X | X | X | X |
| Overlapping lesion of other and unspecified | X | X | X | X | X | X | X | X |
| Mouth, NOS | X | X | X | X | X | X | X | X |
| Salivary parotid gland | | X | X | X | | | | |

X indicates inclusion in "oral cavity cancer" for this database;
INHANCE: International Head and Neck Cancer Epidemiology Consortium;
SEER: Surveillance, Epidemiology and End Results Program;
ACS: American Cancer Society Cancer Facts and Figures Report;
Gillison group: Maura Gillison research group+ recent publications (Chaturvedi et al. 2008, 2011, 2013);
CI5: Cancer incidence in Five Continents;
NCIN: National Cancer Intelligence Network.

**Table 1-3: Inconsistencies in subsites included under "oropharyngeal cancer" in various descriptive databases**

| | Oropharyngeal Cancer | | | | | |
|---|---|---|---|---|---|---|
| **Subsite** | **INHANCE** | **SEER** | **Chaturvedi 2008, 2011, 2013** | **C15** | **NCIN** | **Scottish Cancer Registry** |
| Base of tongue | X | | X | | X | X |
| Lingual tonsil | X | | X | | | X |
| Soft palate, NOS | X | | | | | X |
| Uvula | X | | | | | X |
| Tonsil | X | X | X | | X | X |
| Anterior surface of epiglottis | | X | X | X | X | X |
| Lateral wall of oropharynx | X | X | X | X | X | X |
| Pharynx, NOS | | | X | | | |
| Waldeyer's ring | | | X | | | |
| Overlapping lesion of lip, oral cavity and pharynx | | | | | | |

X indicates that this subsite is included in "oropharyngeal cancer" for this database or study. INHANCE: International Head and Neck Cancer Epidemiology Consortium;
SEER: Surveillance, Epidemiology and End Results Program;
ACS: American Cancer Society Cancer Facts and Figures Report;
CI5: Cancer incidence in Five Continents;
Gillison group: Maura Gillison's research group+ recent publications (Chaturvedi et al. 2008, 2011, 2013);
NCIN: National Cancer Intelligence Network.
The American Cancer Society and GLOBOCAN 2012 do include an oropharyngeal cancer group.

The Scottish Cancer Registry further complicated matters on their website by providing routine cancer statistics on “Cancers of the Lip, Oral Cavity and Pharynx” (defined as including ICD-10 codes C00-C14), “Cancers of the Mouth” (defined as including ICD-10 codes C03-C06), “Cancers of the Oral Cavity” (defined as including ICD-10 codes C01-C06) and “Cancer of the Oropharynx” (defined as including ICD-10 codes C01, C02.4, C05.1, C05.2, C09, C10) separately (Scottish Cancer Registry, 2017).

There also remained a certain level of confusion surrounding the histological types that were included in the various definitions. Although it was clear that neoplasms involving the epithelium were always regarded as oral cancer, the inclusion of tissues surrounding the mucosa such as salivary, muscle, lymphoid, and nerve tissue within this definition was still controversial (Tapia and Goldberg, 2011). However, most authorities limited their definition of oral cavity and oropharyngeal cancer to squamous cell carcinomas as approximately 90% of all malignant lesions involving these subsites were of this type (Barnes, 2005).

### 1.1.5 Clinicians’ perspectives on oral cancer definitions

The World Health Organisation International Agency for Research on Cancer, in their report titled *Pathology & Genetics: Head and Neck Tumours*, summarised the signs and symptoms of oral cavity and oropharyngeal cancer and reported that small carcinomas of the oral cavity often remained asymptomatic, highlighting the need for a “high index of clinical suspicion”, particularly in “high-risk” patients (Barnes, 2005). Symptoms of locally advanced oral cancer included mucosal growth and ulceration, pain (including facial pain, sore throat, neck pain, tongue pain, pain when chewing, mouth pain, gingival pain, pain when swallowing, burning mouth, dental pain, pain in the palate, and ear-ache), paraesthesia, malodour from the mouth, trismus, bleeding, dysphagia and problems using prostheses, mobility of teeth, difficulty in speech, weight loss, and problems in breathing (Haya-Fernández et al., 2004; Barnes, 2005; Cuffari et al., 2006). Extremely advanced stages of cancer were

usually associated with ulcero-proliferative growths and necrosis that extended to the surrounding tissues, while patients in the terminal stages of oral cancer usually exhibited cervical lymphadenopathy, bleeding, skin fistulas, cachexia, and anaemia (Barnes, 2005; Bagan et al., 2010).

Head and neck cancers are typically managed in tertiary settings by a single multidisciplinary team, and guidelines on the management of these cancers usually tend to cluster the individual sites into wider groupings. Malignant neoplasms themselves do not obey strict anatomical boundaries and can often bridge both the oral cavity and oropharyngeal subsites. In primary care, most guidelines for the detection of such lesions consider the two subsites (oral cavity and oropharynx) together as "oral cancer" as their signs and symptoms overlap considerably and dentists and other primary care practitioners potentially have a role in the primary and secondary prevention of cancers affecting both subsites (Kreimer, 2014; NICE, 2015a; NHS Scotland, 2016b). The National Institute for Health and Care Excellence's (NICE) guideline on *"Suspected cancer: recognition and referral"* recommended a "suspected oral cancer referral" in case of unexplained ulcerations in the oral cavity for more than three weeks or a persistent lump in the neck, and an "urgent oral cancer referral" in case of a lump on the lip or in the oral cavity, a red or red and white patch in the oral cavity, or erythroleukoplakia (NICE, 2015b). Similarly, the Scottish Cancer Referral Guidelines provided a list of signs and symptoms for the recognition of all head and neck cancers combined (Table 1-4) (NHS Scotland, 2016b).

Therefore, although it is important to focus on individual subsites from an aetiological and epidemiological perspective, as discussed previously, combining the two and examining them together as oral cancer continues to be more appropriate from a clinical perspective.

**Table 1-4: Scottish Cancer Referral Guidelines for urgent suspicion of cancer referral: Head and Neck Cancer (NHS Scotland, 2016b)**

| |
|---|
| Persistent unexplained head and neck lumps for >3 weeks. |
| Ulceration or unexplained swelling of the oral mucosa persisting for >3 weeks. |
| All red or mixed red and white patches of the oral mucosa persisting for >3 weeks. |
| Persistent hoarseness lasting for >3 weeks (request a chest X-ray at the same time). |
| Dysphagia or odynophagia (pain on swallowing) lasting for >3 weeks. |
| Persistent pain in the throat lasting for >3 weeks. |

### 1.1.6 Oral cancer definitions – conclusions from the literature

The head and neck region encompasses numerous subsites, and cancers affecting these sites vary considerably in aetiology. Therefore, the manner in which subsite groupings are defined may have considerable impact on the outcomes of epidemiological research. The literature review (search strategy shown in Appendix 11) uncovered a general lack of consensus in the definition of "oral cancer", which included variations in the terminology used, thus complicating search strategies and hindering the identification of appropriate studies, as well as the individual subsites (i.e. ICD codes) included within each grouping. Appraisal of the evidence revealed two main schools of thought with regard to the ICD codes included within each subsite grouping. The first was an anatomically driven method of definition, wherein subsites included within the "oral cavity cancer" and "oropharyngeal cancer" groupings were selected based on

their anatomical location and boundaries, while the second was an aetiological method of definition that grouped subsites based on their association with human papilloma virus infections.

Therefore, based on this evidence, the current thesis decided to opt for a "compromise" (anatomical and HPV-associated) method of defining subsites for the descriptive epidemiological analyses examining the burden and trends of oral cavity and oropharyngeal cancer presented later in Chapters 2 and 3. The individual ICD-10 codes included within each subsite grouping have been discussed in detail in the later chapters and have also been shown in Appendix 1. Briefly, **oropharyngeal cancer** was defined as including the base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), and the pharynx (C14); while **oral cavity cancer** included the inner lip (C00.3-C00.9), other and unspecified parts of the tongue (C02), gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06).

However, evidence also showed that, from a clinician's perspective (both primary and secondary care), a more generalised definition of "oral cancer" that combined the two subsites (oral cavity cancer and oropharyngeal cancer) together was more fitting. This was mainly based on the fact that tumours rarely followed specific anatomical boundaries and the signs and symptoms of cancers affecting the various subsites in the head and neck region overlapped considerably. As a result, most guidelines for the detection of oral cancer considered the two subsites (oral cavity and oropharynx) together.

Therefore, a more generalised definition of **oral cancer** [including the base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), pharynx (C14), inner lip (C00.3-C00.9), other and unspecified parts of the tongue (C02), gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06)] that combined oral cavity cancer and oropharyngeal cancer (defined as mentioned previously) was also considered in this thesis, particularly for the analyses presented in Chapter

3 and 4, as this was thought to be more relevant for interpretation of the results from a clinical perspective.

## 1.2 Describing and assessing the incidence burden of head and neck cancer and subsites

It has been estimated that approximately 38 million deaths in the world, representing two-thirds of the total 56 million deaths annually, are caused by non-communicable diseases (NCD), particularly cardiovascular disease, chronic respiratory disorder, diabetes, and cancer (Bray and Soerjomataram, 2015). Between 1990 and 2010, a global transition of sorts was observed, with deaths from communicable diseases decreasing by 17% and those from NCDs increasing by 30% (Bray and Soerjomataram, 2015). The majority (almost 80%) of these NCD-related deaths occurred in low- and middle-income countries, and a large proportion of those occurring in high-income countries were attributed to cancer (Bray and Soerjomataram, 2015).

A literature search for the incidence trends of oral cancer showed that the evidence varied considerably in terms of the subsites considered, with the majority of the studies focusing on head and neck cancer as a whole and laying smaller emphasis on certain subsites. Additionally, the literature also differed in terms of the combinations of individual subsites considered. Therefore, in order to examine the evidence on the burden and trends of oral cancer (and subsites), it is important to first assess the literature of head and neck cancer as oral cancer data are often included within these studies. Moreover, the burden and trends of head and neck cancer also provide an interesting context. Therefore, this section of the thesis first reviews the evidence on the global incidence burden of head and neck cancer, and then discusses variations in trends by individual subsites, gender, age, and socioeconomic status. It then brings the focus closer to home by reviewing the evidence on the incidence burden of oral cancer in the United Kingdom, discusses variations in the trends by

different sociodemographic determinants, and identifies some of the gaps in the literature.

### 1.2.1 Global incidence burden of head and neck cancer over time

The World Health Organisation International Agency for Research on Cancer reported that approximately 529,000 new cases and 292,000 deaths from oral cavity and pharyngeal cancers occurred globally in 2012 (IARC, 2014). Although the individual subsites (lip, oral cavity, nasopharynx and pharynx) did not rank high, combined they represented the seventh most common cancer in terms of incidence in the world (IARC, 2014).

Schottenfeld (2006) pooled together data from the Cancer Incidence in Five Continents (Volumes III to VIII) database and examined the trends of oral cavity and pharyngeal cancer by geographic area and gender for the period between 1968-1972 and 1993-1997. They reported that between 1993 and 1997, the highest age-adjusted annual incidence rates of oral cavity and pharyngeal cancer were observed in males from the Somme and Bas-Rhin regions of France (more than 40 per 100,000 individuals) and females from South Karachi (Pakistan) and Bangalore (India) (more than ten per 100,000 individuals). Moreover, the age-adjusted incidence rates for males had exhibited an overall decline of 30% in some countries such as India, Puerto Rico, Columbia, Singapore, and Israel. In contrast, rates had increased by almost 100% in Japan, Denmark, Spain, Poland, and Germany. Similarly, for females, rates had decreased by 30% among Jews in Israel, Singaporean Indians, and Puerto Ricans, but had almost doubled in Germany, Denmark, Canada, and Switzerland. Strong birth cohort effects on trends were also observed in many countries, with incidence rates first beginning to increase among cohorts born in the early decades of the 20$^{th}$ century and then continuing to rise in the subsequent cohorts. The rising incidence rates between 1968-1989 in Slovakia were largely attributable to greater per capita consumption of tobacco and alcohol, while the trends

observed in countries such as Scotland, Denmark, Wales, and England reflected changes in the consumption of alcohol more than tobacco.

The GLOBOCAN project, operated by the International Agency for Research on Cancer, has been providing estimates of the global cancer burden since 1975 (IARC, 2017a). Parkin et al. (2005), in their summary of these estimates for 2002, reported that there were 274,000 cases of oral cavity cancer globally, and two-thirds of these occurred in males. The highest rates for men were observed in Western and Southern Europe, South Asia, Australia, New Zealand, and South Africa, while those for women were observed in South Asia. These rates largely reflected the high prevalence of key risk factors such as smoking and the consumption of smokeless tobacco (betel quid) in Europe and Asia, respectively.

Warnakulasuriya (2009a) reviewed the global epidemiology of oral and oropharyngeal cancer in various high-risk regions of the world and reported that, in 2004, the highest incidence rates were observed in countries in South and South-East Asia (including Pakistan, India, Taiwan, and Sri Lanka), some parts of Western and Eastern Europe (including France, Hungary, Slovenia, and Slovakia), parts of Latin America and the Caribbean (including Puerto Rico, Brazil, and Uruguay), and some Pacific regions (including Melanesia and Papua New Guinea). Within the European Union, the highest incidence rates were observed in France and Hungary; Spain, Portugal, Switzerland, and Germany exhibited intermediate rates; and the lowest rates were seen in Greece, Finland, Sweden, and Cyprus. Moreover, although incidence rates were higher in western Europe, mortality rates were seen to be higher in the Eastern regions. Over the same period, the highest incidence rates in South America and the Caribbean were observed in Uruguay, Southern Brazil, and Argentina. In Asia, the highest incidence rates were observed in India, with over 100,000 cases being registered per year.

Jemal et al. (2011) summarised the GLOBOCAN 2008 estimates and reported that the highest incidence rates were still observed in South-

Central Asia and Central and Eastern Europe, while the lowest rates were seen in Africa, Eastern Asia, and Central America. Mortality rates decreased in Europe and Asia but increased in some Eastern European countries such as Hungary and Slovakia. This was largely attributed to the "tobacco epidemic", particularly among women. Additionally, several studies also reported an increasing incidence of HPV-associated oral cancers, particularly in the United States and some countries in Europe (Robinson and Macfarlane; Shiboski et al., 2005; Conway et al., 2006 Chaturvedi et al., 2011).

The GLOBOCAN estimates for 2012 showed that the highest incidence rates of oral cancer were still observed in Melanesia, Central and Eastern Europe, and South-Central Asia, while the lowest rates occurred in Eastern Asia and Western Africa (Torre et al., 2015). Incidence rates were seen to decrease among males and increase among females in Southern and Western Europe; decrease in both males and females in Australia, North America, and Asia; and increase in countries in Eastern and Northern Europe (Torre et al., 2015). More recently, Shield et al. (2017) extracted data on all patients that were diagnosed with lip, oral cavity, and pharyngeal cancer in 2012 in 184 countries from the GLOBOCAN database, as well as more detailed information from 68 countries using the Cancer Incidence in Five Continents database. They used these to explore the incidence trends for 2012 by country, age, and sex, and reported that there were 529,500 new cases of lip, oral cavity and pharyngeal cancer globally, of which 70% (n=375,000) were males and 29% (n=154,400) were females. Moreover, this was predicted to rise by almost 62% to 856,000 cases by 2035.

The global trends of head and neck cancer incidence over time have exhibited a close correlation with the changing patterns of alcohol and tobacco consumption. For example, the increasing rates of oral cavity cancer in countries such as Pakistan and China reflected a rise in the consumption of tobacco, alcohol, and areca nut, while steady decreases over the past two decades in the United States represented declining

alcohol and tobacco consumption (Sankaranarayanan et al., 2015). Similarly, increases in the incidence of cancers of the base of the tongue could be attributed to an increase in the prevalence of human papilloma virus infections (Sankaranarayanan et al., 2015).

Therefore, the evidence suggests that the global burden of head and neck cancer varies considerably by global regions and countries, as well as by subsite, age, sex, and socioeconomic status, reflecting differences in aetiology, diagnostic procedures, prognosis, and treatment. The literature on the disparities in the burden of oral cancer by various sociodemographic characteristics has been reviewed in the following sections.

#### 1.2.1.1 Global burden of head and neck cancer: by subsite

Evidence shows that the rates of oral cavity cancer have decreased in various parts of the world, while the rates of oropharyngeal cancer have increased (Blot et al., 1993; Franceschi et al., 2000; Chaturvedi et al., 2008; Auluck et al., 2010; Marur et al., 2010; Mork et al., 2010; Ramqvist and Dalianis, 2010; Chaturvedi, 2012; Gillison et al., 2012a). Chaturvedi et al. (2013) hypothesised that this divergent trend in the incidence of oral cavity and oropharyngeal cancer could be attributed to a fall in tobacco consumption accompanied by an increase in the prevalence of HPV infections. They tested this theory using data from the Cancer Incidence in Five Continents (Volumes VI to IX) database for the period between 1983-2002, and reported significant increases in the incidence of oropharyngeal cancer in several economically developed countries like Japan, Australia, Denmark, and the Netherlands. However, no such increases were observed in economically developing countries such as Columbia, Costa Rica, India, Thailand, and the Philippines. A comparison of the incidence trends of oral cavity cancer and oropharyngeal cancer using age-period-cohort modelling revealed three main patterns, as follows: a) countries that exhibited statistically significant divergent incidence trends characterised by increases in the rates of oropharyngeal cancer and decreases in the rates of oral cavity cancer (USA, Canada, Japan, Slovakia); b) countries that

exhibited an increase in the incidence rates of both subsites, but with oropharyngeal cancer demonstrating a greater increase than oral cavity cancer (Denmark and the UK); and c) countries that exhibited similar trends for both subsites (Brazil and the Netherlands).

These results were corroborated by Simard et al. (2014) who collected data on all patients with head and neck cancer diagnosed between 1983-1987 and 1998-2002 in 83 registries representing 35 countries from the Cancer Incidence in Five Continents (C15) database. They examined the incidence trends by country, sex, and sub-site, and reported that the rates of oral cavity cancer had increased in both men and women in Japan, the United Kingdom, Slovak Republic, Denmark, Czech Republic, Finland and Estonia; remained stable in several South American countries; and decreased in Canada, Philippines, Thailand, the United States, India, and China. The rates of oropharyngeal cancer, on the other hand, had increased in both men and women in the United Kingdom, Belarus, Denmark, Norway, Finland, Czech Republic, and Sweden, and decreased in India and China. The incidence trends of oropharyngeal cancer were seen to differ by sex in other global regions, with only men exhibiting an increase in rates in Canada, Japan, India, and Germany.

Shield et al. (2017) reported that oral cavity cancer exhibited the highest number of new patients (202,000) in 2012, and the global age-standardised rate (ASR) was 2.7 per 100,000 individuals. The proportionate incidence of oral cavity cancer was the lowest in North Africa and West Asia (29 %) and the highest in South-Central Asia (49%), which also exhibited the highest number of incident cases. Country-level examination revealed that Papua New Guinea exhibited the highest ASR (10.6), followed by the Maldives, Sri Lanka, and Pakistan. The number of incident cases of oropharyngeal cancer in 2012 was considerably lower at 100,500, and the age-standardised rates were 1.4 per 100,000 individuals. The contribution of oropharyngeal cancer to all lip, oral cavity, and pharyngeal cancers varied from 34% in North America to as low as 8% in North Africa and Western Asia, and the highest number of incident cases were observed in South-central Asia. Country-

level examination showed the highest ASR (5.0 per 100,000 individuals) in Hungary, followed closely by Slovakia, Germany, and France.

Therefore, the evidence showed that the rates of oropharyngeal cancer had increased in economically developed countries, and it was suggested that this could be attributed to the emergence of a "human papilloma virus epidemic" in the western world, North America, Oceania, and Europe in particular (Chaturvedi et al., 2013; Hashibe and Sturgis, 2013). Forman et al. (2012) suggested that this peak in the prevalence of HPV infections, particularly among women, was the result of a "westernisation" effect (a tendency to have multiple sexual partners at a young age) that was absent or rare among more "conservative societies". In contrast, the high rates of oral cavity cancer in the Indian subcontinent (India and Sri Lanka in particular), South Asia (particularly the southern parts of China and Thailand), and parts of the United Kingdom and Europe with large Asian populations reflected the greater rates of consumption of tobacco and betel quid among these populations (Llewellyn et al., 2001; Warnakulasuriya, 2009a). An interesting point to bear in mind when considering these findings is that although cancers have been historically considered to be non-communicable diseases, the body of evidence demonstrating the role of human papilloma viruses in the aetiology of cervical and oropharyngeal cancers has been mounting steadily (Gillison, 2004; D'Souza, 2007). Therefore, given that HPV can be transmitted through various pathways including open-mouth kissing and oral sexual practices, it may be reasonable to consider HPV-related oropharyngeal cancers as communicable diseases instead.

#### 1.2.1.2 Global burden of head and neck cancer: by gender

Various studies have also reported considerable differences in the incidence trends of head and neck cancer by gender. Chaturvedi et al. (2013) reported that men exhibited a significant increase in the rates of oropharyngeal cancer in several economically developed countries (including the USA, Australia, Canada, Japan, Slovakia, Denmark,

Netherlands, and the United Kingdom), despite a non-significant increase or a decrease in the rates of oral cavity cancer. In contrast, all countries that exhibited increases in the rates of oropharyngeal cancer among women also demonstrated a rise in the rates of oral cavity cancer. Simard et al. (2014) stated that the largest increase in the rates of oral cavity cancer between 1983-1987 and 1998-2002 was observed among males in Finland and women in Spain. Moreover, rates of oral cavity cancer were generally twice as high among males compared to females in most countries, except for Belarus and Slovak Republic where the difference was almost 10-fold. The incidence rates of oropharyngeal cancer, on the other hand, increased among males only in India, Japan, Canada, and Germany. Moreover, the burden of oropharyngeal cancer among males was approximately 2-5 times that observed in females in most countries, except for Belarus and Slovak Republic where the difference was almost 20-fold.

More recently, Shield et al. (2017) reported that 71% of all new cases of lip, oral cavity, and pharyngeal cancer globally occurred in males, while only 29% occurred in females in 2012. Moreover, the global ASR of oral cavity cancer was 3.7 per 100,000 individuals in males and 1.8 per 100,000 individuals in females, while the corresponding numbers for oropharyngeal cancer were 2.3 and 0.5 per 100,000 individuals, respectively. Warnakulasuriya (2009a), in his review of the global trends of oral cavity and oropharyngeal cancer, suggested that the differences in trends by gender could partly be explained by the higher prevalence of risk-habits such as smoking and alcohol consumption among men compared to women.

#### 1.2.1.3 Global burden of head and neck cancer: by age

Cancers of the head and neck primarily affect older individuals due to years of exposure to conventional risk factors such as smoking and alcohol consumption. Schottenfeld (2006) reported that the incidence rates of oral cavity and pharyngeal cancer were approximately 3.1 per 100,000 individuals among patients aged 35-39 years, and this increased to 41.1 and

46.4 per 100,000 individuals among the 65-69 and 80-84 year age-groups, respectively. Similar results were reported by Chaturvedi et al. (2013) in their age-period-cohort analysis of data from the Cancer Incidence in Five Continents database where they observed increasing rates of oropharyngeal cancer among individuals aged greater than 60 years in economically developed countries. These results were further corroborated by several other studies that also reported that the risk of developing oral cancer (defined as C02-C06) increased with age (Warnakulasuriya, 2009a; Shield et al., 2017).

However, more recent evidence suggested a changing trend, with the rates of oral cancer increasing among younger individuals. Van Monsjou et al. (2013) reported that approximately 4-6% of patients with oral cancer were less than 40 years of age and often failed to exhibit any of the conventional risk factors. This increase in the incidence rates of head and neck cancer, and carcinomas involving the tongue in particular, among young people (defined as those less than 30 years of age) was first observed in the USA in the mid-1970's (Shemen et al., 1984; Depue, 1986). This pattern was less pronounced amongst women due to the low frequency of cases. Later on, Schantz and Yu (2002) collected data on patients that were diagnosed with head and neck cancer between 1985-1997 from the SEER database (n=63,409, of which 3339 were less than 40 years of age) and categorised them into three age groups (less than 40 years, 40-64 years, and more than 65 years). Their results showed that the rates of oral cancer had decreased in all of the groups except the "less than 40 years" age group over the study period. Instead, this group had undergone an increase of almost 62% in the incidence rates when compared to the period between 1973-1984, and this was particularly true for tongue cancer. The authors suggested that this was a result of birth cohort effects, with the rates beginning to increase among individuals born in the period between 1938-1942 and peaking in cohorts belonging to the period between 1943 and 1947. These results were corroborated by Llewellyn et al. (2001) in their review of risk factors for oral cancer among

young people where they compared the incidence rates of cancer among birth cohorts from the 1960's and 1970's to those from later decades and reported a doubling and sometimes even trebling of rates among young people in some countries.

More recently, Gayar et al. (2014) used the SEER database to extract information on all patients with oropharyngeal cancer that were less than 45 years of age and had been diagnosed between 1973 and 2009 (n=1603). The authors reported an overall increase in the incidence rates of oropharyngeal cancer (from 0.23 to 0.37 per 100,000 population) among patients aged less than 45 years, with the rise being particularly pronounced (from 0.79 to 1.39 per 100,000 individuals) among patients aged 35 to 44 years.

#### 1.2.1.4 Global burden of head and neck cancer: by socioeconomic status

A socioeconomic inequality in the distribution of head and neck cancer is apparent at the global level, with developing countries consistently exhibiting higher incidence and mortality rates compared to developed countries (Warnakulasuriya, 2009a). In 2012, 65% of all incident cases and 74% of all deaths caused by oral cancer were seen to occur in less developed regions of the world (IARC, 2014). However, these patterns were slightly different when the trends by individual subsites were examined. Chaturvedi et al. (2013) reported that increases in the rates of oropharyngeal cancer between 1983-2002 almost exclusively occurred in economically developed countries, possibly reflecting differences in the prevalence of HPV infections in comparison to economically developing countries.

Upon examining incidence trends by the Human Development Index (HDI), which is a composite measure of life expectancy, education, and per capita income estimated by the United Nations Development Program (UNDP, 2015), Shield et al. (2017) reported that the burden of oral cavity

cancer was higher in countries with low HDIs while that of oropharyngeal cancer was higher in countries with high HDIs. However, this was contradicted to a certain extent by Fidler et al. (2017) who also reviewed the global burden of cancer (all sites) by HDI. They used the fixed cut-off values prescribed by the United Nations and categorised the countries based on their HDI scores into low, medium, high, and very high, where the low and very high categories included the most and least deprived countries, respectively. Their results showed a positive association between the age-standardised incidence rates of oral cancer and the level of human development. Moreover, they also reported that approximately 41% of the global cancer incidence burden in 2012 occurred in very high HDI countries, while only 6% occurred in the low HDI countries. This pattern flipped when mortality rates were examined, with low HDI countries exhibiting poorer survival due to limited access to healthcare. However, it is essential to note here that the authors excluded India and China from this analysis, and both countries currently bear a greater proportion of the global burden of oral cancer. Therefore, this may have skewed the results considerably.

The association between socioeconomic status and the risk of developing oral cancer has been well documented, with the lower social strata in a population consistently exhibiting higher incidence rates, higher mortality rates, and poorer survival rates (Faggiano et al., 1997; Kogevinas and Porta, 1997; Conway et al., 2008; Warnakulasuriya, 2009b). A meta-analysis of forty-one studies with a total sample of 15,344 cases and 33,852 controls reported that low income (OR 2.41), low occupational status (OR 1.84), and low educational attainment (OR 1.85) were associated with a higher risk of developing oral cancer (Conway et al., 2008). Additionally, the effects of low monthly household income on the risk of oral cancer were also more pronounced in low income countries compared to high income countries (Conway et al., 2008). However, Dahlstrom et al. (2015), in their study examining 356 patients that were diagnosed with oropharyngeal cancer at the University of Texas MD Anderson Cancer

Centre, reported that the patients with HPV-positive oropharyngeal cancer that were included in their study exhibited high levels of education, income, and overall socioeconomic status. Further examination revealed that this was particularly true for patients with HPV-positive oropharyngeal cancer who were also non-smokers.

### 1.2.2 Incidence burden of head and neck cancer in the United Kingdom: by subsite, age, gender, and socioeconomic status

Cancer Research UK reported that 11,400 new cases of head and neck cancer (31 cases per day) were diagnosed in the United Kingdom between 2012 and 2014, accounting for approximately 3% of all new cancer cases (CRUK, 2017d). Moreover, the incidence rates of head and neck cancer had increased by 30% since the early 1990s, with a 23% rise in age-standardised rates observed in the most recent decade (2003-2005 to 2012-2014) (CRUK, 2017a). Warnakulasuriya (2009a), in his review of the trends of oral cancer in various high-risk countries, stated that the incidence rates in the United Kingdom had increased by approximately 3% each year since 1989, and this could be largely attributed to an increase in the consumption of alcohol post-World War II (Hindle et al., 2000).

Louie et al. (2015) used population-based cancer registry data from England to examine the trends of head and neck cancer between 1995 and 2011 and calculate projected rates up to 2025. Their results showed that the incidence rates of head and neck cancer had increased by 59% over the sixteen-year study period, and this appeared to be largely driven by a rapid rise in the rates of oropharyngeal cancer (average annual percentage change = +7.3% in males and +6.5% in females). Smaller increases were observed in the rates of oral cavity cancer. Examination of the projected rates showed that the incidence burden of head and neck cancer was expected to continue to rise (overall increase of 35% in males and 49% in females) up to 2025, with the largest predicted increase occurring in the rates of oropharyngeal cancer. Oral cavity cancer, on the other hand, was

predicted to stabilise in men and continue to increase in women. With regard to age, the incidence rates of oropharyngeal cancer had increased in all age-groups, particularly the 50-59 and 60-69 year groups, over the study period, and the median age of oropharyngeal cancer incidence was less than 60 years (Louie et al., 2015).

The most recent detailed analysis of incidence trends of oral cancer in Scotland only examined rates between 1990 and 1999, and reported a general increase in both males and females over the 10-year study period (Conway et al., 2006). Moreover, Scotland also exhibited the highest incidence rates and the greatest lifetime risk of developing oral cancer in the United Kingdom. However, this study was limited by the fact that it examined the combined rates of oral cavity cancer and oropharyngeal cancer, reflecting the thinking at the time that these sites had a common aetiology.

With regard to the patient profile, Macfarlane et al. (1987) first used age-specific cancer incidence data in Scotland in 1987 to report an increase in the risk of tongue cancer among young males. A later study conducted in 1992 analysed incidence and mortality data for the period of 1911 to 1989 and reported a higher risk of oral cancer among Scottish young adults, with the incidence rates increasing by three-fold in the 35-64 year age-group between 1960-1964 and 1985-1989 (MacFarlane et al., 1992). Moreover, a strong cohort effect was also reported, with the rates increasing in every birth-cohort succeeding 1910, and the authors suggested that this could be attributed to an increase in the consumption of alcohol and tobacco (MacFarlane et al., 1992).

Conway et al. (2007) used data from the Scottish Cancer Registry for the period between 1976 and 2002 to examine the incidence trends of oral cancer by deprivation, and reported a socioeconomic inequality in the distribution of oral cancer, with the most deprived areas consistently exhibiting the highest rates. Their results also showed that this inequality first appeared in the late 1970's, and subsequently widened in the 1980's

up to the late 1990's. This was particularly true for males from the most deprived areas of Scotland who exhibited a dramatic increase in the incidence rates (+196%) over the study period. Conversely, women exhibited a slightly different pattern, with increases in the incidence rates being observed at all levels of deprivation, although the greatest increase still occurred in the most deprived areas (Conway et al., 2007). In another small population-based case-control study including 103 patients with head and neck cancer and 91 controls in Scotland, Conway et al. (2010) examined the association between the risk of developing head and neck cancer and the components of socioeconomic class including area-based measures of socioeconomic status, occupational social class, employment, and education. They reported that individuals residing in the most deprived areas of Scotland exhibited a higher risk of developing cancer relative to those living in the least deprived areas (OR 4.66, 95% CI 1.79-12.18). Unemployment (OR 2.27, 95% CI 1.21-4.26) and manual occupational classes were also associated with a higher risk of developing cancer, while higher levels of education appeared to exhibit a protective effect (OR = 0.17, 95% CI 0.05–0.58). However, the authors also stated that smoking appeared to dominate the risk profile, and the statistical significance for all measures of social class were lost upon adjusting for it. Nevertheless, their results did show strong links between certain components of social class and the risk of developing head and neck cancer (Conway et al., 2010).

### 1.2.3 Oral cancer burden – conclusions from the literature

"All cancers are alike, but they are alike in a unique way."

These words, another quote from Siddharth Mukherjee's *The Emperor of all Maladies* (Mukherjee, 2010), fittingly justify the need to elucidate the risk profile of various cancers. This section of the thesis described the incidence trends of head and neck cancer both globally and in the United Kingdom, and explored variations in these trends by several sociodemographic determinants. A review of the literature showed that the

rates of oral cancer were rising globally, and were predicted to continue to do so (Shield et al., 2017). Oropharyngeal cancer incidence was on the rise almost exclusively in economically developed countries, reflecting an increase in the prevalence of HPV infections. In contrast, economically developing countries exhibited a greater incidence burden of oral cavity cancer, and this was attributable to the continuing tobacco epidemic that had already started and declined earlier in the developed countries. Similar trends were also observed in England, with the increasing incidence of oral cancer being largely driven by a rapid rise in the rates of oropharyngeal cancer.

With regard to the patient profile, males were seen to be at a higher risk of developing oral cancer, although there was evidence of increasing incidence rates of oral cavity cancer among women in developing countries, possibly reflecting a surge in tobacco consumption. A direct relationship existed between incidence rates and the level of deprivation, and this was also apparent at the global level, with economically developing countries consistently bearing the greatest burden of cancer. Lastly, although oral cancer was primarily a disease that affected older individuals, there was some evidence of the incidence rates increasing among the younger population. A similar patient profile was also observed in England, with males from lower socioeconomic strata being at the highest risk of developing cancer.

The most recent exploration of incidence trends of oral cancer in Scotland only provided estimates up to 1999, and there were no studies that investigated variations in trends by individual subsites. Moreover, there was also no recent evidence on the patient profile of oral cancer in Scotland, particularly with regard to their socioeconomic status.

## 1.3 Early detection of oral cancer

The World Health Organisation's *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs*, was a six-part series that provided

practical advice for policy-makers and programme managers on ways to plan and implement cancer control programs effectively (WHO, 2006). This report recommended three key steps to planning an effective cancer control program, as follows:

*Step 1* answered the question "where are we now?", in terms of the current state of the cancer problem and cancer control measures in effect. It was proposed that this could be achieved by conducting a "situation analysis" which would include assessment of a) the burden of cancer amenable to early detection, and b) the existing early detection plan and current activities and population coverage of services.

*Step 2* addressed the question "where do we want to be?", the goal of which was to formulate and adopt policies and practices. The WHO recommended a number of steps to answer this, including a) identification of the target population for early detection of cancer, b) identification of gaps in the existing early detection services, c) establishing objectives for early diagnosis and screening, d) assessing the feasibility of early detection interventions, e) addressing ethical aspects, f) setting priorities for early detection, and g) choosing between early diagnosis and screening.

*Step 3* focused on the question "how do we get there?", and this step aimed to identify the actions that were necessary for the implementation of policy. This included a) bridging any gaps in the existing system, b) working as a team, c) procuring the necessary resources, d) implementing the activities that are necessary for early diagnosis and screening, and e) monitoring and evaluation.

The *Early Detection* module of the *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs* series defined an early detection program as "the organised and systematic implementation of early diagnosis or screening (or both), diagnosis, treatment and follow-up", and discussed the two principle strategies for timely recognition of cancer, namely, "early diagnosis" and "screening" (WHO, 2013).

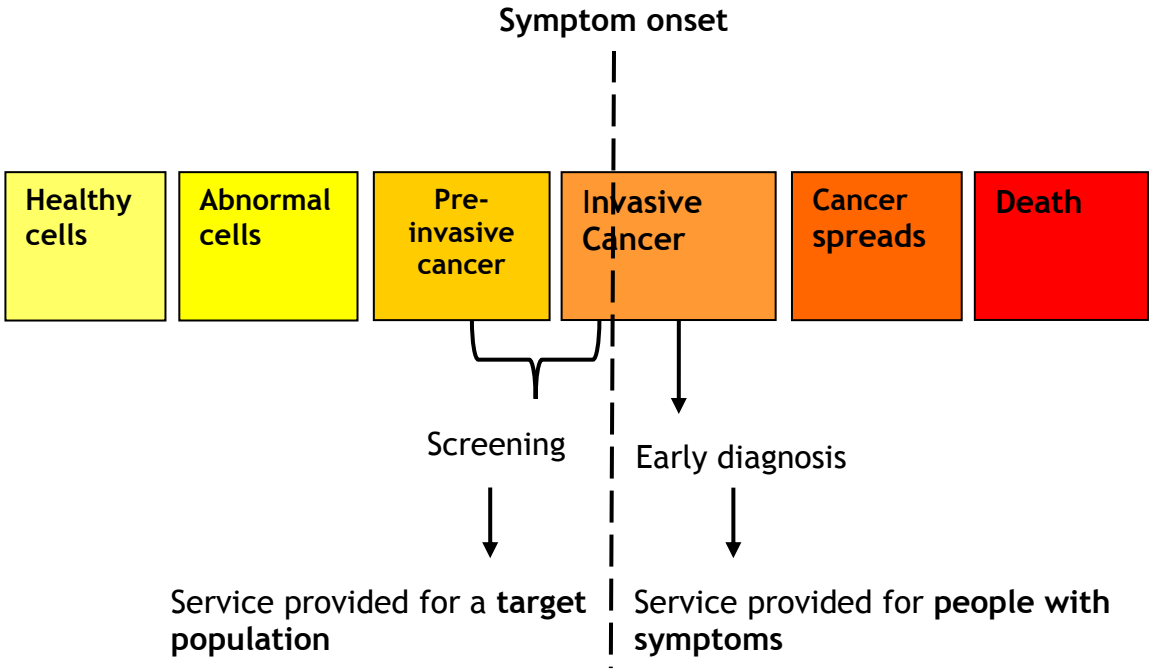
Early diagnosis was helpfully defined by the World Health Organisation as an "awareness (by the public or health professionals) of early signs and symptoms of cancer in order to facilitate diagnosis before the disease becomes advanced" (WHO, 2017b). The *World Health Organisation Guide to Cancer Early Diagnosis*, a part of the *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs: Early Detection Module*, referred to the concept as a form of "down-staging" and emphasised that its main objective was the detection of cancer at the earliest stage possible in order to improve survival and the quality of life (WHO, 2017b).

Screening, on the other hand, was considered as "the systematic application of a screening test in a presumably asymptomatic population, with an aim to identify individuals with an abnormality suggestive of a specific cancer" (WHO, 2013). The *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs* clarified that the main objective of screening was the identification of unrecognised ("pre-clinical") cancer or "pre-cancerous lesions" in an apparently health population.

Therefore, the key difference between the two objectives essentially lay in the clinical stage progression of the disease, as shown in Figure 1-1. In the context of oral cancer, screening aimed to identify oral potentially malignant disorders (OPMD) (Brocklehurst et al., 2013) (discussed later in section 1.3.1.1), while early diagnosis aimed to recognise the signs and symptoms of oral cancer (discussed previously in section 1.1.6) in a timely fashion so as to achieve diagnosis at an earlier stage.

This section of the thesis first examines the literature on the two strategies included within early detection efforts (i.e. screening and early diagnosis) in the context of oral cancer, and discusses the potential role of dental practices in such efforts. It then goes on to consider some of the evidence on missed opportunities for early detection of cancer, including the factors contributing to their existence and the ways to measure them, and then identifies some of the gaps in the literature.

**Figure 1-1: Distinguishing screening from early diagnosis based on symptom onset (image adapted from WHO Guide to Cancer Early Diagnosis)**




## 1.3.1 Early detection of oral cancer via screening

### 1.3.1.1 Potentially malignant disorders

As mentioned previously, the main aim of screening is the "identification of pre-clinical or pre-cancerous lesions in an apparently healthy target population" using tests, examinations, imaging, and other such procedures that can be applied rapidly and can be easily accessed by the target population (WHO, 2013). In 1978, a working group of the World Health Organisation (WHO) first suggested that precancerous conditions of the oral cavity should be classified into two main groups: precancerous lesions and precancerous conditions. A precancerous lesion was defined as "morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart", while a precancerous condition was defined as a "state associated with a significantly increased risk of cancer" (WHO, 1973; Kramer et al., 1978). In 2005, another WHO workshop focusing on oral lesions with a predisposition for malignant transformation substituted the terms "precancerous" or "premalignant" with "potentially malignant", and the distinction between precancerous lesions and

conditions was abandoned and replaced with “oral potentially malignant disorders” (OPMD) (Warnakulasuriya et al., 2007), and this has been widely recognised since (Brocklehurst et al., 2013; Walsh et al., 2013; Speight et al., 2017).

Some of these OPMDs often exhibit molecular, genomic or chromosomal alterations that are usually observed in invasive cancers. Warnakulasuriya et al. (2007), in their report of the consensus views of the WHO Collaborating Centre for Oral Cancer and Precancer Working Group in the United Kingdom, summarised the most common OPMDs and their definitions. These included leukoplakia, erythroplakia, oral submucous fibrosis, actinic keratosis, lichen planus, discoid lupus erythematosus, candidiasis, palatal lesions in reverse smokers, and hereditary disorders with increased risk such as dyskeratosis congenita and epidermolysis bullosa. More recently, Sarode et al. (2011) proposed a new method of classifying OPMDs based on their pathogenesis, wherein lesions were categorised as follows: a) Group I: morphologically altered tissue in which an external factor is responsible for the aetiology and malignant transformation; b) Group II: morphologically altered tissue in which chronic inflammation is responsible for malignant transformation (chronic inflammation mediated carcinogenesis); c) Group III: inherited disorders that do not necessarily alter the clinical appearance of local tissue but are associated with a greater than normal risk of PMD or malignant transformation; and d) Group IV: no clinically evident lesion but oral cavity is susceptible to oral squamous cell carcinoma (OSCC). The authors further divided these categories into subgroups and suggested that this method of classification also had a therapeutic basis to some extent.

The majority of OPMDs present as red or white patches and most commonly occur in the buccal mucosa, gingiva, tongue, and the floor of the mouth (Mortazavi et al., 2014). The affected area may exhibit decreased elasticity, appearing tough on palpation, and is usually painless. However, although these lesions have a statistically increased chance of becoming malignant (Napier and Speight, 2008), occasionally they may remain stable

or regress. Thus, there is a certain level of uncertainty associated with the natural progression of these conditions, making prediction of the fate of each lesion close to impossible. Biopsies are recommended for accurate diagnosis and confirmation of malignant transformation (Amagasa et al., 2006).

#### 1.3.1.2 Screening for oral cancer

Screening tests are not meant to be diagnostic and instead they aim to identify tissue changes that suggest an increased likelihood of developing disease (Wilson and Jungner, 1968). The most commonly used screening test for oral cancer is the conventional oral examination (COE), and various studies have confirmed its simplicity, accuracy and acceptability (Warnakulasuriya et al., 1984; Mehta et al., 1986; Warnakulasuriya and Nanayakkara, 1991; Mathew et al., 1996; Mathew et al., 1997; Sankaranarayanan, 1997). Walsh et al. (2013), in their systematic review comparing conventional oral examination, vital rinsing, light-based detection, biomarkers, and self-examination of the mouth, found that the accuracy of the conventional oral examination was dependant on the prevalence of the disease. However, it consistently exhibited a high level of specificity (greater than 0.80). Downer et al. (1995) reported similar results in their meta-analysis where they observed specificity values of 0.85 to 0.97 for conventional oral examination. Another added advantage of visual examination was that it could be easily performed by non-medical or non-dental health professionals. These studies suggested that the conventional clinical oral examination had “satisfactory performance as a screening test” as it had sensitivity and specificity similar to that of the breast and cervical cancer screening programs (Speight et al., 2017).

However, currently there is insufficient evidence of the effects of visual screening for oral cancer on the mortality rates. Kujan et al. (2006) and, more recently, Brocklehurst et al. (2013) attempted to undertake Cochrane reviews examining the effectiveness of current oral cancer screening methods in reducing mortality. However, both studies were able

to identify only one randomised controlled trial that met the inclusion criteria. This was a community-based, cluster-randomised controlled trial conducted in North Trivandrum, Kerala, India between 1996 and 2004 that investigated the effects of visual screening for oral cancer on the mortality rates in a high-risk population (Sankaranarayanan et al., 2005). The study selected a total of thirteen clusters, of which seven were randomly selected to receive three rounds of oral visual screening at three year intervals and the remaining six clusters received standard care. Four rounds of screening were executed over a fifteen-year period and the five-year survival was found to be significantly higher in the intervention group compared to the control group. A statistically significant difference in the proportion of patients with stage I or II cancer (definitions of the stages of cancer have been discussed later in section 1.3.2.1) was also observed between the two groups. Moreover, Sankaranarayanan et al. (2005) also reported that although no significant difference in mortality was observed between the two groups, tobacco and alcohol users in the intervention group exhibited a 34% decrease in mortality rates compared to the control group and this was statistically significant. Lastly, among those who had completed all four rounds of screening (20% of the eligible population), a 79% and 81% decrease in mortality was observed in the intervention arm and the high-risk group, respectively. This is the only randomised controlled study that has examined the effectiveness of oral cancer screening thus far and, given the high-risk nature of the population selected, provides considerable evidence of the benefits of screening. In Cuba, a national oral cancer control program was established in 1984 wherein dentists were required to carry out visual oral examination in all patients above the age of 15 years. Evaluation of this program showed an increase in the proportion of stage I cases detected between 1983 and 1989 (24% and 49%, respectively) and a decrease in the proportion of stage II and III cases over the same period (Garrote et al., 1995). This suggested that visual oral screening was beneficial for the early detection of cancer. However, this program was limited by the fact that its overall coverage was relatively poor, it lacked a systematic method of recruiting patients

which may have led to an under-representation of high-risk populations, and the compliance with referral was poor.

Currently, oral cancer screening at the population level is not recommended due to the limited evidence on its efficacy in reducing mortality. The Cochrane review conducted by Brocklehurst et al. (2013) concluded that screening via conventional oral examination was effective in reducing mortality among "high-risk" individuals and communities, suggesting that opportunistic screening for oral cancer targeting these communities was a feasible option for early detection. This was further supported by Speight et al. (2006) who used simulation modelling techniques to examine the cost-effectiveness of screening for oral cancer in various primary care facilities. Using decision-analytic modelling, they compared the incremental-cost-effectiveness-ratios (ICERs) of various oral cancer screening strategies including no screening, invitational screening: general medical practice, invitational screening: general dental practice, opportunistic screening: general medical practice, opportunistic screening: general dental practice, opportunistic "high-risk" screening: general medical practice, opportunistic "high-risk" screening: general dental practice, and invitational screening: specialist, and their main outcome measures were quality-adjusted-life-years (QALY) and mean lifetime cost of each strategy. The authors concluded that "high-risk" screening, particularly in general dental practices, was cost-effective. Screening by general practitioners was found to be only marginally more expensive, despite lack of training and lower sensitivity and specificity, and this could potentially be a result of the greater population coverage by GPs. Similar results were reported by another study conducted in the Netherlands that examined the cost-effectiveness of screening for oral lichen planus (a form of OPMD) in a population of 100,000 over a period of one year (Van der Meij et al., 2002). The authors considered two screening strategies, as follows: a) screening by an oral specialist such as an oral and maxillofacial surgeon, and b) screening by a dentist. Using a simple decision tree framework, they estimated that the cost of no screening would be

approximately $3,000,000. The extra cost for screening by an oral specialist was $1,265,229 and that of screening by a dentist was approximately $400,000-425,000. The health gain from screening by a specialist was 592 quality-adjusted life-years (approximately 23.68 lives saved) and that of screening by a dentist was between 775 and 800 QALYs. However, from the perspective of the NHS, this study had several limitations. Firstly, it did not compare a wide range of screening strategies such as GP screening, invitational screening, or opportunistic screening. Secondly, some of the estimations included in the model were not derived in a systematic manner. Thirdly, the generalisability of the results to hospitals in the United Kingdom was unclear and, lastly, the timing of various events was not reported (Van der Meij et al., 2002).

Although screening should ideally be delivered at the population level, the success of such a program is dependent on a number of factors including availability of adequate resources, prevalence of the disease, and compliance of the population with recommended screening measures (WHO, 2017d). Wilson et al. (1968), upon being commissioned by the WHO, developed a report where they defined certain criteria to guide selection of diseases or conditions that were amenable to screening at the population level, including its capacity to be detected at an early stage and the availability of suitable tests and treatment measures. However, if a disease failed to meet these criteria and population screening was not recommended, alternative early detection efforts could be employed including invitational (population-based) screening, workplace screening programs, opportunistic screening, and targeted “high-risk” screening (Speight et al., 2006).

The United Kingdom’s National Screening Committee (UK NSC) proposed 20 criteria that must be fulfilled in order for a screening program to be funded and accepted at the national level and, based on these, suggested that population screening for oral cancer was not recommended (UK NSC, 2003). Speight et al. (2017) recently used these criteria to review the current global status of oral cancer screening for the Global Oral Cancer

Forum meeting held in New York in March 2016. They concluded that although it was feasible to screen for oral cancer, based on the fact that it was frequently preceded by a potentially malignant lesion, there was considerable ambiguity with regard to certain key factors. As mentioned earlier, the natural course of OPMDs is still relatively unclear and not all of them may progress to malignancy; however, the criteria used to define a positive screening test result do not account for this. Based on this, the authors concluded that there was a need for the development of better screening tests and an increased understanding of the natural course of OPMDs before oral cancer screening at the population level could be recommended.

Therefore, overall the evidence currently appears to suggest that, from an efficacy and cost-effectiveness perspective, opportunistic screening for oral cancer targeting high-risk individuals is the most feasible option (Brocklehurst et al., 2013; Walsh et al., 2013).

## 1.3.2 Early detection of oral cancer through timely diagnosis

### 1.3.2.1 Cancer staging

Knowledge regarding the extent of disease was reported to be key to the selection of appropriate treatment by various surgical groups and treatment guidelines. Cancer staging, or identification of the anatomic extent, topography, and histology of a neoplasm, allows easy exchange of information regarding the extent of the disease between clinicians, selection of appropriate treatment, stratification of patients included in clinical studies, determination of prognosis, and assessment of the impacts of early detection efforts (Greene and Sobin, 2008). It is usually completed at the time of diagnosis and may be of two types: clinical (based on physical examination, biopsy, and imaging) or pathological (based on what is discovered surgically). The most commonly used method of staging is the TNM (tumour, node, metastasis) system, developed and maintained by the American Joint Committee on Cancer (AJCC) and the Union for

International Cancer Control (UICC) (Denoix, 1944). This system incorporates all available information about a particular case, including those obtained by radiologic and endoscopic evaluation (National Cancer Institute, 2017). Here, the T category describes the size of the primary tumour in centimetres (Tx: cannot be measured; T0: no evidence of primary tumour; T1-T3: escalating size of primary tumour; T4: involvement of adjacent structures; Tis: carcinoma in situ); N describes the extent of lymph node involvement (Nx: lymph nodes cannot be evaluated; N0: no lymph node involvement; N1-N3: size, location and number of lymph nodes involved; Nx: lymph nodes cannot be evaluated), and M describes the absence or presence of distant metastasis (Mx: cannot be evaluated; M0: no distant metastasis; M1: distant metastasis). The tumour stage specifications vary with the subsite involved. While the staging for extent of lymph node involvement remains the same throughout, T and M may vary, and together they help determine the overall stage (I, II III, IV) of a particular lesion. Stage 1 is the earliest stage of cancer when the tumour is less than two centimetres in size and has not spread to the neighbouring tissues, lymph nodes, and organs, while Stage II includes neoplasms that are greater than two centimetres but less than four centimetres in size and have not spread to the neighbouring lymph nodes and organs (CRUK, 2017c; IARC, 2017b). Stage III include a) cancers that are greater than four centimetres but have not spread to the lymph nodes or other parts of the body, or b) cancers that are of any size but have spread to one lymph node (no bigger than three centimetres) on the same side of the neck. Stage IV is the advanced stage of cancer and is further divided into categories a, b, and c based on the extent of metastasis and the size of the lesion (CRUK, 2017c; IARC, 2017b).

Over the years, changes to the TNM staging system have been based on improvements in the understanding of the natural history and extent of the disease. The head and neck region comprises of a variety of anatomical sites, and neoplasms involving these differ considerably in terms of aetiology, presentation, and pathology, making development of an

accurate staging system complicated. Several studies previously reported inadequacies in the seventh revision of the TNM staging system for head and neck cancer, particularly with regard to the identification of HPV-positive disease (Dahlstrom et al., 2013; Huang et al., 2015). This led to the inclusion of a new stage classification for HPV-positive oropharyngeal cancer in the most recent eighth revision of the TNM staging system for head and neck cancer, reflecting development of a better understanding of the aetiology, character, and prognosis of the disease. Moreover, it also includes clinical and pathological N-definitions and T-N groupings separately. Huang and O'Sullivan (2017), in their overview of this eighth revision of the TNM classification, stated that these changes were necessary as clinical trials now address HPV-positive and HPV-negative oropharyngeal cancer separately and practice guidelines would probably reflect this in the future. Moreover, these changes were also relevant for conversations with patients and their families, cancer surveillance measures, and clinical care.

Stage of cancer at the time of diagnosis has been shown to be one of the most crucial prognostic markers of head and neck cancer (Janot et al., 1996; Iro and Waldfahrer, 1998; Chu and DeVita, 2005), with advanced stage of disease being associated with high mortality (82% 5-year survival rates for localised disease. 51% for regional disease, and 28% for distant metastasis) (Ragin et al., 2007; Goy et al., 2009). Rusthoven et al. reported that the survival rates of patients with late stage (III-IV) carcinoma was significantly lower than that of those with early stage (I-II) cancer ($p=0.04$) (Rusthoven et al., 2010). Moreover, the five-year survival rates decreased drastically as the stage of cancer progressed (from 90% at stage I to 60% at Stage III and 4% at Stage IVc) (Iro and Waldfahrer, 1998; Carvalho et al., 2005). Oral squamous cell carcinomas with very small surface size (less than two centimetres) exhibited higher survival rates compared to those with greater surface size (Moore et al., 1986). Treatment options have also been reported to become increasingly

complex and expensive as the stage of cancer at the time of diagnosis progresses (Shah and Lydiatt, 1995; Lingen et al., 2008).

However, the evidence suggested that over 60% of patients with head and neck cancer are still detected at a late stage (Stage III or Stage IV) when the prognosis was considerably poorer and treatment options were more complex and expensive (Dolan et al., 1998; Holmes et al., 2003; Brandizzi et al., 2005; Lingen et al., 2008). Although the silent nature of the lesion may be partly responsible for this, recent hypotheses suggested that delays in diagnosis may also have a role to play, based on the reasonable assumption that the stage of cancer at the time of diagnosis is a function of the time it had to develop before detection (Mackillop et al., 1996).

#### 1.3.2.2 Early diagnosis of oral cancer

As discussed previously, the main goal of early diagnosis of oral cancer is detection of the disease at the earliest stage possible when the prognosis significantly better. The *WHO Guide to Cancer Early Diagnosis* recommended three key steps to achieving this, as follows: (a) awareness of cancer symptoms and accessing care (patient interval), (b) clinical evaluation, diagnosis, and staging (diagnosis interval), and (c) access to treatment (treatment interval) (WHO, 2017b). All of these steps should ideally be achieved within 90 days, although the exact targets may vary with the type of cancer and the healthcare system (WHO, 2017b). Currently, the Cancer Waiting Time Target of the Scottish Government is a maximum of 62 days from the receipt of referral to the first treatment and 31 days from a decision to treat to actual treatment (ISD Scotland, 2017b). In 2017, 85% of patients that were diagnosed with head and neck cancer in Scotland had met the 62-day target from the receipt of referral to the first treatment (ISD Scotland, 2017b). However, there are several barriers in the form of various types of diagnostic delays that may hinder efforts to achieve these steps and, subsequently, the early diagnosis of cancer.

#### 1.3.2.3 Barriers to early diagnosis: diagnostic delay

The main barrier to the achievement of early diagnosis was diagnostic delay, defined as the total period of time elapsed between first noticing a symptom and diagnosis of the cancer, and it has been reported to have considerable influence on survival (Onizawa et al., 2003; McLeod et al., 2005). It is typically divided into three types, namely, patient, professional, and system delay, and various factors may play a role in the occurrence of these delays (Güneri and Epstein, 2014).

*Patient delay:* this refers to the time elapsed between the first detection of symptom by the patient and the first time he or she consults a healthcare provider. It is specifically a barrier to the first step (awareness of cancer symptoms and accessing care) out of the three that were recommended by the WHO (discussed previously in 1.3.2.2). A systematic review examining factors affecting patient delay was able to identify only eight relevant studies, highlighting the dearth of research and conflicting nature of evidence available in this field (Scott et al., 2006). The authors reported that although there was considerable evidence of patients with oral cancer delaying seeking professional help after noticing symptoms, few of them were able to provide conclusive explanations for doing so. However, similar studies in other cancer sites have suggested that psychosocial factors such as fear, embarrassment, the assumption that symptoms were caused by common ailments, and existence of other social priorities may play a role in such delays (de Nooijer et al., 2001). This was further supported more recently by Güneri and Epstein (2014) in their review where they reported that factors such as fear, denial, worry, and perceptions of social responsibilities affected the duration of delay. A case-series analysis of 306 patients with head and neck cancer in the Netherlands reported that patients were more likely to visit a healthcare provider sooner after self-discovery of symptoms if they had prior knowledge and a higher level of awareness of cancer (Tromp et al., 2005), and this reinforced the theory put forth by a considerably older study that suggested that the most common determinant of delay was cancer

knowledge (Antonovsky and Hartman, 1974). However, Hackett *et al.* suggested that often this delay was a conscious and deliberate act on the part of the patient, rather than a lack of knowledge and worry, and was fuelled by underlying psychosocial factors such as fear and perceptions of social accountability. Moreover, worry, though a complex variable, was seen to be inversely proportional to the duration of delay, with those worrying about a particular symptom often exhibiting reduced delay (Hackett et al., 1973). Kumar *et al.* in their questionnaire study of 79 patients observed an association between patient delay and regular visits to the doctor, socioeconomic status, patient beliefs such as "ill-fated to have cancer" and "family tension due to long treatment", availability of transport and being escorted by someone. However, the definitions of these variables were unclear and the size and directions of these associations were not explained adequately, limiting the interpretability of the results (Kumar et al., 2001).

*Professional delay*: although this usually always starts from the time a patient consults a healthcare provider, the definition of the endpoint has been shown to vary (e.g. referral to specialist, time to biopsy, time to treatment) (Stefanuto et al., 2014). It specifically acts as a barrier to achievement of the second step (clinical evaluation, diagnosis, and staging) out of the three that were recommended by the WHO (discussed previously in 1.3.2.2). Gómez et al. (2010), in their review of factors responsible for diagnostic delay in oral cancer, reported that there was considerable, albeit ambiguous, evidence on a relationship between the academic degrees of clinicians, particularly with regard to general medical practitioners and dentists, and the rapidity of diagnosis. They found that some studies attributed the fact that general medical practitioners were likely to refer patients with oral cancer quicker than dentists to a high index of suspicion, while others put it down to high prevalence of oral lesions and low incidence of oral cancer and suggested that dental clinicians were more likely to offer treatment for such lesions instead of referring the patient, often resulting in delayed diagnosis of cancer. The

authors also reported finding evidence of knowledge gaps regarding the risk factors, preventive measures, and changes associated with oral cancer, particularly in the early stages, among dentists (Gómez et al., 2010). This was further corroborated by Güneri and Epstein (2014) who reported that dental and medical practitioners may fail to recognise malignant lesions of the oral cavity due to the relatively low incidence of these cancers in the general population and their non-specific appearance and potentially insidious nature. They suggested that, in such cases, patients should be referred immediately to minimise delay and the urgency of the referral was the clinician's responsibility. The authors also reported that although dental practitioners were more likely to come upon patients with oral squamous cell carcinomas, only a small proportion of patients showed a tendency to visit dentists upon self-discovery of symptoms, reflecting the tendency of assuming that "dentists were for teeth and gums", and this often resulted in further delays in diagnosis (Güneri and Epstein, 2014).

Other factors that may have an influence on professional delay include vague or unspecific clinical signs (Bruun, 1976), lack of experience or unfamiliarity with the disease (Guggenheimer et al., 1989), low index of suspicion (Holland, 1975), deficient clinical examination (Robbins et al., 1950), and presence of co-morbidities (Allison et al., 1998). Conway et al. (2002), in their paper discussing the role of primary healthcare teams in the prevention and detection of oral cancer, stressed upon the necessity of creating awareness amongst dental practitioners regarding local referral arrangements in order to avoid any delays. Moreover, they also encouraged telephonic conversations with various oral and maxillofacial surgeons, ENT surgeons, or oral medicine consultants, thus avoiding further delays by allowing the practitioner to ensure that the consultant in question dealt with that specific type of case. The authors also suggested that, in case of a diagnosis of cancer, the patient should be referred to the appropriate services by means of a telephonic conversation as well as a letter marked urgent.

*System delay*: this refers to any delays caused by "system" factors such as limited accessibility to healthcare, availability of specific treatments, and high associated costs. This too typically acts as a barrier to achievement of the second step out of the three that were recommended by the WHO (discussed previously in 1.3.2.2). Güneri and Epstein (2014) reported that scheduling or system delays were mainly caused by barriers in the health care system, availability of resources, and healthcare economics. Additionally, access to health care facilities and availability of the appropriate treatments may also have a role to play.

Seoane et al. (2012), in their meta-analysis of data from ten studies and nine countries, examined the association between various time intervals considered in studies focusing on diagnostic delay and a range of outcome measures such as survival and the TNM stage of head and neck cancer. Their pooled ORs using TNM stage as the outcome of interest showed a substantial increase in the risk of late stage cancer with diagnostic delay, and this increase in risk was greater for professional delay than for patient delay. Moreover, diagnostic delay was also moderately associated with increased mortality of head and neck cancer, and this relationship was particularly strong for referral delay (Seoane et al., 2012).

### 1.3.3 The role of dental practices and alternative healthcare settings in the early detection of oral cancer

General dental practitioners, through regular patient contact, are placed in an ideal position to increase awareness of the known risk factors of oral cancer, deliver preventive advice, examine the oral soft tissues of patients for OPMDs, and prevent recurrence or spread of the cancer (Conway et al., 2002). They also play a crucial role in the management of oral cancer through patient counselling and early referral which, in turn, facilitates early diagnosis and prompt treatment (Conway et al., 2002).

Conway et al. (2002), in their paper discussing the role of primary healthcare teams in the prevention and detection of oral cancer, suggested

that provision of a thorough extra- and intra-oral examination during regular dental check-ups could help in the early detection of potentially malignant or malignant lesions. Briefly, they suggested that the extra-oral examination included a thorough inspection of the skin of the outer lip and the lymph node groups in the neck for any abnormalities such as lymphadenopathy, which usually presents as a hard, asymmetrical swelling or mass that is often tender on touch. The authors stated that this could be achieved by standing behind the patient and palpating the neck starting from the submental group of lymph nodes under the chin, posteriorly onto the submandibular group, followed by the jugulodigastric group, and finally down along the deep cervical chain of lymph nodes. They recommended that this should then be followed by an examination of the oral mucosa for any evidence of ulcerations, lumps, indurated or fixated areas, poor wound healing, or evidence of potentially malignant conditions such as oral sub-mucous fibrosis, leukoplakia, or erythroplakia. The “high-risk” areas included the floor of the mouth, which could be examined by asking the patient to touch his palate with the tip of his tongue, and the posterior and lateral aspects of the tongue, which could be examined by pulling on the tongue using gauze, thus permitting complete visualisation of both right and left borders. Other dangerous areas included the retromolar areas and the hard and soft palate, which could be examined using the dental mirror. The dorsal surface of the tongue could be inspected by asking the patient to stick out his tongue and checking for any abnormalities.

However, although visual examination of the oral cavity is part of a regular dental visit, timely detection and referral of oral cancer in the dental setting is also largely dependent on patients consulting dentists frequently enough to achieve this. Research from around the world suggests that the proportion of patients with oral cancer that had contacted a general dental practitioner on a regular basis was considerably low, thus automatically limiting the opportunities for early detection in the dental setting. Tromp et al. (2005), in their case-series analysis consisting of 306 patients that

were diagnosed with head and neck cancer between 2000 and 2002 in a tertiary referral centre in the Netherlands, reported that only 12% of the sample had contacted a dentist first upon detecting symptoms, and 82% had been in contact with their general practitioner instead. Similar results were reported by another clinical cohort study in Western Australia that examined the dental attendance patterns of all patients that were diagnosed with oral cavity and oropharyngeal cancer between January 2005 and December 2009 in one teaching hospital, and found that the majority of the patients did not have regular contact with a dentist (mean duration since last dental visit: 5.6 years) (Frydrych and Slack-Smith, 2011). With regard to patient access to opportunities for early detection of oral cancer, Netuveli et al. (2006) used data from the Health Survey for England (2001) (n=13,784) and the British Household Panel Survey (n=5547) to examine the association between dental attendance patterns and various known risk factors of oral cancer. Their results showed that the likelihood of attending a dental practice regularly decreased as the number of factors favouring carcinogenesis (i.e. patients who exhibited high risk scores for all five of the examined factors — age, sex, alcohol consumption, smoking, and low intake of fruits and vegetables) and, subsequently, the risk of developing oral cancer increased. This was particularly striking in case of smoking. Moreover, the low probability of regular dental attendance in this "high-risk" group appeared to remain stable over time (over 1-, 3-, 5-, and 10-year periods). The authors termed this as the "inverse screening law" and suggested that opportunistic screening in dental practices would not be an efficient early detection strategy in the United Kingdom as only those who were at the lowest risk of developing cancer would be screened (Netuveli et al., 2006). These results were further corroborated by another study that also used data from the British Household Panel Survey to examine the association between dental attendance patterns and the known risk factors of oral cancer including socioeconomic status (Yusof et al., 2006). Their results showed that "high-risk" individuals (defined as males, above 40 years of age, with low socioeconomic status and education, manual occupational social class, and smokers) usually exhibited poorer dental

attendance patterns. These studies highlighted the role of alternative settings, particularly general practitioners and other specialist practices, in the early detection of oral cancer.

The notion of involving other primary healthcare services in early detection efforts was first proposed in 1990 when Prout et al. (1990) examined 130 patients that were diagnosed with head and neck cancer between September 1, 1985 and March 31, 1988 in Boston, and reported that 94% of them had visited a healthcare provider at least once in the 24 months prior to diagnosis. The services contacted were typically those that the subjects considered as their "regular source of care", and the authors stated that these findings emphasised the need to integrate these services in strategies for the early detection of head and neck cancer. More recently, Reid et al. (2004) created a study dataset consisting of 11,312 patients diagnosed with head and neck cancer (defined as including the lip, oral cavity, pharynx, and larynx) between 1991 and 1999 in the United States by linking data from the Surveillance, Epidemiology and End Results (SEER) Program with files from the Centre for Medicare and Medicaid Services Program, and reported that 93% of the patients with localised stage disease and 88% of the patients with advanced stage disease had contacted a general practitioner at least once in the year before diagnosis. The authors stated that these contacts formed the "basis of opportunistic screening" for head and neck cancer. A systematic review of 12 studies examining patient acceptance of oral cancer screening in non-dental settings reported that undiagnosed cases appeared to prefer seeking help from a general practitioner in case of noticing symptoms, and also favoured general medical practice settings over dental clinics for oral cancer screening (Paudyal et al., 2014). Ligier et al. (2016) examined the medical consultation patterns of 342 patients that were diagnosed with head and neck cancer (defined as including the anatomic subsites oral cavity, oropharynx, hypopharynx, and larynx) in 2010 in a high-incidence region in France. The patients (n=342) were identified from four French cancer registries, and their medical data were matched with data on the

uptake of healthcare, provided by the French National Health Insurance General Regime. The authors reported that only 21% of the patients had visited a dentist in the two to twelve months prior to diagnosis, and this proportion decreased as the level of deprivation increased. However, the vast majority (86%) of the patients had consulted a general medical practitioner over the same period, and a dose-response association was observed between the number of GP consultations and a localised stage of cancer at the time of diagnosis, suggesting that "medical monitoring" had an influence on stage. Although the authors mentioned that their results were generalisable to countries with similar health care set-ups, their sample size was relatively small and this may have affected the accuracy and precision of the results.

More locally and recently in the United Kingdom, Crossman et al. (2016) randomly selected 200 out of the 478 patients with oral and oropharyngeal cancer included in the 2010 Cancer Patient Experience Survey (which consisted of 67,713 adults treated for cancer between January and March 2010 at one of the 158 National Health Service hospitals in England), and sent them a postal questionnaire that collected information on the health services they had contacted before receiving a diagnosis of cancer and the symptoms that had prompted them to do so. They found that only 32% of the patients had been referred to secondary care by a dentist, while 56% had been referred by a general practitioner instead. The authors concluded that GPs played a crucial role in the early detection of oral cancer, and listed common signs and symptoms that could be used for assessment and decision-making.

In England, the National Cancer Intelligence Network linked data from the Administrative Hospital Episode Statistics database with Cancer Waiting Times data, cancer screening programme data, and cancer registration data to examine the "Routes to Diagnosis" for patients that were diagnosed with cancer (all sites) between 2006 and 2013 (Elliss-Brookes et al., 2012). They found that 21% of all oral cavity cancer and 26% of all oropharyngeal cancer diagnoses in England occurred following GP referrals

in 2013. Moreover, diagnoses via the "Two-weeks Wait (TWW)" route, defined as including "all urgent GP referrals with a suspicion of cancer", and the "Other Outpatient" route, defined as "an elective route starting with an outpatient appointment", had increased between 2006 and 2013. The authors clarified that there was also the possibility that some of the referrals via the latter route ("Other Outpatient") were originally initiated by general practitioners (Elliss-Brookes et al., 2012; NCIN, 2017).

### 1.3.4 Missed opportunities for the early detection of oral cancer

Society's expectations of a prompt diagnosis of cancer, although context-specific, often conflicts with the challenges associated with its actual achievement, and this is becoming increasingly apparent to healthcare professionals and researchers. This has resulted in a sudden escalation of research focusing on the ways to identify errors in the diagnostic process and strategies to minimise associated diagnostic delays.

Diagnostic errors, known to cause harm to patients, are usually a result of both system and cognitive contributory factors. Recently, Singh et al. rebranded these errors as "missed opportunities" in the diagnostic process, and began to explore ways to define as well as measure them (Singh, 2014). The main idea behind this rebranding was to shift the focus and, subsequently, resources from attribution of blame to learning from these situations. Lyratzopoulos et al. (2015) defined missed opportunities as "instances where post-hoc judgement indicates that alternative decisions or actions could have led to a more timely diagnosis, that is, something different could have been done or considered under the given circumstances to reach a more prompt diagnosis". Recognition of these missed opportunities could inform policy decisions and facilitate the identification of areas where health services could be improved. This would consequently contribute to the "situation analysis of existing cancer services" (including assessment of the current population coverage of services, the cost of strategies currently in place, barriers to provision of

care including delays, and the quality of care provided) recommended by the World Health Organisation in the *Guide to Cancer Early Diagnosis* (WHO, 2017b).

#### 1.3.4.1 Factors contributing to missed opportunities

Most missed opportunities are usually the result of a complex interplay of various patient, provider, and system factors, some of which have been discussed previously in section 1.3.2.3, and understanding this web is crucial for the development of strategies to minimise diagnostic errors and delays in diagnosis (Singh et al., 2013). This calls for a multidisciplinary approach that takes psychology, human factors, and informatics into account. As elaborated by Lyratzopoulos et al. (2015), the "model of pathways to treatment" proposed by Scott et al. (2013) divides the entire patient process into four intervals (symptom appraisal, help-seeking, diagnosis, and pre-treatment), and the diagnostic interval is relevant for missed opportunities. This diagnostic process can be further divided into three main phases. The first is the initial diagnostic assessment phase, which represents the first clinical encounter between the patient and a health care practitioner and typically includes recording of medical history, clinical examination and diagnosis reasoning. The second phase is diagnostic test performance and interpretation, and this generally includes execution and interpretation of diagnostic tests such as blood tests, endoscopies, imaging, and associated decisions. The final phase is diagnostic follow-up and coordination, which includes all decisions and tasks that are completed based on the results of the diagnostic tests performed in the previous phase.

Lyratzopoulos et al. (2015), in their review of the evidence on missed opportunities for the timely diagnosis of cancer, reported that they could occur in any one of these three diagnostic stages, and that there were a vast range of factors that contributed to their occurrence. For example, factors contributing to missed opportunities in the *initial diagnostic assessment phase* included inadequate history taking and examination;

rigid consultation norms; cognitive factors that hinder optimal clinical assessment and reasoning such as anchoring bias (focusing on a single piece of information), availability bias, “commitment to a steer”, presence of co-morbidities among older individuals, unfamiliarity with cancer presentations, and “epidemiological bias” that make prompt suspicion of cancer even more difficult, particularly in cases of rare cancers and in low-risk groups; language barriers; access and system time constraints; and referral norms (Lyratzopoulos et al., 2015). The factors contributing to missed opportunities in the *diagnostic test performance and interpretation* phase included “no-show” events and lack of system resilience in coping with them; diagnostic testing process complexity; and inadequacies in the investigation strategy, while those contributing to the *diagnostic follow-up and coordination* phase were patient factors such as patients not feeling empowered enough to or simply not knowing how to seek out their test results; over-reliance on “patient call-back”; and lack of follow-up or appreciation of abnormal test-results.

#### 1.3.4.2 Evidence of missed opportunities in the diagnosis of cancer - retrospective clinical reviews

A large proportion of the evidence on the occurrence of missed opportunities in the diagnostic process is based on retrospective reviews of cohorts of patients with cancer. For example, Singh et al. (2010) retrospectively reviewed all of the electronic health records of patients that were newly diagnosed with primary lung cancer at two geographically dispersed Veterans Affairs (VA) medical centres. They identified two main types of missed opportunities, and these were Type 1, which included episodes of care where a failure to recognise predefined “clinical clues” was observed, and Type 2, where there was a failure to complete a diagnostic procedure, consultation or requested follow-up in response to a predefined clue within a 30-day period. The authors undertook a detailed review of all progress reports, consultation, laboratory, and radiology reports, and all additional data relevant to the diagnostic process, and found that 38% of the 633 new cases of lung cancer showed evidence of

missed opportunities for early diagnosis. The median period between observation of the first symptom and pathologic diagnosis was 132 days in patients with at least one event of missed diagnosis. In contrast, this period was equal to only 19 days in patients with no evidence of missed opportunities. Type 1 missed opportunities were observed in approximately 25% of the patients (median delay period of 168 days), while Type 2 missed opportunities were observed in 21% of the patients (median delay period of 141.5 days) (Singh et al., 2010). Mitchell et al. (2013) analysed data from the Significant Event Audit (SEA) in the North of England to better understand the pathway to diagnosis of lung cancer. The SEA is a quality improvement technique that is widely used in primary care practice in the United Kingdom, and it can be applied to any aspect of healthcare in order to obtain a structured understanding of the circumstances surrounding a particular event of interest (Pringle et al., 1995). The authors identified a total of nine out of 132 cases where opportunities for early diagnosis were missed, and reported the circumstances surrounding these events with an aim to provide a learning opportunity (Mitchell et al., 2013). In another study examining missed opportunities for cervical cancer screening among 642 women diagnosed with cervical cancer at the Kaiser Permanente Medical Care program in Northern California, 60% of the women were reported to have not undergone a PAP smear in the 36 months prior to diagnosis, of which 75% had had contact with primary care services within the same period (Kinney et al., 1998).

These studies showed that retrospectively reviewing cohorts of patients with cancer was an efficient way to detect missed opportunities as it permitted identification of the location of the error and examination of the reasons for its occurrence (e.g. presence of comorbidities, inadequate understanding of test results etc). Moreover, it also made quantification of the associated delay possible, thus exposing crucial areas where efforts to improve diagnostic quality may be focused.

#### 1.3.4.3 Evidence of missed opportunities in the diagnosis of cancer - epidemiological evidence

In addition to retrospective case reviews, there is also a considerable amount of epidemiological evidence on the existence of missed opportunities for early diagnosis of cancer. The review conducted by Lyratzopoulos et al. (2015) found that several studies had used "surrogate markers" for missed opportunities, including multiple general practitioner consultations before referral (Lyratzopoulos et al., 2012; Lyratzopoulos et al., 2013), emergency attendances (Elliss-Brookes et al., 2012; Mitchell et al., 2013), and abnormal or "red flag" findings (such as a lump in the neck, hoarseness, dysphagia, ulceration, or weight loss in the case of oral cancer) (Murphy et al., 2014; Douglas et al., 2017).

In another study, Lyratzopoulos et al. (2012) used data from the 2010 National Cancer Patient Experience Survey conducted in England to explore variations in the number of pre-referral general practitioner consultations among 41,299 patients with 24 different types of cancers. They hypothesised that the number of such visits was an indicator of patient experience, and attempted to identify factors that acted as independent predictors of three or more pre-referral consultations. Ahmed et al. (2014) stated that patient experience could be "conceptualised both as patients' experiences of care and as feedback received from patients about those experiences", and the National Health Service in England specified eight domains (physical comfort, respect, emotional support, information and communication, and access to care) that were crucial for a "good" patient experience (NHS, 2012). Lyratzopoulos et al. (2012) observed large variations in the proportions of patients who had visited a general practitioner (GP) three times or more before referral, and these variations appeared to be associated with the type of cancer diagnosed (lowest for breast cancer and malignant melanoma; highest for multiple myeloma and pancreatic cancer). Women, younger patients, and those belonging to ethnic minority groups were more likely to visit a general practitioner more than three times pre-referral, although the variations were less

prominent when examined by socioeconomic characteristics, providing a certain level of reassurance that a comprehensive coverage system like the National Health Service in the United Kingdom was capable of providing equitable care. The authors concluded that the patients that were diagnosed with more well-known cancers were less likely to have had a large number of pre-referral consultations. Similar results were reported by the National Audit of Cancer Diagnosis in Primary Care conducted in England in 2009/2010 where almost 38% out of 229 patients that were diagnosed with oropharyngeal cancer had consulted their general practitioner two or more times for cancer-related issues before being referred to a specialist for assessment (Rubin et al., 2011).

Research from Denmark suggested that the frequency of diagnostic tests and hospital visits of patients subsequently diagnosed with cancer was considerably higher than those with no cancer in the months preceding diagnosis (Christensen et al., 2012; Ahrensberg et al., 2013; Hansen et al., 2015). Christensen et al. (2012), in their national registry based case-control study, compared the monthly general practitioner consultation frequencies of all patients with cancer (diagnosed between 2001 and 2006 and identified from the Danish Cancer Registry) in the year before diagnosis to that of 1,272,100 gender-matched controls from the general population. They found that the patients with cancer exhibited a modest increase in GP consultations five to six months before diagnosis, and that this number peaked one month before diagnosis. Moreover, the number of hospital visits and diagnostic examinations began to rise approximately three to four months before diagnosis, and this escalated steeply two months before diagnosis. Overall, patients with cancer were seen to utilise health services significantly more than the reference population throughout the study period (one year before diagnosis) (Christensen et al., 2012).

Similarly, Hansen et al. (2015) reported that patients with colorectal cancer had higher odds of consulting a general practitioner more than five times in the year preceding diagnosis compared to patients without cancer.

They also observed a significant increase in the number of GP consultations nine months before diagnosis, and this finally peaked one month before diagnosis (Hansen et al., 2015). However, in contrast to Lyratzopoulos et al. (2012), these studies did not account for a referral period and considered diagnosis as the end-point. As a result, it was unclear at what point these contacts shifted from being missed opportunities for early detection via screening to becoming missed opportunities for early diagnosis, caused by delays in the diagnostic process itself. Nevertheless, they do highlight the significance of unusual patterns of health service contacts in the identification of opportunities for early detection.

Although these kinds of epidemiological data do not provide any information regarding the nature of these consultations and not all of these instances would have been necessarily associated with missed opportunities for the early detection of cancer, it did provide a strong indication that there were potentially missed opportunities amongst at least some of the patients with cancer (Rubin et al., 2011; Lyratzopoulos et al., 2015).

## 1.4 Summary of debates and gaps in the literature

This section of the thesis summarises some of the key debates and conclusions from the literature, discusses some of the gaps identified in the evidence, and then provides a rationale for this thesis.

The first issue encountered upon commencement of a literature search for epidemiological evidence on the incidence trends of head and neck cancer (and subsites) was a lack of consensus and considerable debate surrounding the way in which these sites were defined. This included an absence of unanimity in the terminology used as well as the specific ICD codes included within each subsite grouping. Upon reviewing the literature, two main schools of thought with regard to the specific definitions of the individual subsites (i.e. ICD codes included within each grouping) were identified. The first was an anatomical method of definition based on the

physical boundaries of the individual subsites, and the second was an aetiological (risk factors) driven method of definition where the subsites were defined based on their association with HPV infections. Based on this evidence, the current thesis developed and proposed a "compromise" approach which utilised a mixed (anatomical and HPV-associated) method of defining subsites for the descriptive epidemiological analyses presented later in Chapters 2 and 3. The individual ICD codes included in each group have been shown in Appendix 1. Briefly, **oropharyngeal cancer** was defined as including the base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), and the pharynx (C14); while **oral cavity cancer** included the inner lip (C00.3-C00.9), other and unspecified parts of the tongue (C02), gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06). However, the evidence also showed that tumours rarely followed the specific anatomical boundaries of the oral cavity and oropharynx, and the signs and symptoms of both cancers overlapped considerably. Moreover, most clinical guidelines for the detection of oral cancer appeared to combine and address both subsites together. Given that dentists and other healthcare practitioners have a role in the primary and secondary prevention of cancers affecting both subsites (oral cavity and oropharynx), a more generalised definition of "oral cancer" that combined the two subsites appeared to be more appropriate from a clinical perspective. Therefore, this was the approach adopted in the analyses presented in Chapters 3 and 4.

Global epidemiological evidence showed that the incidence burden of head and neck cancer was rising, and these trends varied considerably by subsite and various sociodemographic characteristics (Shield et al., 2017). The incidence rates of oropharyngeal cancer were rising almost exclusively in higher income countries, reflecting an increase in the prevalence of HPV infections, while the burden of oral cavity cancer was increasing in lower income countries, and this could be attributed to the continuing tobacco epidemic that had already started to decline earlier in the high-income

countries. In the United Kingdom, the incidence rates of head and neck cancer had increased between 1995 and 2011, and this appeared to be largely driven by a rapid rise in the rates of oropharyngeal cancer (Louie et al., 2015). Moreover, examination of projected rates revealed that this upward trend was expected to persist up to 2025. The most recent examination of the incidence burden of oral cancer (defined as C00-C06, C09-C10) in Scotland only focused on trends up to 1999, and also examined both oral cavity cancer and oropharyngeal cancer together as one subsite (Conway et al., 2006).

With regard to the patient profile, males were seen to consistently exhibit higher incidence rates of oral cancer compared to females irrespective of subsite, although there was some evidence of an increasing burden of oral cavity cancer among women in lower income countries, possibly reflecting a sudden surge in tobacco consumption among this group. Socioeconomic inequality in the distribution of oral cancer was observed, with the rates of cancer increasing as the level of deprivation increased. This gap by deprivation was also apparent at the global level, with economically developing countries consistently bearing the greater burden of cancer compared to the economically developed countries (Warnakulasuriya, 2009a; Shield et al., 2017). However, when considering the individual subsites, data from the United States appeared to suggest a substantially different patient profile for oropharyngeal cancer, with patients being predominantly male, exhibiting higher socioeconomic status, and being considerably younger (Dahlstrom et al., 2015). There have been no population studies to date that have examined the within-country burden of oropharyngeal cancer relative to socioeconomic status. The literature review also showed that the majority of patients with head and neck cancer were primarily older individuals, although there was some evidence of incidence rates increasing among the younger population (defined as being less than 30 years), particularly for tongue cancer (Depue, 1986). A similar patient profile was also observed in the United Kingdom, with males, individuals aged less than 70 years, and those with lower

socioeconomic status being at the highest risk of developing oral cancer (Conway et al., 2007; Conway et al., 2008; Louie et al., 2015).

Seoane et al. (2015), in their systematic review and meta-analysis, showed that early stage of cancer at the time of diagnosis improved prognosis considerably and decreased the cost of treatment. General dental practitioners appear to have a potentially pivotal role in the early detection of oral cancer through regular patient contact. However, this is largely dependent on the general dental practice attendance patterns of patients with oral cancer. Evidence suggested that the "inverse screening law", which stated that those at the highest risk of developing oral cancer were also least likely to consult a general dental practitioner on a regular basis, was applicable in the United Kingdom (Netuveli et al., 2006; Yusof et al. 2006). In England, examination of the routes to diagnosis of cancer showed that a majority of oral cancer referrals appeared to be coming from sources that were out-with the dental setting (Elliss-Brookes et al., 2012). These studies appeared to suggest a potential role of alternative healthcare services in the early detection of oral cancer.

The World Health Organisation, in their *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs* report, clarified that the two main strategies for early detection of oral cancer were screening and early diagnosis (WHO, 2006). Currently, there is insufficient evidence in favour of oral cancer screening at the population level, and various cost-effectiveness analyses have shown that targeted opportunistic screening of "high-risk" individuals appeared to be more feasible (Speight et al., 2006). With regard to early diagnosis of cancer, the WHO referred to it as a form of "down-staging", and recommended three key steps to achieving this, including a) awareness of cancer signs and symptoms and accessing care (patient interval), b) clinical evaluation, diagnosis and staging (diagnosis interval), and c) access to treatment (treatment interval), all of which should be accomplished within 90 days (WHO, 2013).

Missed opportunities for the early diagnosis of cancer may occur at any stage of the diagnostic process, and these are usually indicative of delays that occurred at the patient, professional, and system levels (Lyratzopoulos et al. 2015). A wide range of influences may play a role in the occurrence of these delays, including psychological factors, low index of suspicion due to a low prevalence of the disease, lack of experience or unfamiliarity with the disease, presence of co-morbidities, poor access to healthcare services, and limited resources. Such missed opportunities can be examined and measured by means of retrospective clinical reviews as well as a variety of "surrogate markers" such as unusual patterns of pre-referral consultations with healthcare services and emergency presentations. There is a considerable amount of research that shows existence of such missed opportunities for early detection of cancer, and the majority of these are in relation to cervical and breast cancer. However, there are limited studies investigating missed opportunities for early detection of oral cancer.

The studies reviewed in this chapter led to the identification of several gaps in the literature. Although it is well-known that early stage at the time of diagnosis of oral cancer is associated with significantly better prognosis, a large proportion of the patients continue to be diagnosed at a later stage. General dental practitioners appear to have a pivotal role in the early detection of oral cancer, but the feasibility of this is largely dependent on the dental attendance patterns of patients and the volume of the disease. Therefore, the first gap identified in the literature was that there were no studies that provided recent as well as projected estimates of the incidence burden of head and neck cancer in Scotland by individual subsites and various sociodemographic characteristics. Moreover, there was also no information on the socioeconomic profile of the distribution of oral cavity cancer and oropharyngeal cancer at the population level, with studies from the US suggesting that oropharyngeal cancer had a different, more affluent patient profile (Dahlstrom et al., 2015). Secondly, although the evidence suggested that those at the highest risk of developing oral

cancer were also least likely to contact general dental practitioners on a regular basis, all of these studies were undertaken over a decade ago and none of them considered a population approach. There was limited information on the dental attendance patterns of patients with oral cancer in Scotland, and no evidence on the distribution of the incidence burden in relation to the location and socioeconomic profile of the area in which the general dental practices were located. Examination of this could assist in the identification of areas with particularly high incidence of oral cancer, which future early detection efforts could then target. Thirdly, although there was a considerable amount of evidence that confirmed the existence of missed opportunities for early detection of cancer, the majority of it was in relation to cervical and breast cancer. There were no studies that investigated missed opportunities for the early detection of oral cancer. Fourthly, the healthcare service contacts made by patients with oral cancer in Scotland prior to diagnosis had not been explored, and these contacts could be considered as potential missed opportunities for early diagnosis. Lastly, the potential role of alternative healthcare services in the early detection of oral cancer was unknown, and there was also no evidence on the routes to diagnosis of oral cancer among patients in Scotland.

Overall, although the literature suggested that the importance of oral cancer as a public health problem had been recognised, the size of this problem and its relationship with early detection efforts was still somewhat overlooked. Moreover, while a lot of the emphasis on oral cancer screening efforts had been focused in the dental setting, the potential role of other healthcare settings in early detection remained relatively under-explored.

## 1.5 Aims, objectives and hypotheses

The overarching ***aim*** of this thesis was to investigate opportunities for the early detection of oral cancer in Scotland. The objectives and hypotheses

have been numbered according to the chapter and order in which they appear in this thesis.

**Chapter 2 Aim: To examine the incidence burden and sociodemographic profile of patients with head and neck cancer in Scotland.**

**Chapter 2 Hypotheses**

**Chapter 2 hypothesis (a):** The trends of head and neck cancer are increasing and are projected to continue to do so.

**Chapter 2 hypothesis (b):** This increase in incidence rates of head and neck cancer will largely be driven by an increase in the rates of oropharyngeal cancer.

**Chapter 2 hypothesis (c):** The patient profile of oropharyngeal cancer will differ from other subsites, particularly in relation to socioeconomic status.

**Chapter 2 hypothesis (d):** In relation to the socioeconomic distribution of head and neck cancer, there will be a clear stratification of "high-risk" areas in the more deprived communities that could be utilised to target early detection initiatives.

**Chapter 2 Objectives**

**Chapter 2 objective (a):** To create a cohort of patients with head and neck cancer (and subsites) using data from the Scottish cancer Registry.

**Chapter 2 objective (b):** To describe and analyse the incidence burden and trends of oral cavity, oropharyngeal and laryngeal cancer in Scotland between 1975 and 2012 by key sociodemographic determinants including age, sex, area-based socioeconomic deprivation, geographic region and year of diagnosis.

**Chapter 2 objective (c):** To compute future projected incidence rates up to 2025 for all head and neck, oral cavity, oropharyngeal, and laryngeal cancer by key sociodemographic determinants including age, sex, area-based socioeconomic deprivation, geographic region and year of diagnosis.

**Chapter 2 objective (d):** To produce a sociodemographic risk profile of all patients with head and neck, oral cavity, oropharyngeal and laryngeal cancer for stratification.

**Chapter 3 Aim: To investigate whether early detection of oral cancer in dental settings is a realistic expectation, given the current burden and sociodemographic risk profile of the disease and the location and distribution of general dental practices in Scotland.**

**Chapter 3 Hypotheses**

**Chapter 3 hypothesis (a):** The number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) a general dental practitioner in Scotland can expect to see will be low.

**Chapter 3 hypothesis (b):** Dentists working in more deprived areas will expect to see a greater number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) compared to dentists working in relatively less deprived areas.

**Chapter 3 Objectives**

**Chapter 3 objective (a):** To collate data from the Scottish Cancer Registry and routine administrative NHS Scotland data on dental practice distribution, dental workforce, and population dental registration and participation (attendance) rates.

**Chapter 3 objective (b):** To estimate the number of patients with oral cancer (oral cavity and oropharyngeal cancer) an NHS primary care dentist may expect to see per year and over time.

**Chapter 3 objective (c):** To examine how the estimates of the number of patients with oral cancer (oral cavity and oropharyngeal cancer) may vary with the location and distribution of dental practices in relation to the socioeconomic deprivation of the area.

**Chapter 3 objective (d):** To link Scottish Cancer Registry data with routine NHS dental service payment claims data to calculate dental attendance rates of patients with oral cancer (oral cavity and oropharyngeal cancer) in the two years preceding diagnosis.

**Chapter 4 Aim: To identify potentially missed opportunities for the early detection of oral cancer in dental and alternative healthcare settings.**

**Chapter 4 Hypotheses**

**Chapter 4 hypothesis (a):** There are a number of potentially missed opportunities for the early detection of oral cancer in dental and other healthcare services.

**Chapter 4 hypothesis (b):** These potentially missed opportunities increase in frequency in the months directly prior to the start of the referral period.

**Chapter 4 Objectives**

**Chapter 4 objective (a):** To create a longitudinal population cohort by linking the available routine administrative health service data including hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescriptions with the Scottish Cancer Registry oral cancer data.

**Chapter 4 objective (b):** To calculate the proportion of patients with oral cancer who had contacted all/any of the healthcare services (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescriptions) in the two years prior to diagnosis, and examine the mean number of contacts made over the same period.

**Chapter 4 objective (c):** To calculate the proportion of patients with oral cancer who had contacted each of the services (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescriptions) individually over the two years prior to the start of the referral period, examine the mean number of contacts made with each service, and assess any variations by year and six-month periods prior to the start of the referral period in order to identify any alternative opportunities for early detection efforts.

**Chapter 4 objective (d):** To undertake a focused examination of primary dental care service contacts of patients with oral cancer by analysing the frequency and reasons for consultation by year and six-month periods in order to identify any "potentially missed" opportunities for early detection in the dental setting.

**Chapter 4 objective (e):** To examine the nature of contacts made by patients with oral cancer during the one month period directly preceding diagnosis, defined here as the "referral period", in order to assess the feasibility of using this data to examine the routes to diagnosis of oral cancer.

# 2 Incidence trends of head and neck cancer in Scotland (1975-2012), projected rates up to 2025, and determinants of trends.

## 2.1 Introduction

According to the World Health Organisation International Agency for Research on Cancer (WHO IARC), head and neck cancers including all neoplasms of the lip, oral cavity, and pharynx were the seventh most common in terms of incidence globally in 2012 (approximately 529,000 new cases annually) (IARC, 2014). The literature review in Chapter 1 of this thesis showed that the increasing incidence burden of head and neck cancer globally appeared to be largely driven by a rapid rise in the rates of oropharyngeal cancer, and this was particularly true in developed countries like Canada, United States, Japan, Switzerland, Australia, England and parts of Eastern Europe (Chaturvedi et al., 2011; Forte et al., 2012; Chaturvedi et al., 2013; Hong et al., 2014). Rates of oral cavity cancer were also rising among men and women in some European countries, stabilising in certain Asian countries, and decreasing in Canada and USA (Chaturvedi et al., 2013; Simard et al., 2014). With regard to the risk profile of head and neck cancer, males consistently exhibited higher incidence rates, irrespective of subsite (Shield et al., 2017), and a socioeconomic inequality existed in the distribution of cancer, with higher levels of deprivation being associated with a greater risk of developing cancer (Conway et al., 2008). Specifically, low levels of education (OR 1.85, 95% CI: 1.60 - 2.15), low income (OR 2.41, 95% CI: 1.59 - 3.65) and low occupational status (OR 1.84, 95% CI: 1.47 - 2.31) were significantly associated with an increase in risk of developing oral cancer. This chapter of the thesis first summarises some of the evidence on the trends and risk profile of head and neck cancer in the United Kingdom and identifies some of the gaps in the literature. It then lists the specific aims and objectives of this study, describes the data and methodology used, discusses the

findings and offers possible explanations for them and, finally, deliberates the strengths and limitations of the study.

Louie et al. (2015) used population-based cancer registry data in England to examine the incidence burden of head and neck cancer between 1995 and 2011 and reported an upward trend (59% increase in incidence rates). These rates were expected to continue to rise by 35% in males and 49% in females up to 2025. Moreover, this increase appeared to be largely driven by a rapid rise in the rates of oropharyngeal cancer (average annual percentage change = +7.3% in males and +6.5% in females), while smaller increases were observed in the rates of oral cavity cancer. The incidence rates of oropharyngeal cancer increased in all age-groups, particularly the 50-59 and 60-69 year groups, over the study period, and the median age of incidence was less than 60 years (Louie et al., 2015). These results were corroborated by Tataru et al. (2017) who used data from the former Thames Cancer Registry to examine trends of head and neck cancer in London between 1985 and 2010 by age, sex, site, deprivation, and ethnicity. Their results showed that the age-standardised incidence rates of head and neck cancer had increased by 40% in males and 87% in females over the study period, and this upward trend was statistically significant for oral cavity, oropharyngeal, and thyroid cancer. Moreover, approximately six out of ten patients with head and neck cancer were from the most deprived areas of London, and the greatest proportion of diagnosed patients were white males above 65 years of age.

The most recent detailed analysis of incidence trends of oral cancer in Scotland only examined rates between 1990 and 1999, and reported a general increase in European age-standardised incidence rates of 28% in males and 33% in females over the 10-year study period (Conway et al., 2006). Moreover, Scotland also exhibited the highest incidence rates and the greatest lifetime risk of developing oral cancer in the United Kingdom. However, this study was limited by the fact that it examined rates of oral cavity cancer and oropharyngeal cancer combined, reflecting the thinking at the time that these sites had a common aetiology.

With regard to patient profile, several studies reported an increased risk of head and neck cancer among young males in Scotland (Macfarlane et al., 1987; MacFarlane et al., 1992). Moreover, a strong cohort effect was also reported, with the rates increasing in every birth-cohort succeeding 1910, and the authors suggested that this could be attributed to a surge in the consumption of alcohol and tobacco (MacFarlane et al., 1992). In Scotland, Conway et al. (2007) used cancer registry data to examine trends of oral cancer between 1976 and 2002 by deprivation, and reported a socioeconomic gap in incidence rates that first appeared in the late 1970's and subsequently widened in the 1980's up to the late 1990's. This was particularly true for males from the most deprived areas of Scotland who exhibited an increase of 196% in incidence rates over the study period. Women, on the other hand, exhibited a slightly different pattern with increases in incidence rates being observed in all levels of deprivation, although the greatest increase still occurred in the most deprived areas (Conway et al., 2007). Upon examining the association between risk of developing head and neck cancer and the components of socioeconomic class (area-based measures of socioeconomic status, occupational social class, employment, and education) using data from 103 patients with head and neck cancer and 91 controls in Scotland, Conway et al. (2010) found that individuals residing in the most deprived areas exhibited a higher risk of developing cancer relative to those living in the least deprived areas (OR 4.66, 95% CI 1.79-12.18). Unemployment (OR 2.27, 95% CI 1.21-4.26) and manual occupational classes were also associated with a higher risk of developing cancer, while higher levels of education exhibited a protective effect (OR = 0.17, 95% CI 0.05–0.58). However, the authors clarified that smoking appeared to dominate the risk profile and the statistical significance for all measures of social class were lost upon adjusting for it. Nevertheless, their results did show strong links between certain components of social class and the risk of developing head and neck cancer (Conway et al., 2010).

Therefore, evidence from around the globe as well as within the United Kingdom reports a rapid increase in the rates of oropharyngeal cancer and a stabilisation in the incidence of oral cavity cancer over time, highlighting the differences in the aetiology of the two. Moreover, younger males from lower socioeconomic strata appear to be at the highest risk of developing cancer, irrespective of subsite. However, currently, there are no recent estimates of the trends of oral cancer in Scotland by subsite and various determinants such as age, sex, and socioeconomic status, and research in this area will help inform strategies for prevention and early detection.

## 2.2 Aim, hypotheses and objectives

Therefore, the ***aim*** of this study was to examine the incidence burden and sociodemographic profile of patients with head and neck cancer in Scotland.

The individual ***hypotheses*** were:

**Chapter 2 hypothesis (a):** The trends of head and neck cancer are increasing and are projected to continue to do so.

**Chapter 2 hypothesis (b):** This increase in incidence rates of head and neck cancer will largely be driven by an increase in the rates of oropharyngeal cancer.

**Chapter 2 hypothesis (c):** The patient profile of oropharyngeal cancer will differ from other subsites, particularly in relation to socioeconomic status.

**Chapter 2 hypothesis (d):** In relation to the socioeconomic distribution of head and neck cancer, there will be a clear stratification of “high-risk” areas in the more deprived communities that could be utilised to target early detection initiatives.

The individual ***objectives*** were:

**Chapter 2 objective (a):** To create a cohort of patients with head and neck cancer (and subsites) using data from the Scottish Cancer Registry.

**Chapter 2 objective (b):** To describe and analyse the incidence burden and trends of oral cavity, oropharyngeal and laryngeal cancer in Scotland between 1975 and 2012 by key sociodemographic determinants including age, sex, area-based socioeconomic deprivation, geographic region and year of diagnosis.

**Chapter 2 objective (c):** To compute future projected incidence rates up to 2025 for all head and neck, oral cavity, oropharyngeal, and laryngeal cancer by key sociodemographic determinants including age, sex, area-based socioeconomic deprivation, geographic region and year of diagnosis.

**Chapter 2 objective (d):** To produce a sociodemographic risk profile of all patients with head and neck, oral cavity, oropharyngeal and laryngeal cancer for stratification.

## 2.3 Patients and methods

### 2.3.1 Ethical considerations

An initial data access request was submitted to the Scottish Cancer Registry, part of the Information and Statistics Division (ISD) of the NHS National Services Scotland (NHS NSS). As the data was non-patient identifiable, no application to the Public Benefit and Privacy Panel was necessary and access was approved by the Caldicott Guardian for NHS NSS. A Confidential Data Release Form was signed by the author and Professor David Conway (Appendix 6). The West of Scotland Research Ethics Committee identified this project as “Surveillance” and formally confirmed that NHS ethical approval would not be required (Appendix 3). Additionally, ethical approval was also obtained from the Research Ethics Committee of the Institute of Medicine, Veterinary, and Life Sciences, University of Glasgow (Appendix 4).

### 2.3.2 Data

Data on all patients with head and neck cancer (ICD-10 codes shown in Appendix 1) diagnosed in Scotland between 1975 and 2012 were included in this study. The information requested included cancer subsite (determined using ICD-10 codes), sex of the patient, health board region of the patient's residence, year of diagnosis, age of the patient at the time of diagnosis, and deprivation quintile of the patient's residence.

The three-digit ICD-10 codes were grouped into subsites, as follows: **oropharyngeal cancer** which included base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), and pharynx (C14); **oral cavity cancer** which included inner lip (C00.3-C00.9), other and unspecified parts of the tongue (C02), gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06); and **laryngeal cancer**(C32). Additionally, an all head and neck cancer grouping which included all of the above-mentioned subsites along with hypopharynx, salivary glands, and outer lip was also created. The final sample included only the head and neck cancer, oral cavity cancer, oropharyngeal cancer, and laryngeal cancer groupings, and all ICD codes not included in these groupings were deleted.

Age was grouped into five-year categories and, based on NHS health board boundaries, the geographic regions were grouped into North (Grampian, Highland, Islands), East (Borders, Fife, Forth Valley, Lothian, Tayside), and West (Ayrshire and Arran, Dumfries & Galloway, Greater Glasgow & Clyde, Lanarkshire). Socioeconomic status was measured by the area-based Carstairs Deprivation index grouped into deciles (Carstairs v1991) (ISD Scotland, 2017c). This index is measured at the postcode sector level and takes four variables into account, namely: male unemployment, households with no car, overcrowded households, and the percentage of people in social classes IV and V. It is calculated using census data and is available for the years 1971, 1981, 1991, and 2001.

Annual mid-year population estimates by age, sex, deprivation indices and geographic regions were also collated for the period between 1975 and 2012 (National Records Scotland, 2017).

An additional sub-group analysis was performed on patients that were diagnosed between 2001 and 2012 in order to utilise the more recently developed small area-based socioeconomic index, the Scottish Index of Multiple Deprivation (SIMD 2009) (Donnelly, 2009). This is calculated taking seven domains of deprivation into consideration, namely: income, employment, education, housing, health, crime and geographical access. It is measured at the data-zone level, thus resulting in coverage of smaller populations than the Carstairs index.

### 2.3.3 Statistical analysis

Initial data management included deleting records that were duplicates or had missing data and creating new variables including subsites, age groups, and health board regions. Thereafter, incidence rates per 100,000 population (1975-2012) and projected rates up to 2025 were calculated for all subsites by age, sex, deprivation (measured by Carstairs 1991), health board region, and year of diagnosis. Direct standardisation was undertaken using the European Standard population to account for changes in the age composition of the population and allow easier comparison between areas (Waterhouse, 1976). Adjusted Poisson regression rate-ratios were used to compare the subsites by age, sex, deprivation, health board region, and year of diagnosis.

A sub-group analysis was also performed on patients that were diagnosed between 2001 and 2012. All examined variables remained the same, except for deprivation which was measured by deciles of the Scottish Index of Multiple Deprivation (SIMD) 2009. All statistical analyses were performed using SAS V9.3 on Windows 7 Enterprise.

## 2.4 Results

### 2.4.1 Final sample

Our study comprised of 28,217 individuals diagnosed with head and neck cancer between 1975 and 2012, of which 19,755 (70%) were males and 8462 (30%) were females. The mean age was 63.8 years (standard deviation: ± 12.3 years). The age-standardised incidence rates of cancer per 100,000 individuals and the fully adjusted Poisson regression rate-ratios by sociodemographic characteristics have been shown in Tables 2-1 and 2-2, respectively.

The sub-group analysis using SIMD as an indicator of socioeconomic status consisted of 11,416 patients that were diagnosed with head and neck cancer between 2001 and 2012. Of these, 8009 (70%) were males and 3407 (30%) were females. The age-standardised incidence rates of cancer per 100,000 individuals and the fully adjusted Poisson regression rate-ratios by sociodemographic characteristics for this sub-group have been presented in Tables 2-3 and 2-4, respectively.

**Table 2-1: EASR per 100,000 person-years by age, sex, geographic region, deprivation (Carstairs 1991), and year of diagnosis (1975-2012).**

| | HNC | | OPC | | OCC | | Larynx | |
|---|---|---|---|---|---|---|---|---|
| | N | Rate | N | Rate | N | Rate | N | Rate |
| **Age** | | | | | | | | |
| 0-25 | 135 | 0.28 | 7 | 0.01 | 35 | 0.07 | 5 | 0.01 |
| 26-30 | 87 | 0.94 | 2 | 0.02 | 29 | 0.31 | 5 | 0.05 |
| 31-35 | 145 | 1.54 | 9 | 0.10 | 44 | 0.47 | 16 | 0.17 |
| 36-40 | 294 | 3.46 | 36 | 0.42 | 79 | 0.93 | 67 | 0.79 |
| 41-45 | 537 | 6.39 | 80 | 0.96 | 177 | 2.11 | 150 | 1.79 |
| 46-50 | 1185 | 15.13 | 179 | 2.32 | 408 | 5.27 | 402 | 5.19 |
| 51-55 | 1817 | 22.80 | 261 | 3.38 | 603 | 7.79 | 674 | 8.67 |
| 56-60 | 2484 | 32.17 | 349 | 4.72 | 756 | 10.19 | 1001 | 13.41 |
| 61-65 | 2648 | 38.64 | 348 | 5.37 | 803 | 12.29 | 1091 | 16.62 |
| 66-70 | 2736 | 41.80 | 328 | 5.26 | 866 | 13.84 | 1119 | 17.75 |
| 71-75 | 2334 | 45.52 | 260 | 5.27 | 747 | 15.11 | 935 | 18.79 |
| 76-80 | 1656 | 44.71 | 175 | 4.81 | 609 | 16.66 | 572 | 15.65 |
| 81-85+ | 1015 | 30.61 | 109 | 3.30 | 421 | 12.75 | 293 | 8.88 |
| **Sex** | | | | | | | | |
| Male | 19755 | 20.67 | 3352 | 3.60 | 5851 | 6.28 | 7744 | 8.29 |
| Female | 8462 | 8.41 | 1272 | 1.27 | 3467 | 3.46 | 2009 | 2.01 |
| **Region** | | | | | | | | |
| North | 9768 | 13.55 | 1547 | 2.18 | 3201 | 4.50 | 3375 | 4.74 |
| East | 4431 | 14.56 | 786 | 2.59 | 1467 | 4.84 | 1286 | 4.24 |
| West | 14018 | 14.95 | 2291 | 2.50 | 4650 | 5.06 | 5092 | 5.53 |
| **Carstairs** | | | | | | | | |
| 1 | 4254 | 21.53 | 682 | 3.51 | 1354 | 6.95 | 1644 | 8.42 |
| 2 | 3499 | 17.40 | 534 | 2.77 | 1122 | 5.80 | 1337 | 6.89 |
| 3 | 3059 | 15.44 | 490 | 2.53 | 983 | 5.07 | 1107 | 5.69 |
| 4 | 3050 | 15.56 | 545 | 2.83 | 948 | 4.92 | 1090 | 5.65 |
| 5 | 2676 | 13.63 | 431 | 2.23 | 893 | 4.61 | 901 | 4.64 |
| 6 | 2717 | 14.00 | 426 | 2.22 | 939 | 4.90 | 927 | 4.83 |
| 7 | 2483 | 12.68 | 426 | 2.20 | 855 | 4.41 | 766 | 3.95 |
| 8 | 2453 | 12.62 | 402 | 2.09 | 848 | 4.41 | 785 | 4.08 |
| 9 | 2154 | 11.06 | 364 | 1.88 | 736 | 3.81 | 656 | 3.39 |
| 10 | 1872 | 9.63 | 324 | 1.68 | 640 | 3.31 | 540 | 2.79 |

| Year | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1975 | 502 | 12.57 | 69 | 1.75 | 140 | 3.73 | 180 | 4.50 |
| 1976 | 439 | 10.95 | 55 | 1.42 | 135 | 3.52 | 153 | 3.75 |
| 1977 | 521 | 12.66 | 63 | 1.60 | 155 | 3.95 | 173 | 4.25 |
| 1978 | 485 | 11.70 | 60 | 1.51 | 130 | 3.32 | 187 | 4.55 |
| 1979 | 513 | 12.57 | 55 | 1.40 | 148 | 3.79 | 176 | 4.29 |
| 1980 | 531 | 12.99 | 55 | 1.42 | 152 | 3.81 | 190 | 4.65 |
| 1981 | 594 | 14.30 | 49 | 1.20 | 184 | 4.63 | 220 | 5.32 |
| 1982 | 585 | 13.94 | 54 | 1.32 | 215 | 5.28 | 203 | 4.95 |
| 1983 | 634 | 14.92 | 77 | 1.90 | 188 | 4.62 | 249 | 6.04 |
| 1984 | 589 | 14.03 | 51 | 1.22 | 200 | 4.88 | 231 | 5.60 |
| 1985 | 643 | 15.03 | 74 | 1.78 | 215 | 5.22 | 4.87 | 5.89 |
| 1986 | 621 | 14.65 | 61 | 1.46 | 187 | 4.50 | 246 | 5.90 |
| 1987 | 608 | 14.17 | 62 | 1.46 | 226 | 5.44 | 214 | 5.08 |
| 1988 | 651 | 15.00 | 73 | 1.73 | 224 | 5.32 | 242 | 5.73 |
| 1989 | 674 | 15.29 | 88 | 2.08 | 219 | 5.18 | 252 | 5.94 |
| 1990 | 718 | 16.30 | 86 | 2.03 | 242 | 5.70 | 278 | 6.59 |
| 1991 | 720 | 16.37 | 97 | 2.29 | 244 | 5.74 | 274 | 6.47 |
| 1992 | 710 | 16.03 | 92 | 2.14 | 236 | 5.55 | 302 | 7.06 |
| 1993 | 719 | 16.22 | 91 | 2.13 | 234 | 5.43 | 288 | 6.73 |
| 1994 | 739 | 16.43 | 91 | 2.09 | 259 | 5.98 | 282 | 6.49 |
| 1995 | 750 | 16.61 | 104 | 2.40 | 267 | 6.19 | 253 | 5.79 |
| 1996 | 864 | 18.72 | 124 | 2.83 | 271 | 5.49 | 340 | 7.77 |
| 1997 | 768 | 16.76 | 138 | 3.11 | 245 | 5.55 | 255 | 5.81 |
| 1998 | 826 | 17.94 | 103 | 2.33 | 296 | 6.64 | 279 | 6.37 |
| 1999 | 865 | 18.61 | 138 | 3.09 | 298 | 6.71 | 313 | 7.09 |
| 2000 | 804 | 17.11 | 133 | 2.96 | 267 | 5.93 | 305 | 6.85 |
| 2001 | 880 | 19.81 | 152 | 3.35 | 289 | 6.51 | 314 | 7.13 |
| 2002 | 858 | 19.12 | 150 | 3.28 | 304 | 6.80 | 286 | 6.41 |
| 2003 | 893 | 19.65 | 162 | 3.51 | 324 | 7.08 | 289 | 6.46 |
| 2004 | 906 | 19.80 | 182 | 3.95 | 306 | 6.68 | 304 | 6.71 |
| 2005 | 883 | 18.98 | 182 | 3.79 | 315 | 6.79 | 276 | 6.06 |
| 2006 | 931 | 19.86 | 191 | 3.98 | 304 | 6.50 | 310 | 6.69 |
| 2007 | 961 | 20.20 | 202 | 4.17 | 341 | 7.17 | 291 | 6.17 |
| 2008 | 910 | 18.79 | 203 | 4.13 | 324 | 6.70 | 276 | 5.77 |
| 2009 | 1029 | 20.97 | 266 | 5.25 | 339 | 6.97 | 281 | 5.83 |
| 2010 | 1025 | 20.71 | 241 | 4.73 | 344 | 7.00 | 306 | 6.29 |
| 2011 | 1016 | 20.32 | 253 | 4.93 | 328 | 6.56 | 288 | 5.86 |
| 2012 | 1124 | 22.04 | 320 | 6.17 | 357 | 7.04 | 270 | 5.35 |

EASR: European age standardised rates, HNC: Head & neck cancer; OPC: Oropharyngeal cancer; OCC: Oral cavity cancer; N: Number of events

**Table 2-2: Adjusted Poisson regression rate-ratios for subsites by age, sex, geographic region, deprivation (Carstairs 1991), and year of diagnosis (1975-2012)**

| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** |
| **Age** | | | | | | | | | | | | |
| 0-25 | 0.02 | 0.02-0.02 | **<.001** | 0.01 | 0.00-0.01 | **<.001** | 0.02 | 0.01-0.02 | **<.001** | 0.00 | 0.00-0.00 | **<.001** |
| 26-30 | 0.07 | 0.05-0.08 | **<.001** | 0.02 | 0.01-0.03 | **<.001** | 0.07 | 0.05-0.09 | **<.001** | 0.02 | 0.01-0.03 | **<.001** |
| 31-35 | 0.10 | 0.09-0.12 | **<.001** | 0.04 | 0.03-0.07 | **<.001** | 0.10 | 0.08-0.13 | **<.001** | 0.04 | 0.02-0.06 | **<.001** |
| 36-40 | 0.24 | 0.21-0.26 | **<.001** | 0.17 | 0.13-0.22 | **<.001** | 0.20 | 0.17-0.24 | **<.001** | 0.17 | 0.13-0.21 | **<.001** |
| 41-45 | 0.46 | 0.43-0.50 | **<.001** | 0.45 | 0.38-0.53 | **<.001** | 0.45 | 0.39-0.51 | **<.001** | 0.37 | 0.32-0.44 | **<.001** |
| 46-50 (ref.) | - | | | - | | | - | | | - | | |
| 51-55 | 1.62 | 1.53-1.71 | **<.001** | 1.62 | 1.44-1.83 | **<.001** | 1.58 | 1.43-1.75 | **<.001** | 1.82 | 1.64-2.02 | **<.001** |
| 56-60 | 2.38 | 2.25-2.51 | **<.001** | 2.21 | 1.97-2.49 | **<.001** | 2.31 | 2.10-2.54 | **<.001** | 3.02 | 2.74-3.33 | **<.001** |
| 61-65 | 2.79 | 2.65-2.95 | **<.001** | 2.34 | 2.08-2.63 | **<.001** | 2.73 | 2.49-2.99 | **<.001** | 3.73 | 3.39-4.10 | **<.001** |
| 66-70 | 3.06 | 2.90-3.23 | **<.001** | 2.19 | 1.93-2.47 | **<.001** | 3.04 | 2.77-3.34 | **<.001** | 4.29 | 3.90-4.72 | **<.001** |
| 71-75 | 3.39 | 3.21-3.58 | **<.001** | 2.03 | 1.78-2.32 | **<.001** | 3.30 | 3.00-3.64 | **<.001** | 4.74 | 4.30-5.23 | **<.001** |
| 76-80 | 3.44 | 3.24-3.65 | **<.001** | 1.97 | 1.71-2.28 | **<.001** | 3.54 | 3.20-3.91 | **<.001** | 4.32 | 3.89-4.80 | **<.001** |
| 81-85+ | 2.36 | 2.20-2.52 | **<.001** | 1.08 | 0.90-1.29 | 0.398 | 2.66 | 2.39-2.97 | **<.001** | 2.56 | 2.26-2.90 | **<.001** |
| **Sex** | | | | | | | | | | | | |
| Male | 2.72 | 2.66-2.79 | **<.001** | 3.10 | 2.90-3.30 | **<.001** | 2.11 | 2.02-2.20 | **<.001** | 4.77 | 4.54-5.01 | **<.001** |
| Female (ref.) | - | | | - | | | - | | | - | | |

| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | **p** | **RR** | **95% CI** | **p** | **RR** | **95% CI** | **p** | **RR** | **95% CI** | **p** |
| **Region** | | | | | | | | | | | | |
| North | - | | | - | | | - | | | - | | |
| East | 0.85 | 0.82-0.88 | **<.001** | 0.81 | 0.74-0.88 | **<.001** | 0.88 | 0.83-0.94 | **<.001** | 1.01 | 0.95-1.08 | 0.738 |
| West | 0.81 | 0.78-0.84 | **<.001** | 0.85 | 0.78-0.92 | **<.001** | 0.89 | 0.84-0.95 | **<.001** | 0.98 | 0.92-1.05 | 0.527 |
| **Carstairs 1991** | | | | | | | | | | | | |
| 1 | 2.59 | 2.45-2.74 | **<.001** | 2.49 | 2.18-2.86 | **<.001** | 2.40 | 2.18-2.65 | **<.001** | 3.34 | 3.02-3.69 | **<.001** |
| 2 | 1.83 | 1.72-1.93 | **<.001** | 1.83 | 1.59-2.11 | **<.001** | 1.86 | 1.69-2.06 | **<.001** | 2.50 | 2.26-2.77 | **<.001** |
| 3 | 1.66 | 1.57-1.76 | **<.001** | 1.67 | 1.45-1.92 | **<.001** | 1.62 | 1.47-1.79 | **<.001** | 2.07 | 1.87-2.30 | **<.001** |
| 4 | 1.66 | 1.57-1.76 | **<.001** | 1.85 | 1.61-2.12 | **<.001** | 1.56 | 1.41-1.73 | **<.001** | 2.06 | 1.86-2.28 | **<.001** |
| 5 | 1.47 | 1.38-1.56 | **<.001** | 1.44 | 1.25-1.66 | **<.001** | 1.47 | 1.32-1.62 | **<.001** | 1.71 | 1.54-1.91 | **<.001** |
| 6 | 1.42 | 1.34-1.51 | **<.001** | 1.35 | 1.17-1.56 | **<.001** | 1.47 | 1.33-1.63 | **<.001** | 1.70 | 1.53-1.89 | **<.001** |
| 7 | 1.30 | 1.22-1.38 | **<.001** | 1.32 | 1.15-1.53 | **<.001** | 1.33 | 1.20-1.47 | **<.001** | 1.39 | 1.24-1.55 | **<.001** |
| 8 | 1.26 | 1.19-1.34 | **<.001** | 1.24 | 1.07-1.43 | **0.004** | 1.30 | 1.17-1.44 | **<.001** | 1.40 | 1.26-1.56 | **<.001** |
| 9 | 1.12 | 1.05-1.19 | **<.001** | 1.13 | 0.97-1.31 | 0.107 | 1.14 | 1.02-1.26 | 0.019 | 1.19 | 1.06-1.33 | **0.003** |
| 10 (ref.) | - | | | - | | | - | | | - | | |

| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | **p** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | **p** |
| **Year** | | | | | | | | | | | | |
| 1975 (ref.) | - | | | - | | | - | | | - | | |
| 1976 | 0.88 | 0.77-1.00 | **0.049** | 0.79 | 0.56-1.13 | 0.204 | 0.96 | 0.76-1/22 | 0.732 | 0.84 | 0.68-1.04 | 0.118 |
| 1977 | 1.02 | 0.91-1.16 | 0.698 | 0.90 | 0.64-1.27 | 0.566 | 1.10 | 0.87-1.38 | 0.426 | 0.95 | 0.77-1.17 | 0.645 |
| 1978 | 0.94 | 0.83-1.07 | 0.355 | 0.86 | 0.61-1.22 | 0.403 | 0.92 | 0.72-1.16 | 0.475 | 1.00 | 0.82-1.23 | 0.972 |
| 1979 | 1.01 | 0.89-1.14 | 0.872 | 0.79 | 0.55-1.12 | 0.191 | 1.04 | 0.83-1.31 | 0.736 | 0.96 | 0.78-1.18 | 0.699 |
| 1980 | 1.04 | 0.92-1.18 | 0.507 | 0.79 | 0.55-1.12 | 0.183 | 1.06 | 0.84-1.34 | 0.606 | 1.04 | 0.84-1.27 | 0.736 |
| 1981 | 1.15 | 1.02-1.29 | **0.024** | 0.70 | 0.48-1.00 | 0.055 | 1.28 | 1.03-1.60 | **0.027** | 1.19 | 0.97-1.44 | 0.091 |
| 1982 | 1.11 | 0.99-1.25 | 0.080 | 0.77 | 0.54-1.09 | 0.144 | 1.49 | 1.20-1.84 | **<.001** | 1.09 | 0.89-1.33 | 0.427 |
| 1983 | 1.18 | 1.05-1.33 | **0.006** | 1.09 | 0.79-1.51 | 0.607 | 1.30 | 1.04-1.61 | **0.020** | 1.31 | 1.08-1.58 | **0.006** |
| 1984 | 1.13 | 1.00-1.27 | **0.052** | 0.72 | 0.50-1.03 | 0.073 | 1.37 | 1.10-1.69 | **0.005** | 1.24 | 1.02-1.50 | **0.035** |
| 1985 | 1.19 | 1.06-1.34 | **0.003** | 1.04 | 0.75-1.44 | 0.825 | 1.45 | 1.18-1.80 | **<.001** | 1.29 | 1.06-1.56 | **0.010** |
| 1986 | 1.17 | 1.04-1.32 | **0.007** | 0.85 | 0.60-1.20 | 0.363 | 1.27 | 1.02-1.58 | **0.034** | 1.29 | 1.06-1.56 | **0.010** |
| 1987 | 1.14 | 1.01-1.28 | **0.034** | 0.86 | 0.61-1.21 | 0.386 | 1.52 | 1.23-1.88 | **<.001** | 1.11 | 0.91-1.36 | 0.293 |
| 1988 | 1.20 | 1.07-1.35 | **0.002** | 1.01 | 0.73-1.40 | 0.950 | 1.50 | 1.21-1.85 | **<.001** | 1.25 | 1.03-1.52 | **0.024** |
| 1989 | 1.22 | 1.08-1.37 | **<.001** | 1.21 | 0.88-1.66 | 0.233 | 1.45 | 1.17-1.79 | **<.001** | 1.29 | 1.07-1.56 | **0.009** |
| 1990 | 1.28 | 1.14-1.44 | **<.001** | 1.18 | 0.86-1.62 | 0.306 | 1.60 | 1.30-1.96 | **<.001** | 1.42 | 1.18-1.71 | **<.001** |
| 1991 | 1.29 | 1.15-1.44 | **<.001** | 1.33 | 0.97-1.81 | 0.072 | 1.61 | 1.30-1.98 | **<.001** | 1.40 | 1.16-1.69 | **<.001** |
| 1992 | 1.26 | 1.12-1.41 | **<.001** | 1.25 | 0.92-1.71 | 0.160 | 1.55 | 1.25-1.91 | **<.001** | 1.51 | 1.25-1.81 | **<.001** |
| 1993 | 1.26 | 1.13-1.42 | **<.001** | 1.23 | 0.90-1.68 | 0.198 | 1.52 | 1.23-1.88 | **<.001** | 1.44 | 1.19-1.73 | **<.001** |
| 1994 | 1.29 | 1.16-1.45 | **<.001** | 1.22 | 0.89-1.67 | 0.212 | 1.67 | 1.36-2.05 | **<.001** | 1.39 | 1.15-1.67 | **<.001** |
| 1995 | 1.29 | 1.16-1.45 | **<.001** | 1.38 | 1.02-1.88 | **0.036** | 1.72 | 1.40-2.10 | **<.001** | 1.23 | 1.01-1.48 | **0.037** |
| 1996 | 1.46 | 1.30-1.63 | **<.001** | 1.63 | 1.22-2.19 | **0.001** | 1.71 | 1.40-2.10 | **<.001** | 1.65 | 1.37-1.97 | **<.001** |
| 1997 | 1.32 | 1.18-1.48 | **<.001** | 1.80 | 1.35-2.41 | **<.001** | 1.55 | 1.26-1.90 | **<.001** | 1.25 | 1.03-1.50 | **0.026** |
| 1998 | 1.39 | 1.25-1.56 | **<.001** | 1.34 | 0.99-1.82 | **0.057** | 1.85 | 1.51-2.26 | **<.001** | 1.35 | 1.11-1.62 | **0.002** |
| 1999 | 1.44 | 1.29-1.60 | **<.001** | 1.77 | 1.33-2.37 | **<.001** | 1.86 | 1.52-2.27 | **<.001** | 1.51 | 1.25-1.80 | **<.001** |
| 2000 | 1.32 | 1.18-1.48 | **<.001** | 1.70 | 1.27-2.27 | **<.001** | 1.65 | 1.34-2.02 | **<.001** | 1.44 | 1.19-1.72 | **<.001** |

| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | **p** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | **p** |
| **Year** | | | | | | | | | | | | |
| 2001 | 1.43 | 1.28-1.60 | **<.001** | 1.93 | 1.45-2.56 | **<.001** | 1.70 | 1.39-2.09 | **<.001** | 1.47 | 1.23-1.77 | **<.001** |
| 2002 | 1.37 | 1.23-1.53 | **<.001** | 1.85 | 1.39-2.46 | **<.001** | 1.79 | 1.46-2.19 | **<.001** | 1.31 | 1.09-1.58 | **0.005** |
| 2003 | 1.42 | 1.27-1.58 | **<.001** | 1.99 | 1.50-2.64 | **<.001** | 1.88 | 1.54-2.29 | **<.001** | 1.34 | 1.12-1.62 | **0.002** |
| 2004 | 1.42 | 1.27-1.58 | **<.001** | 2.22 | 1.68-2.93 | **<.001** | 1.77 | 1.44-2.16 | **<.001** | 1.35 | 1.12-1.63 | **0.001** |
| 2005 | 1.36 | 1.22-1.51 | **<.001** | 2.19 | 1.66-2.89 | **<.001** | 1.83 | 1.50-2.24 | **<.001** | 1.22 | 1.01-1.47 | **0.040** |
| 2006 | 1.39 | 1.25-1.55 | **<.001** | 2.27 | 1.72-2.99 | **<.001** | 1.70 | 1.39-2.07 | **<.001** | 1.37 | 1.14-1.65 | **<.001** |
| 2007 | 1.42 | 1.28-1.58 | **<.001** | 2.38 | 1.81-3.13 | **<.001** | 1.88 | 1.54-2.29 | **<.001** | 1.26 | 1.04-1.52 | **0.016** |
| 2008 | 1.32 | 1.18-1.47 | **<.001** | 2.31 | 1.76-3.04 | **<.001** | 1.75 | 1.43-2.14 | **<.001** | 1.19 | 0.98-1.43 | 0.076 |
| 2009 | 1.46 | 1.31-1.63 | **<.001** | 3.02 | 2.32-3.94 | **<.001** | 1.81 | 1.48-2.20 | **<.001** | 1.20 | 0.99-1.45 | **0.057** |
| 2010 | 1.46 | 1.32-1.63 | **<.001** | 2.72 | 2.08-3.56 | **<.001** | 1.82 | 1.49-2.22 | **<.001** | 1.28 | 1.07-1.54 | **0.008** |
| 2011 | 1.44 | 1.29-1.60 | **<.001** | 2.81 | 2.15-3.66 | **<.001** | 1.75 | 1.43-2.13 | **<.001** | 1.18 | 0.98-1.43 | 0.077 |
| 2012 | 1.53 | 1.37-1.70 | **<.001** | 3.45 | 2.66-4.48 | **<.001** | 1.86 | 1.53-2.26 | **<.001** | 1.12 | 0.92-1.35 | 0.257 |

RR: Rate-ratio; p: p value; HNC: Head & neck cancer; OPC: Oropharyngeal cancer; OCC: Oral cavity cancer.

**Table 2-3: EASR per 100,000 person-years by age, sex, geographic region, deprivation (SIMD 2009), and year of diagnosis (2001-2012)**

| | HNC | | OPC | | OCC | | Larynx | |
|---|---|---|---|---|---|---|---|---|
| | N | Rate | N | Rate | N | Rate | N | Rate |
| **Age** | | | | | | | | |
| 0-25 | 70 | 0.36 | 5 | 0.03 | 24 | 0.13 | 1 | 0.01 |
| 26-30 | 45 | 1.17 | 5 | 0.13 | 19 | 0.49 | 5 | 0.13 |
| 31-35 | 68 | 1.66 | 10 | 0.24 | 29 | 0.71 | 7 | 0.17 |
| 36-40 | 172 | 3.75 | 39 | 0.85 | 60 | 1.31 | 32 | 0.70 |
| 41-45 | 379 | 7.96 | 119 | 2.50 | 131 | 2.75 | 71 | 1.49 |
| 46-50 | 698 | 15.57 | 243 | 5.42 | 235 | 5.24 | 150 | 3.35 |
| 51-55 | 1294 | 31.10 | 406 | 9.76 | 396 | 9.52 | 326 | 7.83 |
| 56-60 | 1756 | 45.52 | 463 | 12.00 | 571 | 14.80 | 526 | 13.63 |
| 61-65 | 1933 | 55.99 | 444 | 12.86 | 635 | 18.39 | 611 | 17.70 |
| 66-70 | 1674 | 57.47 | 312 | 10.71 | 559 | 19.19 | 616 | 21.15 |
| 71-75 | 1438 | 57.92 | 213 | 8.58 | 478 | 19.25 | 538 | 21.67 |
| 76-80 | 1019 | 52.60 | 161 | 8.31 | 355 | 18.32 | 367 | 18.94 |
| 81-85+ | 598 | 46.20 | 61 | 4.71 | 249 | 19.24 | 173 | 13.37 |
| **Sex** | | | | | | | | |
| Male | 8009 | 26.76 | 1866 | 6.23 | 2330 | 7.78 | 2761 | 9.22 |
| Female | 3407 | 10.62 | 638 | 1.99 | 1545 | 4.82 | 730 | 2.28 |
| **Region** | | | | | | | | |
| North | 1790 | 16.07 | 461 | 4.14 | 601 | 5.40 | 472 | 4.24 |
| East | 4033 | 17.15 | 836 | 3.56 | 1394 | 5.93 | 1231 | 5.24 |
| West | 5593 | 20.44 | 1207 | 4.41 | 1880 | 6.87 | 1788 | 6.54 |

| | HNC | | OPC | | OCC | | Larynx | |
|---|---|---|---|---|---|---|---|---|
| | N | Rate | N | Rate | N | Rate | N | Rate |
| **SIMD** | | | | | | | | |
| 1 | 1897 | 29.90 | 392 | 6.18 | 606 | 9.55 | 673 | 10.61 |
| 2 | 1596 | 25.51 | 352 | 5.63 | 500 | 7.99 | 543 | 8.68 |
| 3 | 1460 | 23.32 | 299 | 4.77 | 494 | 7.89 | 472 | 7.54 |
| 4 | 1230 | 19.66 | 243 | 3.88 | 411 | 6.57 | 407 | 6.50 |
| 5 | 1113 | 17.91 | 237 | 3.81 | 395 | 6.36 | 317 | 5.10 |
| 6 | 1035 | 16.76 | 239 | 3.87 | 363 | 5.88 | 295 | 4.78 |
| 7 | 904 | 14.64 | 227 | 3.68 | 318 | 5.15 | 244 | 3.95 |
| 8 | 853 | 13.97 | 215 | 3.52 | 302 | 4.95 | 214 | 3.50 |
| 9 | 705 | 11.55 | 169 | 2.77 | 245 | 4.01 | 182 | 2.98 |
| 10 | 623 | 10.19 | 131 | 2.14 | 241 | 3.94 | 144 | 2.35 |
| **Year** | | | | | | | | |
| 2001 | 880 | 19.81 | 152 | 3.35 | 289 | 6.51 | 314 | 7.13 |
| 2002 | 858 | 19.12 | 150 | 3.28 | 304 | 6.80 | 286 | 6.41 |
| 2003 | 893 | 19.65 | 162 | 3.51 | 324 | 7.08 | 289 | 6.46 |
| 2004 | 906 | 19.80 | 182 | 3.95 | 306 | 6.68 | 304 | 6.71 |
| 2005 | 883 | 18.98 | 182 | 3.79 | 315 | 6.79 | 276 | 6.06 |
| 2006 | 931 | 19.86 | 191 | 3.98 | 304 | 6.50 | 310 | 6.69 |
| 2007 | 961 | 20.20 | 202 | 4.17 | 341 | 7.17 | 291 | 6.17 |
| 2008 | 910 | 18.79 | 203 | 4.13 | 324 | 6.70 | 276 | 5.77 |
| 2009 | 1029 | 20.97 | 266 | 5.25 | 339 | 6.97 | 281 | 5.83 |
| 2010 | 1025 | 20.71 | 241 | 4.73 | 344 | 7.00 | 306 | 6.29 |
| 2011 | 1016 | 20.32 | 253 | 4.93 | 328 | 6.56 | 288 | 5.86 |
| 2012 | 1124 | 22.04 | 320 | 6.17 | 357 | 7.04 | 270 | 5.35 |

EASR: European age standardised rates, HNC: Head & neck cancer; OPC: Oropharyngeal cancer; OCC: Oral cavity cancer; N: Number of events.

**Table 2-4: Subgroup analysis- Adjusted Poisson regression rate-ratios for subsites by age, sex, geographic region, deprivation (SIMD 2009), and year of diagnosis (2001-2012)**

| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** |
| **Age** | | | | | | | | | | | | |
| 0-25 | 0.02 | 0.02-0.03 | **<0.001** | 0 | 0.00-0.01 | **<0.001** | 0.02 | 0.01-0.03 | **<0.001** | 0 | 0.00-0.01 | **<0.001** |
| 26-30 | 0.07 | 0.05-0.10 | **<0.001** | 0.02 | 0.01-0.06 | **<0.001** | 0.09 | 0.06-0.14 | **<0.001** | 0.04 | 0.01-0.09 | **<0.001** |
| 31-35 | 0.10 | 0.08-0.13 | **<0.001** | 0.05 | 0.02-0.08 | **<0.001** | 0.13 | 0.09-0.19 | **<0.001** | 0.05 | 0.02-0.10 | **<0.001** |
| 36-40 | 0.24 | 0.20-0.28 | **<0.001** | 0.16 | 0.11-0.22 | **<0.001** | 0.25 | 0.19-0.33 | **<0.001** | 0.20 | 0.14-0.30 | **<0.001** |
| 41-45 | 0.51 | 0.45-0.58 | **<0.001** | 0.47 | 0.37-0.58 | **<0.001** | 0.52 | 0.42-0.65 | **<0.001** | 0.44 | 0.33-0.59 | **<0.001** |
| 46-50 (ref) | - | | | - | | | - | | | | | |
| 51-55 | 2.00 | 1.83-2.20 | **<0.001** | 1.81 | 1.55-2.12 | **<0.001** | 1.82 | 1.55-2.14 | **<0.001** | 2.34 | 1.93-2.84 | **<0.001** |
| 56-60 | 2.94 | 2.69-3.21 | **<0.001** | 2.23 | 1.91-2.61 | **<0.001** | 2.83 | 2.43-3.30 | **<0.001** | 4.08 | 3.40-4.89 | **<0.001** |
| 61-65 | 3.6 | 3.30-3.92 | **<0.001** | 2.37 | 2.03-2.77 | **<0.001** | 3.51 | 3.02-4.07 | **<0.001** | 5.31 | 4.44-6.34 | **<0.001** |
| 66-70 | 3.71 | 3.40-4.06 | **<0.001** | 2.01 | 1.70-2.38 | **<0.001** | 3.65 | 3.14-4.25 | **<0.001** | 6.35 | 5.31-7.59 | **<0.001** |
| 71-75 | 3.81 | 3.48-4.18 | **<0.001** | 1.65 | 1.37-1.98 | **<0.001** | 3.70 | 3.17-4.33 | **<0.001** | 6.69 | 5.58-8.01 | **<0.001** |
| 76-80 | 3.59 | 3.26-3.96 | **<0.001** | 1.66 | 1.36-2.03 | **<0.001** | 3.60 | 3.06-4.25 | **<0.001** | 6.17 | 5.10-7.46 | **<0.001** |
| 81-85+ | 3.35 | 3.00-3.73 | **<0.001** | 1.00 | 0.76-1.33 | 0.977 | 3.92 | 3.28-4.68 | **<0.001** | 4.73 | 3.80-5.89 | **<0.001** |
| **Sex** | | | | | | | | | | | | |
| Male | 2.81 | 2.70-2.92 | **<0.001** | 3.31 | 3.02-3.62 | **<0.001** | 1.82 | 1.71-1.94 | **<0.001** | 4.60 | 4.24-5.00 | **<0.001** |
| Female(ref) | - | | | | | | | | | | | |
| **Region** | | | | | | | | | | | | |
| North (ref) | - | | | - | | | - | | | - | | |
| East | 1.06 | 1.00-1.12 | **0.05** | 0.86 | 0.77-0.97 | **0.012** | 1.10 | 1.00-1.21 | **0.057** | 1.20 | 1.08-1.33 | **<0.001** |
| West | 1.07 | 1.02-1.14 | **0.011** | 0.93 | 0.83-1.04 | 0.185 | 1.11 | 1.01-1.22 | **0.028** | 1.21 | 1.09-1.34 | **<0.001** |

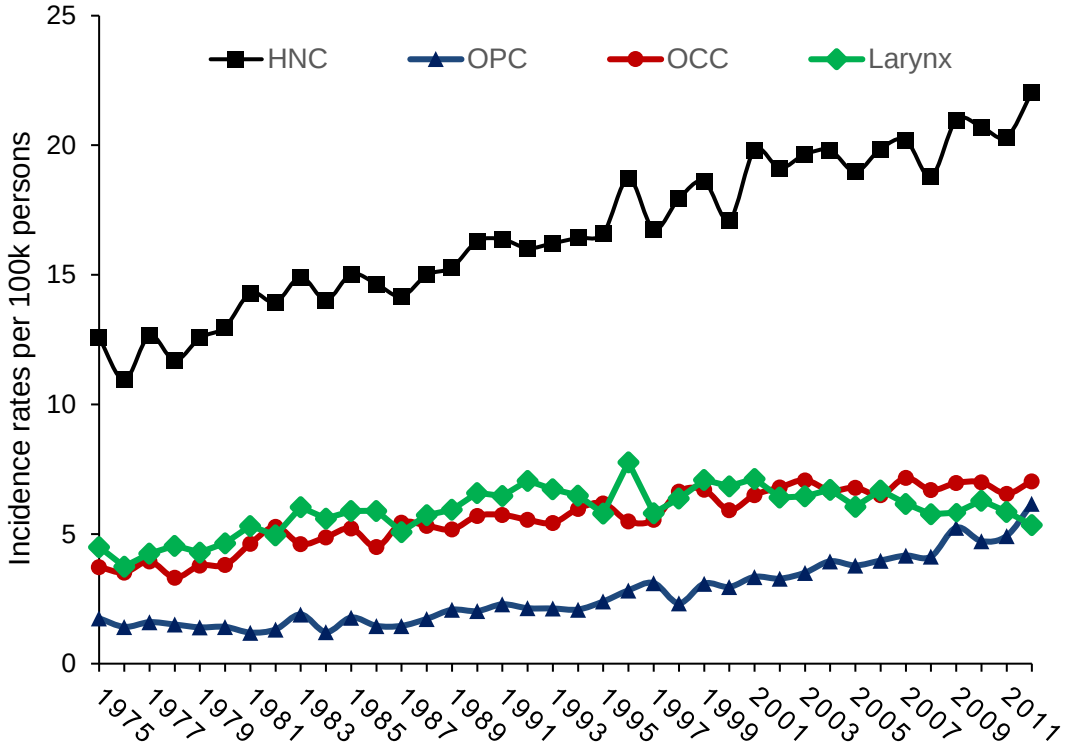
| | HNC | | | OPC | | | OCC | | | Larynx | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | ***p*** | **RR** | **95%** | ***p*** | **RR** | **95% CI** | ***p*** | **RR** | **95% CI** | ***p*** |
| **SIMD** | | | | | | | | | | | | |
| 1 | 3.3 | 3.01-3.62 | <0.001 | 3.33 | 2.72-4.07 | <0.001 | 2.69 | 2.31-3.13 | <0.001 | 4.98 | 4.15-5.97 | <0.001 |
| 2 | 2.6 | 2.37-2.85 | <0.001 | 2.83 | 2.31-3.46 | <0.001 | 2.08 | 1.78-2.43 | <0.001 | 3.75 | 3.11-4.51 | <0.001 |
| 3 | 2.31 | 2.10-2.54 | <0.001 | 2.33 | 1.89-2.86 | <0.001 | 2.00 | 1.71-2.33 | <0.001 | 3.19 | 2.64-3.84 | <0.001 |
| 4 | 1.89 | 1.72-2.08 | <0.001 | 1.82 | 1.47-2.25 | <0.001 | 1.62 | 1.38-1.90 | <0.001 | 2.67 | 2.21-3.23 | <0.001 |
| 5 | 1.73 | 1.57-1.91 | <0.001 | 1.74 | 1.41-2.16 | <0.001 | 1.58 | 1.35-1.86 | <0.001 | 2.13 | 1.75-2.60 | <0.001 |
| 6 | 1.58 | 1.43-1.75 | <0.001 | 1.72 | 1.39-2.13 | <0.001 | 1.44 | 1.22-1.69 | <0.001 | 1.96 | 1.60-2.39 | <0.001 |
| 7 | 1.36 | 1.23-1.51 | <0.001 | 1.61 | 1.30-2.00 | <0.001 | 1.25 | 1.05-1.47 | 0.01 | 1.60 | 1.30-1.96 | <0.001 |
| 8 | 1.35 | 1.22-1.49 | <0.001 | 1.60 | 1.29-1.99 | <0.001 | 1.24 | 1.04-1.46 | 0.014 | 1.47 | 1.19-1.81 | <0.001 |
| 9 | 1.12 | 1.00-1.25 | 0.042 | 1.25 | 1.00-1.57 | 0.053 | 1.01 | 0.84-1.21 | 0.923 | 1.26 | 1.01-1.56 | 0.041 |
| 10 (ref.) | - | | | - | | | - | | | - | | |
| **Year** | | | | | | | | | | | | |
| 2001 (ref.) | - | | | - | | | - | | | - | | |
| 2002 | 0.97 | 0.88-1.07 | 0.52 | 0.98 | 0.78-1.23 | 0.864 | 1.05 | 0.89-1.23 | 0.586 | 0.91 | 0.77-1.07 | 0.235 |
| 2003 | 1.00 | 0.91-1.10 | 0.977 | 1.05 | 0.84-1.31 | 0.667 | 1.11 | 0.94-1.30 | 0.216 | 0.91 | 0.78-1.07 | 0.252 |
| 2004 | 1.01 | 0.92-1.10 | 0.906 | 1.17 | 0.94-1.45 | 0.163 | 1.03 | 0.88-1.21 | 0.689 | 0.95 | 0.81-1.11 | 0.516 |
| 2005 | 0.97 | 0.88-1.06 | 0.516 | 1.15 | 0.93-1.43 | 0.198 | 1.05 | 0.90-1.23 | 0.53 | 0.85 | 0.73-1.00 | **0.054** |
| 2006 | 1.01 | 0.92-1.11 | 0.798 | 1.20 | 0.97-1.48 | 0.101 | 1.01 | 0.86-1.18 | 0.944 | 0.95 | 0.81-1.11 | 0.516 |
| 2007 | 1.03 | 0.91-1.13 | 0.478 | 1.25 | 1.01-1.54 | **0.039** | 1.12 | 0.95-1.31 | 0.169 | 0.88 | 0.75-1.04 | 0.126 |
| 2008 | 0.97 | 0.88-1.06 | 0.464 | 1.24 | 1.00-1.53 | **0.046** | 1.05 | 0.89-1.23 | 0.571 | 0.83 | 0.70-0.97 | **0.021** |
| 2009 | 1.08 | 0.99-1.18 | 0.101 | 1.60 | 1.31-1.95 | **<0.001** | 1.08 | 0.92-1.27 | 0.326 | 0.83 | 0.71-0.98 | **0.024** |
| 2010 | 1.06 | 0.97-1.16 | 0.209 | 1.43 | 1.17-1.75 | **<0.001** | 1.08 | 0.93-1.27 | 0.317 | 0.89 | 0.76-1.04 | 0.155 |
| 2011 | 1.04 | 0.95-1.13 | 0.442 | 1.48 | 1.21-1.81 | **<0.001** | 1.02 | 0.87-1.19 | 0.814 | 0.83 | 0.71-0.97 | **0.021** |
| 2012 | 1.13 | 1.04-1.24 | **0.005** | 1.85 | 1.53-2.25 | **<0.001** | 1.10 | 0.94-1.28 | 0.242 | 0.77 | 0.65-0.90 | **0.001** |

SIMD: Scottish index of multiple deprivation; RR: Rate-ratio; *p:* p value; HNC: Head & neck cancer; OPC: Oropharyngeal cancer; OCC: Oral cavity cance

### 2.4.2 Trends over time

Overall, the incidence rates of head and neck cancer appeared to have increased significantly over the study period (1975-2012), with the rates in 2012 being approximately 1.53 (RR 1.53, 95% CI 1.37-1.70) times that in 1975. This increase was largely driven by a dramatic rise in the incidence rates of oropharyngeal cancer (RR 3.45, 95% CI 2.66-4.48), while rates of oral cavity cancer exhibited a significantly smaller increase over the same period (RR 1.86, 95% CI 1.53-2.26) (Figure 2-1). Laryngeal cancer exhibited a very small increase in incidence rates between 1975 and 2012, but this was not statistically significant (RR 1.12, 95% CI 0.92-1.35).

**Figure 2-1:** European age-standardised incidence rates between 1975-2012 by subsite



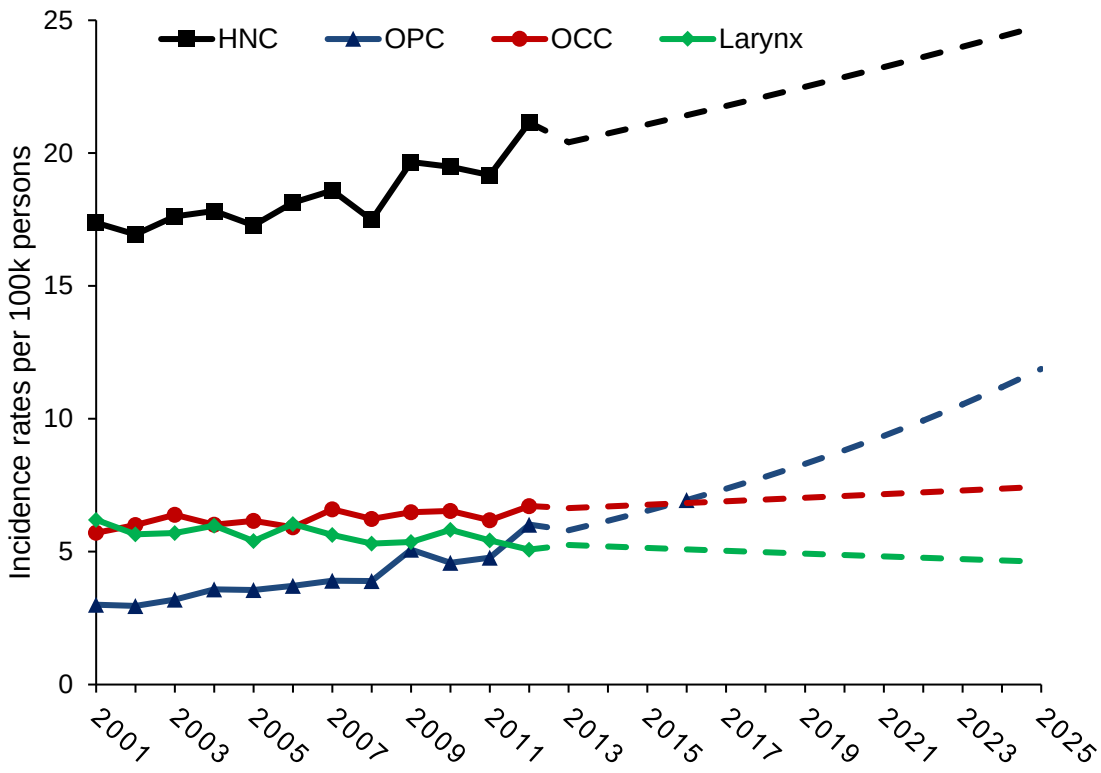

HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

The sub-group analysis showed that the rates of head and neck cancer increased rapidly in the most recent decade (2001-2012), with the rates in 2012 being 1.13 (RR 1.13, 95% CI 1.04-1.24) times the rates seen in 2001. Once again, this appeared to be driven by a rapid increase in the incidence rates of oropharyngeal cancer, which almost doubled (RR 1.85,

95% CI 1.53-2.25) over this period. Rates of oral cavity cancer remained relatively stable between 2001 and 2012 (RR 1.10, 95% CI 0.94-1.28), and rates of laryngeal cancer decreased slightly (RR 0.77, 95% CI 0.65-0.90) over the same period (Figure 2-2).

Incidence projections up to 2025 showed a sharp increase in the rates of head and neck cancer, and oropharyngeal cancer was expected to be largely responsible for this. Moreover, rates of oropharyngeal cancer were expected to bypass the rates of oral cavity cancer, which were expected to have only a relatively modest increase. Rates of laryngeal cancer were predicted to decrease up to 2025 (Figure 2-2).

**Figure 2-2:** European age-standardised incidence rates per 100k persons between 2001-2012 (bold lines) and projected rates (dotted lines) up to 2025 by subsite



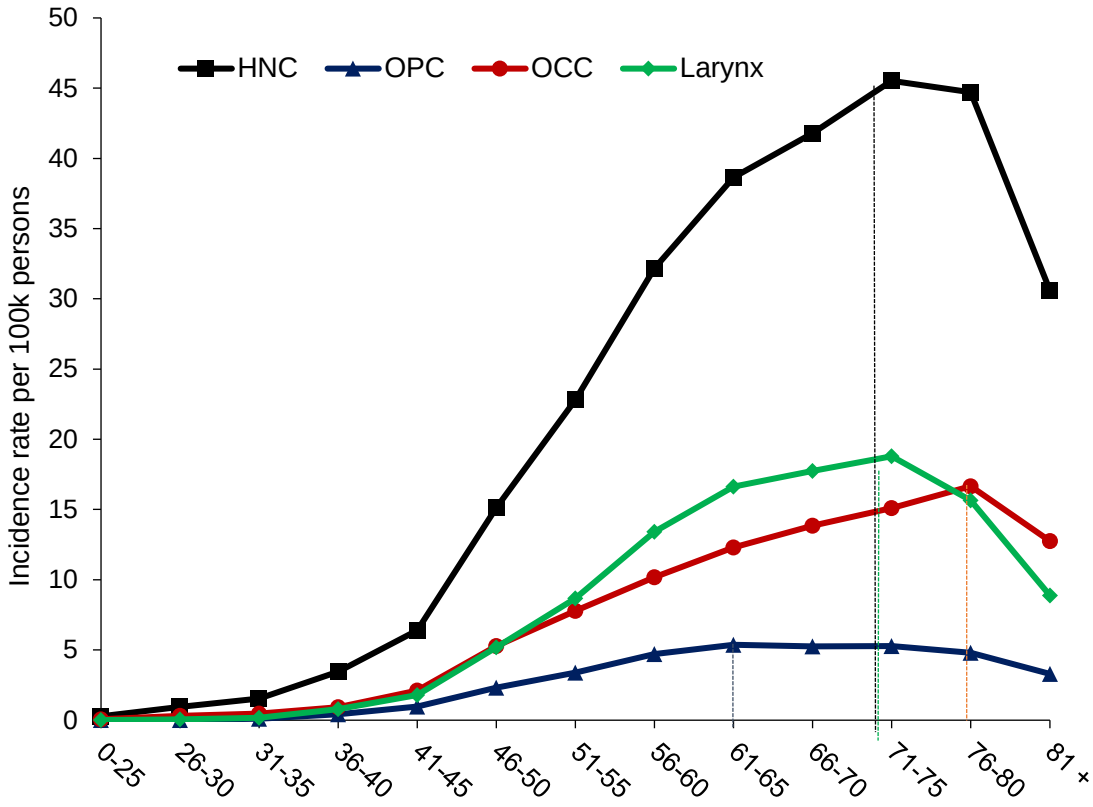

HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

### 2.4.3 Trends by age

Head and neck cancer appeared to be a disease primarily affecting older individuals, with a greater number of the patients included in this study being above 45 years of age (Table 2-1). The incidence rates were seen to peak in the 71-75 year age group, and then begin to decline in the 80+ age group. This decrease in rates in the 80+ age group was likely a result of survival bias, that is, the incidence numbers represented only those individuals who had survived long enough to be diagnosed with cancer, and excluded those who had died from other unrelated causes before they could receive a diagnosis of cancer.

The peak incidence of oropharyngeal cancer was observed in the 61-65 year age-group, while that of oral cavity cancer and laryngeal cancer were seen in the 76-80 and 71-75 year age-groups, respectively (Figure 2-3). The 41-45 year age-group was chosen as the reference category in the model as incidence numbers below this were very small. Regression analysis showed that rates of oropharyngeal cancer were more than double in the 61-65 age-group (RR 2.34, 95% CI 2.08-2.63) compared to the reference category (41-45 age-group), and this was statistically significant (Table 2-2). Relative to the reference group, the highest rate-ratios for oral cavity cancer (RR 3.54, 95% CI 3.20-3.91) and laryngeal cancer (RR 4.74, 95% CI 4.30-5.23) were observed in the 76-80 and 71-75 years age-groups, respectively (Table 2-2).

**Figure 2-3:** European age-standardised incidence rates by age-group

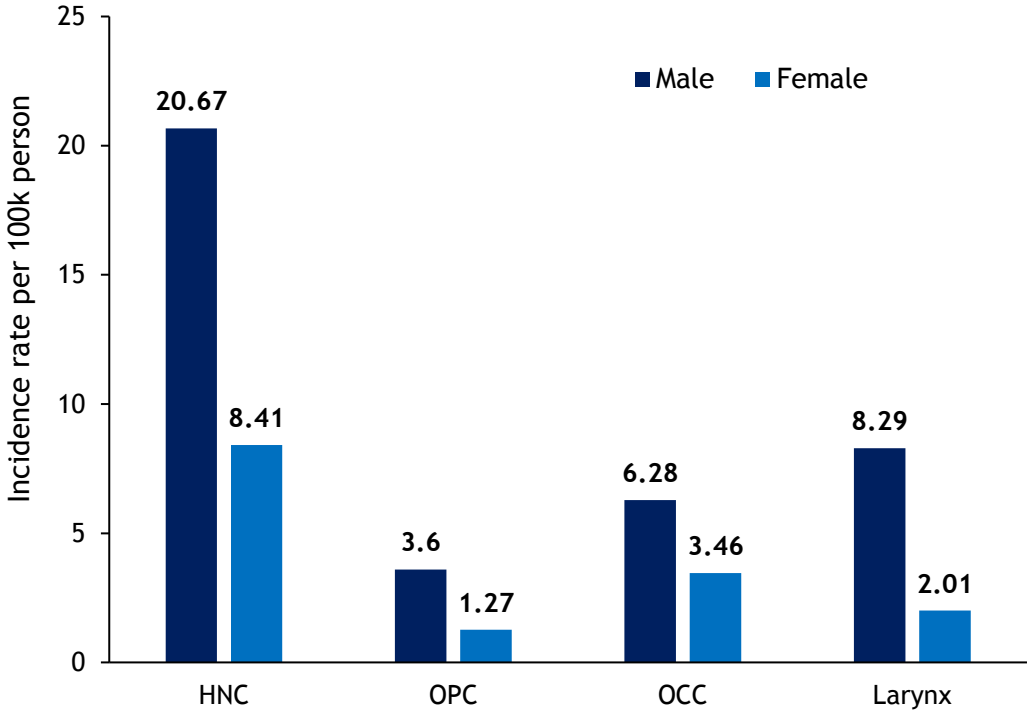



HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

### 2.4.4 Trends by sex

Males were found to exhibit considerably higher incidence rates than females, and this was consistent for all subsites (Table 2-1, Figure 2-4). Regression analysis showed that the rates of head and neck cancer among males was 2.72 times the rates among females, and this was statistically significant. The corresponding rate-ratios for the other subsites were as follows: 3.10 (95% CI 2.90-3.30) for oropharyngeal cancer, 2.11 for oral cavity cancer (95% CI 2.02-2.20), and 4.77 laryngeal cancer (95% CI 4.54-5.01) (Table 2-2), and these were all statistically significant.

**Figure 2-4: European age-standardised incidence rates (1975-2012) by sex**




HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

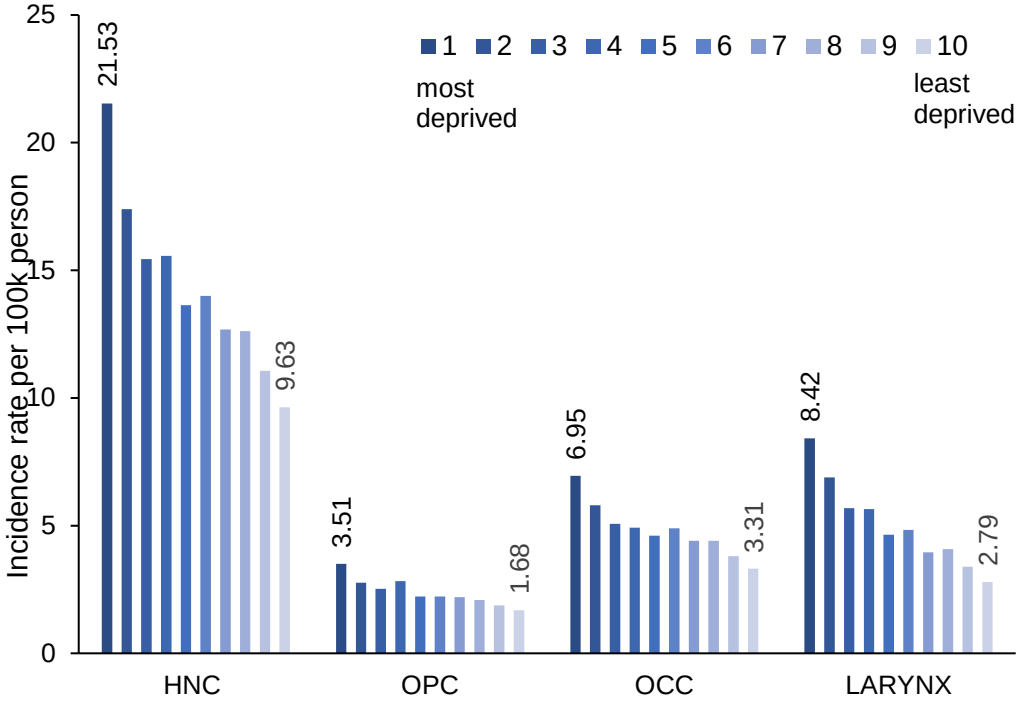
### 2.4.5 Trends by geographic region

No major differences in incidence burden were observed between the different geographic regions, irrespective of subsite, with rate-ratios of the North, East, and West health board regions being quite similar (Table 2-1).

### 2.4.6 Trends by socioeconomic status

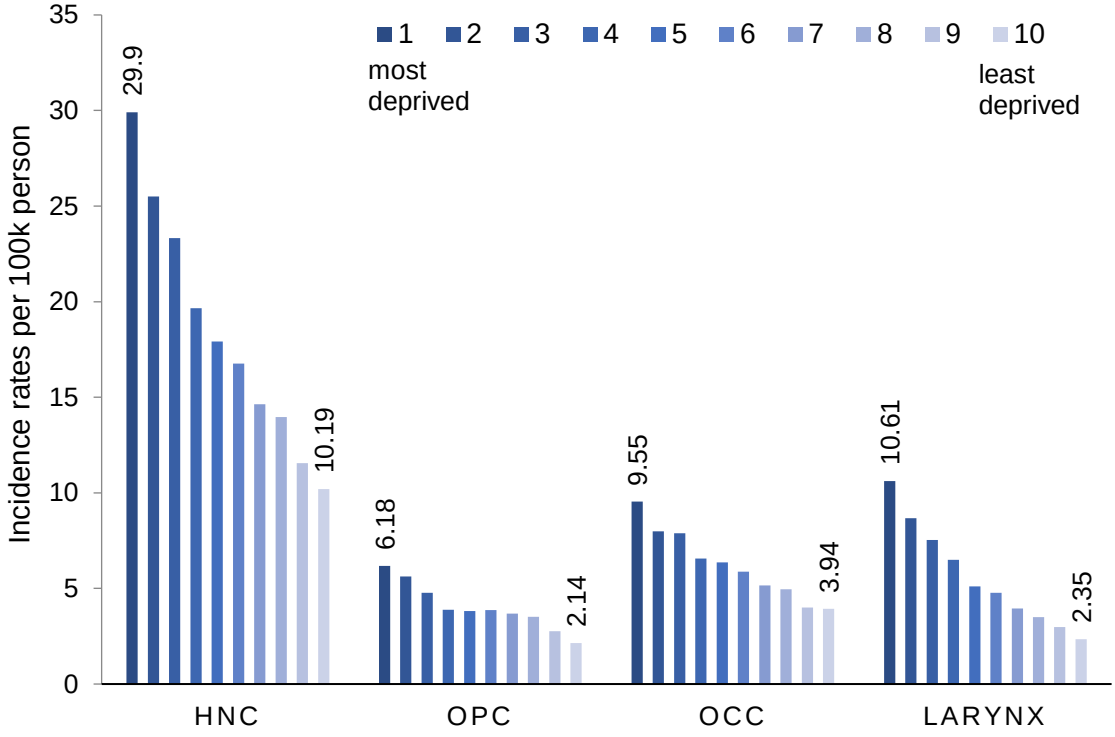
The most deprived areas of Scotland (Carstairs 1) consistently exhibited higher rates of cancer compared to the least deprived areas (Carstairs 10), irrespective of subsite (Table 2-1). Moreover, a dose-like effect was seen to exist, with the rates of cancer increasing as level of deprivation increased (Figure 2-5). This socioeconomic inequality and dose-like effect persisted in the additional sub-group analysis of patients that were diagnosed between 2001 and 2012 using SIMD as an indicator of deprivation (Figure 2-6).

**Figure 2-5: European age-standardised incidence rates (1975-2012) for each subsite by Carstairs 1991 (where 1= most deprived, 10=least deprived)**




HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

**Figure 2-6: European age-standardised incidence rates per 100k persons (2001-2012) for each subsite by Scottish Index of Multiple Deprivation 2009 (where 1=most deprived, 10= least deprived)**




HNC: Head and neck cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer

Regression analysis of patients that were diagnosed between 1975 and 2012 showed that the rates of head and neck cancer in the most deprived areas (Carstairs 1) was 2.59 (RR 2.59 95% CI 2.45-2.74) times that of the least deprived areas (Carstairs 10), and this was statistically significant (Table 2-2). The corresponding rate-ratios for the other subsites were as follows: RR 2.49, 95%CI 2.18-2.86 for oropharyngeal cancer; RR 2.40, 95%CI 2.18-2.65 for oral cavity cancer; and RR 3.34, 95% CI 3.02-3.69 for larynx (Table 2-2).

The additional regression analysis of more recent patients that were diagnosed between 2001 and 2012 showed that the rates of head and neck cancer in the most deprived areas (SIMD 1) was 3.3 (RR 3.3 95% CI 3.01-3.62) times the rates seen in the least deprived areas (SIMD 10), and this was statistically significant (Table 2-4). This inequality persisted upon examination of the other subsites; moreover, the socioeconomic gap appeared to have widened for oropharyngeal cancer (RR 3.33, 95% CI 2.72-4.07) and laryngeal cancer (RR 4.98; 95% CI 4.15-5.97), but remained relatively unchanged for oral cavity cancer (RR 2.69; 95% CI 2.31-3.13) between 2001 and 2012 (Table 2-4).

## 2.5 Discussion

### 2.5.1 Key points, comparison with other work, and potential explanations

This study was the first national descriptive epidemiological study to examine trends of head and neck cancer in Scotland by subsite and socioeconomic status. The results showed that the incidence rates of oropharyngeal cancer were almost at par with the rates of oral cavity cancer and had overtaken those of laryngeal cancer by the year 2012. Moreover, this increasing trend was expected to persist, with the rates of oropharyngeal cancer bypassing oral cavity cancer by 2025. Conversely, rates of oral cavity cancer were predicted to remain relatively stable and rates of laryngeal cancer were expected to decrease up to 2025. Males consistently exhibited higher rates of cancer, irrespective of subsite, and the peak age of incidence of oropharyngeal

cancer was approximately 5-10 years lower than the other subsites. A socioeconomic inequality in incidence was observed across all subsites, with the most deprived areas consistently exhibiting the highest rates of cancer relative to the least deprived areas. Additionally, this socioeconomic inequality exhibited a dose-effect relationship, with the rates of cancer rising as levels of deprivation increased.

Similar results were reported by Chaturvedi et al. (2013) who used data from the Cancer Incidence in Five Continents database to carry out an age-period-cohort analysis, and reported an increase in the incidence of oropharyngeal cancer accompanied by a relative stabilising of rates of oral cavity cancer globally. In England, a detailed cancer registry analysis showed that the incidence rates of head and neck cancer increased by 59% between 1995 and 2011, and this was largely driven by an increase in the rates of oropharyngeal cancer (average annual percentage change = +7.3% in males and +6.5% in females) (Louie et al., 2015). This was in general agreement with the results of the current study which showed an increase of 32% in incidence rates of head and neck cancer in Scotland over the same time period (1995–2011), and this was also driven by a rapid rise in the rates of oropharyngeal cancer. Additionally, Louie et al. (2015) also reported that the rates of head and neck cancer were predicted to continue to escalate up to 2025, and oropharyngeal cancer was expected to be largely responsible for this increased burden. Meanwhile, oral cavity cancer was predicted to stabilise in men and continue to increase in women. The projection estimates in the current study showed a similar increase in the rates of head and neck cancer, driven largely by a rapid rise in the rates of oropharyngeal cancer, in Scotland. Moreover, the peak incidence of oropharyngeal cancer in Scotland was observed in the 61–65 age-group, and this was in agreement with the trends observed in England where rates of oropharyngeal cancer were higher in younger individuals (less than 60 years) (Louie et al., 2015). HPV type 16 has been shown to play an aetiological role in oropharyngeal cancer (Gillison, 2004; D'Souza, 2007), and Hashibe and Sturgis (2013) proposed that the changing profile of head and neck cancer incidence could be explained by the controlling

of a “tobacco epidemic while a human papillomavirus epidemic emerges”. The plateauing in the rates of oral cavity cancer may be a result of the decreasing global rates of smoking observed in the recent past. This theory was further supported by the decreasing incidence rates of laryngeal cancer, whose key risk factors include smoking and alcohol consumption (CRUK, 2018), observed in the most recent decade as it indicated a reduction in the prevalence of these risk factors. The increase in the rates of oropharyngeal cancer possibly reflect the changes in sexual behaviours among recent birth cohorts, which in turn increases risk of exposure to oral HPV infection (Chaturvedi et al., 2013; Louie et al., 2015).

The results of this study showed higher incidence rates amongst men compared to women, and this was in agreement with another retrospective analysis conducted by Chaturvedi et al. (2008) in the United States. A brief presentation on cancer incidence in Scotland showed that oropharyngeal cancer was potentially the fastest increasing cancer in the country, particularly amongst men (Junor et al., 2010). This difference in the rates between sexes could be explained to some extent by the greater prevalence of HPV among men compared to women (Chaturvedi et al., 2011; Gillison et al., 2012b; Hashibe and Sturgis, 2013).

However, in contrast to a previous small clinical series (Dahlstrom et al., 2015), the current study showed that the socioeconomic inequalities in incidence rates of cancer persisted irrespective of subsite in Scotland, with the most deprived areas of the country consistently exhibiting the highest rate-ratios relative to the least deprived areas. This difference may be explained partly by the fact that previous studies examining trends of head and neck cancer in Scotland combined oral cavity cancer and oropharyngeal cancer and examined them as one subsite (Conway et al., 2006), and this may have resulted in a masking of the differential rates. Therefore, this study examined the rates of head and neck cancer as a whole as well as by individual subsites (oral cavity cancer, oropharyngeal cancer, and larynx), thus permitting a more detailed

exploration of differences in the determinants of incidence trends. Another possible explanation for this inequality could be that higher socioeconomic position often reinforces healthy behaviours such as maintenance of oral hygiene and regular physical exercise (Liberatos et al., 1988; Ross and Wu, 1995), while education and higher-level occupations are often associated with better access to health services and reduced exposure to occupational risk factors of head and neck cancer (Riechelmann, 2002).

### 2.5.2 Data quality

This study utilised robust, routinely collected administrative data from the Scottish Cancer Registry (SMR06). The quality indicators for registration of head and neck cancer tumours at the Scottish Cancer Registry are high, with approximately 85% of patients being microscopically confirmed and less than 2% Death Certificate Only registrations (Parkin et al., 2005; UKIACR, 2017). Several studies have also provided evidence of the high (95.4%), and constantly improving, case-ascertainment (Brewster et al., 1994; Brewster et al., 1997; Brewster et al., 2002; ISD Scotland, 2016a), and the levels of completeness of data in 2016 were 96% for patient information and 96.4% for tumour information (UKIACR, 2017).

### 2.5.3 Strengths and limitations

The main strength of this study lay in the quality of the data used (Section 2.5.2). Use of national level data resulted in a population-representative cohort spanning several decades, which improved the strength and generalisability of the results. Finally, examination of individual subsites separately as well as together permitted a more detailed exploration of the differences in the determinants that were driving these trends.

The limitations of this study were mainly those related to limited availability of data, and included lack of information on HPV status, behavioural factors (e.g. tobacco and alcohol consumption), and stage of

cancer at the time of diagnosis. This information could have provided a clearer picture of the risk profile of patients with head and neck cancer. Secondly, this study used geographic area-based measures of socioeconomic status. Such deprivation indices assign all individuals living within a certain area the same score, making interpretation of these measures complex. When used as a surrogate individual measure, it may be inferred that all individuals living in a certain socioeconomic area have the same individual socioeconomic status, and this has been described as an "ecological fallacy" (Berkman and Macintyre, 1997; Macintyre and Ellaway, 2000). However, such ecological interpretation may be advantageous in terms of indicating the social and physical environment or circumstances, for example, adequate access to health care services. Ideally, a combination of individual and area-based socioeconomic measures would be combined in a multi-level analysis to take account of individual and area effects. Thirdly, although previous studies have reported high levels of reliability for cancer registration data, particularly with regard to demographic, diagnostic and treatment information (Brewster, 2002), there are no recent estimates of this currently available. Therefore, there is a possibility of misclassification in the data, particularly with regard to the ICD10 codes assigned to lesions in cases where practitioners were unable to identify the origin of the primary tumour. Lastly, although examination of the incidence trends by individual subsites provided greater clarity from an epidemiological perspective, further research could also include examination of the trends of oral cancer as a whole [defined as including the base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), pharynx (C14), inner lip (C00.3-C00.9), other and unspecified parts of the tongue (C02), gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06)] in Scotland over time by various sociodemographic determinants.

## 2.6 Conclusion

In conclusion, this study shows the changing trends in the burden and determinants of head and neck cancer. Oropharyngeal cancer is an emerging public health problem, with the rates dramatically increasing

in Scotland. Despite previous reports, the sociodemographic determinants of oropharyngeal cancer are not substantially different from other head and neck cancers, particularly in relation to gender and SES profile.

# 3 Is detecting oral cancer in general dental practices a realistic expectation? - A population-based study using population-linked data in Scotland.

## 3.1 Introduction

Chapter 2 of this thesis examined the incidence rates of head and neck cancer by subsite in Scotland and reported an upward trend between 1975 and 2012. This appeared to be largely driven by a rapid increase in the rates of oropharyngeal cancer, while those of oral cavity cancer exhibited a slower increase and then stabilised over the same period. Moreover, the rates of head and neck cancer were expected to continue to rise up to 2025, and males living in the most deprived areas of Scotland were at the highest risk of developing cancer, irrespective of subsite.

In June 2012, the General Dental Council was presented with a case where a senior dental officer employed by NHS Ayrshire and Arran failed to "adequately examine or assess a malignant ulcer" in a patient treated between December 2009 and June 2010 (Evans, 2012). This patient subsequently died from the cancer. Another similar case was reported in December 2013 in Northern Ireland where a senior dentist failed to diagnose a potentially malignant lesion that had existed for 15 years in a patient, and subsequently faced 46 charges of misconduct at the disciplinary hearing conducted by the General Dental Council (BBC News, 2013). The dentist, following a public hearing, was ultimately "struck off" the GDC register in September 2014. These incidents brought the topic of oral cancer screening and early detection into focus once again, and the GDC announced that "Oral Cancer: Improving Early Detection" would be included as a recommended subject for continuing professional development (CPD) (General Dental Council, 2017). This decision was based not only on the failure of dentists in detecting oral cancer in a timely manner, but also on the increasing incidence and potentially life-threatening nature of this disease.

The World Health Organisation defined screening as “the systematic application of a screening test in a presumably asymptomatic population, with an aim to identify individuals with an abnormality suggestive of a specific cancer” (WHO, 2013). The United Kingdom National Screening Committee published a list of criteria that must be fulfilled in order for a mass screening program for a disease to be recommended, and Speight et al. (2017) recently used this list to assess the current global status of oral cancer screening. They concluded that although oral cancer screening was feasible, as it was frequently preceded by a potentially malignant lesion, there was insufficient evidence in support of the effectiveness of a population-wide screening program, and targeted screening of high-risk individuals (identified by smoking and alcohol behaviours) was recommended instead. Moreover, this was previously reported to be the most cost-effective option by Speight et al. (2006) who used simulation modelling techniques to examine the cost-effectiveness of screening for oral cancer in various primary care facilities.

General dental practitioners are placed in an ideal position to examine the oral soft tissues of patients for cancerous or pre-cancerous lesions through regular patient contact, thus increasing the opportunities for early detection of oral cancer and the delivery of appropriate advice to increase awareness of known risk factors. In England, *Saving Lives: Our Healthier Nation* (UK Government, 1999) and *Modernising NHS Dentistry - Implementing the NHS Plan* (UK Government, 2000) recommended incorporation of the dental team in the delivery of preventive advice in order to increase the public health role of the team through a common risk factor approach (Grabauskas and Leparski, 1987; WHO, 2000). Moreover, the dental team can also play a crucial role in the management of oral cancer through patient counselling and early referral which, in turn, facilitates early diagnosis and prompt treatment (Conway et al., 2002).

However, given the relatively low volume of the disease in Scotland (as reported in Chapter 2), the feasibility of early detection of oral cancer in

general dental practices remains unclear. In Britain, anecdotal evidence suggests that a dentist may expect to see “few, if any, cases of mouth cancer during their career” (McCarthy, 2016). Similar concerns were raised in relation to general medical practitioners in England identifying childhood cancer. Feltbower et al. (2004), in their Short Opinion published in the British Journal of Cancer in 2004, examined the distribution of childhood cancer cases by Primary Care Trusts in England and Wales, in an attempt to understand the likelihood of a single general practitioner referring a case of childhood cancer for treatment. They considered Yorkshire as a representative area of England and Wales, and used data from the Yorkshire Specialist Register of Cancer in Children and Young People, a population-based register recording cancer cases from various sources, and the 2001 local authority mid-year population estimates to calculate the incidence of childhood cancer per Primary Care Trust. Their results showed that a single general practitioner in Yorkshire would see one case of childhood cancer every twenty years. Currently there are very few studies that have attempted to use this methodology to estimate the distribution of oral cancer by general dental practices. A thorough literature search returned only one Letter to the Editor published in the British Dental Journal in April 2014 (Ogden et al., 2015). The authors reflected the attendance pattern of the general population (approximately 60% reported to visit the dentist regularly) to the total number of incident cases of mouth cancer per year to estimate that approximately 4060 out of 6767 cases must have visited the dentist. This represented approximately one case per ten dentists. They then included potentially malignant lesions such as leukoplakia and erythroplakia to their calculation, along with a population rate of 2.5%, and estimated that approximately 24 potentially malignant lesions occurred in a year or, in other words, two a month (Ogden et al., 2015). However, the authors failed to clarify the definition of oral cancer that was used and the time period considered, and also did not take registration rates into consideration.

Timely detection and referral of oral cancer in the dental setting is also largely dependent on patients consulting dentists frequently enough to

achieve this. The literature review presented in Chapter 1 identified several studies from the Netherlands, Western Australia, and France that reported poor dental attendance patterns among patients with oral cancer (Tromp et al., 2005; Frydrych and Slack-Smith, 2011; Ligier et al., 2016). More locally, Netuveli et al. (2006) used data from the Health Survey for England (2001) (n=13,784) and the British Household Panel Survey (n=5547) to examine the association between dental attendance patterns and various known risk factors of oral cancer, and reported that the likelihood of attending a dental practice regularly decreased as the number of factors favouring carcinogenesis (age, sex, alcohol consumption, smoking, low intake of fruits/vegetables) and, subsequently, the risk of developing oral cancer increased. The authors termed this as the "inverse screening law" and suggested that opportunistic screening in dental practices would not be an efficient preventive strategy in the United Kingdom as only those who were at low risk of developing cancer would be screened. These results were further supported by Yusof et al. (2006) who also used data from the British Household Panel Survey to examine the association between dental attendance patterns and known risk factors of oral cancer, including socioeconomic status, and found that "high-risk" individuals (defined as males, above 40 years of age, low SES and education, manual occupational social class, smokers) exhibited poorer dental attendance patterns.

Dental Workforce Reports in Scotland for 2012 showed that although there were socioeconomic inequalities in access to health care services such as medical practices, the distribution of dental practices did not follow this pattern (Audit Scotland, 2012), with the most deprived areas of Scotland also exhiibting a higher number of dental practices. Published dental registration rates for adults in the same year showed considerable population coverage of these services, with approximately 78% and 73% of the adult population from the most and least deprived areas, respectively, being registered with a general dental practice (ISD Scotland, 2016b). However, in contrast to the registration rates, the published participation rates for adults exhibited a socioeconomic skew,

with only 74% of registered adults from the most deprived areas and 82% of registered adults from the least deprived areas having attended a dental practice in the previous two years. However, currently there are no studies that accurately estimate the distribution of patients with oral cancer by the location of primary care general dental practices (GDP) in Scotland, nor take into consideration how these trends may vary with area-based socioeconomic deprivation. Moreover, no studies have accurately investigated whether the patients that were diagnosed with oral cancer were registered or attended general dental practices prior to diagnosis and, given the changing incidence of oral cancer noted previously, there are no recent estimates of the likelihood of a general dental practitioner encountering a patient with the disease. Given the overall low number of patients with oral cancer in Scotland, the feasibility of carrying out screening at the primary care level is unknown, and quantification of the number of patients a practitioner may expect to encounter per year may help us develop a better understanding of whether a more stratified or targeted approach is necessary. Research in this area will also help us understand the distribution of the burden of oral cancer in Scotland and inform strategies for targeting training and future referral pathways.

## 3.2 Aim, hypotheses and objectives

Therefore, the ***aim*** of this study was to investigate whether early detection of oral cancer in dental settings is a realistic expectation, given the current burden and sociodemographic risk profile of the disease, and the location and distribution of general dental practices in Scotland.

The ***hypotheses*** were:

**Chapter 3 hypothesis (a):** The number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) a general dental practitioner in Scotland can expect to see will be low.

**Chapter 3 hypothesis (b):** Dentists working in more deprived areas will expect to see a greater number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) compared to dentists working in relatively less deprived areas.

The individual ***objectives*** were:

**Chapter 3 objective (a):** To collate data from the Scottish Cancer Registry and routine administrative NHS Scotland data on dental practice distribution, dental workforce, and population dental registration and participation (attendance) rates.

**Chapter 3 objective (b):** To estimate the number of patients with oral cancer (oral cavity and oropharyngeal cancer) an NHS primary care dentist may expect to see per year and over time.

**Chapter 3 objective (c):** To examine how the estimates of the number of patients with oral cancer (oral cavity and oropharyngeal cancer) may vary with the location and distribution of dental practices in relation to the socioeconomic deprivation of the area.

**Chapter 3 objective (d):** To link Scottish Cancer Registry data with routine NHS dental service payment claims data to calculate dental attendance rates of patients with oral cancer (oral cavity and oropharyngeal cancer) in the two years preceding diagnosis.

## 3.3 Patients and methods

### 3.3.1 Ethical considerations

As mentioned earlier in Section 2.3.1, an initial data access request was submitted to the Scottish Cancer Registry, which is part of the Information Services Division (ISD) of the NHS National Services Scotland (NHS NSS). As the data was non-patient-identifiable, no application to the Public Benefit and Privacy Panel (PBPP) was necessary and access was approved by the Caldicott Guardian for NHS NSS. A Confidential Data Release Form was signed by the author and Professor David Conway

(Appendix 6). The West of Scotland Research Ethics Committee (WOSRES) identified this project as 'Surveillance' and formally confirmed that NHS ethical approval would not be required (Appendix 3).

An application for ethical approval was made to the University of Glasgow, College of Medicine, Veterinary and Life Sciences Ethics Committee, and was received on the 15th of December 2015 (Appendix 5).

As the data included in the additional linked dataset was generated by the NHS and patient-identifiable, access could only be arranged upon approval from the Public Benefit and Privacy Panel for Health and Social Care (PBPP). The electronic Data Research and Innovation Service (eDRIS) serves as a single point of contact to assist researchers in navigating the PBPP application process and organising data access in a secure environment, and their aim is to help conduct research in an easier, more efficient and convenient way. First contact with eDRIS involved submission of a research protocol that detailed the background, aims and objectives and the implications of the study to be undertaken. Thereafter, a research co-ordinator (Mark McCartney based at National Services Scotland) was assigned, who provided assistance with the PBPP application process including identification of appropriate datasets and relevant variables. The necessary Information Governance training was obtained by completion of an e-learning course (Research Data and Confidentiality e-learning course) conducted by the Medical Research Council on the 22nd of September 2015 (Appendix 7). The final PBPP application was submitted on the 21st of January 2016 for consideration at the panel meeting that was held on the 23rd of February 2016. Following several unforeseen delays, PBPP approval was finally received on the 21st of April 2016 (Appendix 9), and the application was then forwarded to the relevant teams for processing and uploading of data onto the NHS NSS eDRIS National Safe Haven (remote access). There was considerable unexpected delay in this step, and the linked datasets were finally uploaded in October 2016.

### 3.3.2 Data

This study used data from the Scottish Cancer Registry (SMR06) and the Management Information and Dental Accounting System (MIDAS) datasets, details of which have been provided later in Chapter 4. Briefly, the Scottish Cancer Registry, started in 1958, collects and stores information on all Scottish residents diagnosed with malignancies (ISD Scotland, 2017d), while the MIDAS database, which is the computerised payment system for the General Dental Service in Scotland, processes and stores information on all individuals registered with an NHS dental practice in a dynamic fashion.

This study included all patients that were diagnosed with oral cavity cancer and oropharyngeal cancer (as defined previously in Chapter 2) between 2010 and 2012 and registered with the Scottish Cancer Registry. Briefly, oral cavity cancer included ICD-10 codes C00.3-C00.9 and C02-C06 while oropharyngeal cancer included codes C01, C2.4, C09, C10, and C14. Additionally, these two subsites were also combined and examined as oral cancer (OC; ICD10 codes C00.3-C00.9, C01-C06, C09-C10, C14).

Socioeconomic status was measured by the recently developed small area-based socioeconomic index, the Scottish Index of Multiple Deprivation (SIMD 2009), which combines data from seven domains of deprivation including income, employment, education, housing, health, crime, and geographical access (Donnelly, 2009). It is measured initially at the data-zone level, thus allowing greater coverage of smaller populations, and grouped into fifths of the population (where 1 = most deprived areas, 5 = least deprived areas).

Data on the number of primary care dentists per year per SIMD fifth were collected from NHS National Services Scotland (ISD Scotland, 2016c) and used to calculate the mean number of dentists per SIMD fifth over the study period (2010 to 2012). In this study, primary care dentists comprised of those working in the general dental services (GDS) including non-salaried and salaried dentists, but excluded Community Dental Services, now known as the Public Dental Services in Scotland.

Dental registration and participation (attendance) rates for all adults in Scotland as of 30th September 2012 were accessed from the Information Services Division website and NHS Scotland online publications (ISD Scotland, 2012; ISD Scotland, 2016b).

Additionally, a dataset that anonymously linked individual patient records (all patients that were diagnosed with oral cancer, oral cavity cancer, and oropharyngeal cancer between 2010 and 2012) to their MIDAS records in the two years prior to diagnosis using the NHS Scotland unique ID number was also obtained. The MIDAS variables included were the patient's gender, patient's age at the time of contact, socioeconomic deprivation level (measured by SIMD v2009), start and stop dates of treatment, and treatment received. Here, the "start date of treatment" variable was used as an indicator of contact, and each unique date was considered as one contact irrespective of the number of claims made. This variable also included all contacts made as part of routine dental check-ups.

### 3.3.3 Statistical Analysis

Initial data management included checking for any missing variables and assessing the distribution of patients and practitioners. The expected number of patients per general dental practitioner, based on the assumption that all of them were seen by one, was calculated by dividing the number of patients that were diagnosed with oral cancer, oral cavity cancer, and oropharyngeal cancer per year by the number of dentists registered with the NHS in the same year.

However, given that the whole population is not necessarily registered with an NHS general dental practitioner and only a proportion of those that are will consult a dentist regularly, there is a possibility that this simple calculation is an overestimation. Therefore, published registration and participation (attendance) rates for each SIMD fifth were then applied to obtain a more accurate estimate of the number of patients that a general dental practitioner would likely encounter per year (ISD Scotland, 2016b). Registration rates included all individuals in

the general population who were registered with an NHS GDP, while participation (attendance) rates represented the proportion of registered patients who had contacted a general dental practitioner for either examination or treatment (or both) in the last two years.

The additional linked dataset was used to calculate the number and proportion of diagnosed patients by subsite and SIMD that had contacted a primary dental care service in the two years preceding diagnosis. These proportions were then applied to obtain a more realistic estimate of the number of patients a general dental practitioner would likely encounter per year.

## 3.4 Results

This study included 1988 patients that were diagnosed with oral cancer between 2010 and 2012, of which 1127 were oral cavity cancer and 861 were oropharyngeal cancer. Among the patients with oral cavity cancer, 57% were male (n=646) and 43% were female (n=481), while 74% (n=634) of patients with oropharyngeal cancer were male and 26% (n=227) were female. The patient demographics by subsite have been shown in Table 3-1.

Under the assumption that all patients were seen by a general dental practitioner, the overall estimated number of patients per GDP per year in Scotland was 0.22 for oral cancer (one patient every 4.5 years), 0.12 for oral cavity cancer (one patient every 8.3 years), and 0.09 for oropharyngeal cancer (one patient every 11.1 years) (Table 3-2). Upon application of published dental registration and participation (attendance) rates, these estimates increased to 0.13 for oral cancer (one patient every 8 years), 0.07 for oral cavity cancer (one patient every 14 years), and 0.05 for oropharyngeal cancer (one patient every 20 years). No major differences by deprivation fifths of the practice location was observed (Table 3-2). The estimated number of patients per GDP per year in the most deprived areas were 0.13 (one patient every 8 years) for oral cancer, 0.07 (one patient every 14 years) for oral cavity cancer, and 0.05 (one patient ever 20 years) for oropharyngeal cancer,

while the corresponding numbers in the least deprived areas were 0.11 (one patient every 9.10 years) for oral cancer, 0.06 (one patient every 16.7 years) for oral cavity cancer, and 0.04 (one patient every 25 years) for oropharyngeal cancer.

**Table 3-1: Demographics of patients that were diagnosed with oral cancer, oral cavity cancer, and oropharyngeal cancer between 2010 and 2012**

| | **OCC (n, %)** | **OPC (n, %)** | **OC** (n, %) |
|---|---|---|---|
| **Sex** | | | |
| Male | 646 (57.3) | 634 (73.6) | 1280 (64.4) |
| Female | 481 (42.7) | 227 (26.4) | 708 (35.6) |
| **SIMD** | | | |
| 1 (Most deprived) | 291 (25.8) | 237 (27.5) | 528 (26.6) |
| 2 | 244 (21.7) | 183 (21.3) | 427 (21.5) |
| 3 | 245 (21.7) | 177 (20.6) | 422 (21.2) |
| 4 | 194 (17.2) | 153 (17.8) | 347 (17.5) |
| 5 (Least deprived) | 153 (13.6) | 111 (12.9) | 264 (13.3) |

OC: Oral cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer; SIMD: Scottish Index of Multiple Deprivation 2009;

**Table 3-2: Estimates of the expected and actual number of oral cancer cases (2010-2012) a GDP may encounter per year (taking published dental registration and participation, and actual attendance rates into consideration), and calculation of the number of years elapsed before one patient is seen.**

| SIMD | | 100% dental registration and participation (attendance) assumed | | | | Application of published registration and participation (attendance) rates | | | | | Application of actual attendance rates | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean no. of patients over three years | Mean no. of dentists over three years | Estimation of number of patients per dentist | Estimation of no. of years before one patient encountered | Reg. rates (%) | Part. rates (%) | Estimation of no. of patients visiting dentist in last one year | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered | Proportion of patients that contacted dentist in two years before diagnosis (%) ** | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered |
| OC | **All Scotland** | **662.66** | **3025.33** | **0.22** | **4.55** | **73.7** | **78.7** | **384.35** | **0.13** | **7.69** | **46.4** | **0.10** | **10.00** |
| | 1 (Most deprived) | 176.00 | 771.33 | 0.23 | 4.35 | 77.8 | 73.6 | 100.79 | 0.13 | 7.69 | 45.2 | 0.10 | 10.00 |
| | 2 | 142.33 | 790 | 0.18 | 5.56 | 74.2 | 77.2 | 81.53 | 0.10 | 10.00 | 44.3 | 0.08 | 12.50 |
| | 3 | 140.66 | 631 | 0.22 | 4.55 | 71.5 | 79.2 | 79.65 | 0.12 | 8.33 | 47.4 | 0.12 | 8.33 |
| | 4 | 115.66 | 439 | 0.26 | 3.85 | 71.7 | 81.5 | 67.59 | 0.15 | 6.67 | 48.8 | 0.13 | 7.70 |
| | 5 (Least deprived) | 88.000 | 478.66 | 0.18 | 5.56 | 73.2 | 82.0 | 52.82 | 0.11 | 9.10 | 47.8 | 0.09 | 11.11 |

| SIMD | | 100% dental registration and participation (attendance) assumed | | | | Application of published registration and participation (attendance) rates | | | | | Application of actual attendance rates | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean no. of patients over three years | Mean no. of dentists over three years | Estimation of number of patients per dentist | Estimation of no. of years before one patient encountered | Reg. rates (%) | Part. rates (%) | Estimation of no. of patients visiting dentist in last one year | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered | Proportion of patients that contacted dentist in two years before diagnosis (%) ** | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered |
| OCC | **All Scotland** | **375.66** | **3025.33** | **0.12** | **8.33** | **73.7** | **78.7** | **217.89** | **0.07** | **14.29** | **49.1** | **0.06** | **16.67** |
| | 1 (Most deprived) | 97.66 | 771.33 | 0.12 | 8.33 | 77.8 | 73.6 | 55.92 | 0.07 | 14.29 | 47.4 | 0.06 | 16.67 |
| | 2 | 81.33 | 790 | 0.10 | 10 | 74.2 | 77.2 | 46.58 | 0.05 | 20.00 | 47.8 | 0.05 | 20.00 |
| | 3 | 81.66 | 631 | 0.13 | 7.69 | 71.5 | 79.2 | 46.24 | 0.07 | 14.29 | 49.7 | 0.06 | 16.67 |
| | 4 | 65.00 | 439 | 0.15 | 6.67 | 71.7 | 81.5 | 37.98 | 0.08 | 12.5 | 55.1 | 0.08 | 12.50 |
| | 5 (Least deprived) | 51.00 | 477.66 | 0.11 | 9.09 | 73.2 | 82.0 | 30.61 | 0.06 | 16.67 | 42.6 | 0.05 | 20.00 |

| | | 100% dental registration and participation (attendance) assumed | | | | Application of published registration and participation (attendance) rates | | | | | Application of actual attendance rates | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean no. of patients over three years | Mean no. of dentists over three years | Estimation of number of patients per dentist | Estimation of no. of years before one patient encountered | Reg. rates (%) | Part. rates (%) | Estimation of no. of patients visiting dentist in last one year | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered | Proportion of patients that contacted dentist in two years before diagnosis (%) ** | Estimation of number of patients per dentist | Estimation of no. of years before one patients encountered |
| **OPC** | **All Scotland** | **287** | **3025.33** | **0.09** | **11.11** | **73.7** | **78.7** | **166.47** | **0.05** | **20.00** | **42.9** | **0.04** | **25.00** |
| | 1 (Most deprived) | 80.00 | 771.33 | 0.10 | 10 | 77.8 | 73.6 | 45.80 | 0.05 | 20.00 | 42.3 | 0.04 | 25.00 |
| | 2 | 62.33 | 790 | 0.07 | 14.29 | 74.2 | 77.2 | 35.70 | 0.04 | 25.00 | 39.7 | 0.03 | 33.33 |
| | 3 | 59.33 | 631 | 0.09 | 11.11 | 71.5 | 79.2 | 33.59 | 0.05 | 20.00 | 44.2 | 0.04 | 25.00 |
| | 4 | 51.00 | 439 | 0.12 | 8.33 | 71.7 | 81.5 | 29.80 | 0.06 | 16.67 | 40.9 | 0.05 | 20.00 |
| | 5 (Least deprived) | 37.00 | 477.66 | 0.07 | 14.29 | 73.2 | 82.0 | 22.20 | 0.04 | 25.00 | 53.7 | 0.04 | 25.00 |

OC: Oral cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer; SIMD: Scottish Index of Multiple Deprivation 2009; Reg. rates: Registration rates; Part. rates: Participations rates.
**Taken from Table 3-3

The additional linked dataset exhibited a small difference in the number of patients (1%), but this was considered to be too small to have significantly affected the results. Individual patient data linkage showed that 54% of patients with oral cancer, 51% of patients with oral cavity cancer, and 57% of patients with oropharyngeal cancer had no contact with an NHS primary care dentist in the two years preceding diagnosis (Table 3-3). Some inequities in dental contacts were observed, with 55% (n=356) of patients with oral cancer, 53% (n= 194) of patients with oral cavity cancer, and 58% (n= 162) of patients with oropharyngeal cancer from the most deprived areas of Scotland (SIMD 1) having no contact with an NHS primary care dentist in the two years preceding diagnosis. Conversely, 52% (n=74) of patients with oral cancer, 57% (n=43) of patients with oral cavity cancer, and 46% (n=31) of patients with oropharyngeal cancer from the least deprived areas of Scotland (SIMD 5) had no contact with a primary dental care service in the two years preceding diagnosis (Table 3-3). However, this difference in proportions was quite small and likely did not have any clinical significance.

Upon application of these dental attendance proportions, the results showed that a general dental practitioner would encounter one patient with oral cancer every ten years, one patient with oral cavity cancer every 17 years, and one patient with oropharyngeal cancer every 25 years (Table 3-2).

**Table 3-3:Number and percentages of patients with oral cancer, oral cavity cancer, and oropharyngeal cancer (2010-2012) who made contact with a general dental practitioner in the two years preceding diagnosis- all Scotland by SIMD**

| Contact | | SIMD (n, %) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 (Most deprived) | 2 | 3 | 4 | 5 (Least deprived) | Missing SIMD | Total |
| OC | Yes | 294<br>45.23 | 182<br>44.39 | 195<br>47.45 | 164<br>48.81 | 68<br>47.89 | 8 | **911**<br>**46.43** |
| | No | 356<br>54.7 | 228<br>55.61 | 216<br>52.55 | 172<br>51.19 | 74<br>52.11 | 5 | **1051**<br>**53.57** |
| | Total | **650** | **410** | **412** | **335** | **142** | **13** | **1962** |
| OCC | Yes | 175<br>47.43 | 112<br>47.86 | 118<br>49.79 | 103<br>55.08 | 32<br>42.67 | 4 | **544**<br>**49.10** |
| | No | 194<br>52.57 | 122<br>52.14 | 119<br>50.21 | 84<br>44.92 | 43<br>57.33 | 2 | **564**<br>**50.90** |
| | Total | **371** | **234** | **237** | **187** | **75** | **6** | **1108** |
| OPC | Yes | 119<br>42.35 | 70<br>39.77 | 77<br>44.25 | 61<br>40.94 | 36<br>53.73 | **4** | **367**<br>**42.97** |
| | No | 162<br>57.65 | 106<br>60.23 | 97<br>55.75 | 88<br>59.06 | 31<br>46.27 | **3** | **487**<br>**57.03** |
| | Total | **282** | **177** | **175** | **149** | **67** | **7** | **854** |

OC: Oral cancer; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer; SIMD: Scottish Index of Multiple Deprivation 2009.

## 3.5 Discussion

### 3.5.1 Key points, comparison with other work, and potential explanations

This was the first national descriptive epidemiological study that attempted to estimate the proportion of patients with oral cancer, oral cavity cancer, and oropharyngeal cancer that had attended a primary dental care service in Scotland in the two years preceding diagnosis, and to also accurately estimate the number of patients that a general dental practitioner may encounter over time. The results showed that the majority of patients that were included in this study had made no contact with a primary care general dental practice in the two years prior to diagnosis, thus automatically limiting opportunities for early detection. These results were in agreement with several other studies conducted in France, The Netherlands, and Western Australia (Tromp et al., 2005; Frydrych and Slack-Smith, 2011) that also reported poor dental attendance patterns in the majority of patients with head and neck cancer, oral cancer, and oropharyngeal cancer (reviewed previously in Chapter 1). Of these, the most recent study conducted in a high-incidence region in France reported that the majority (80%) of patients with head and neck cancer (n=342; defined as including the anatomic subsites oral cavity, oropharynx, hypopharynx, and larynx) included in their study had not consulted a dentist in the two to twelve months prior to diagnosis (Ligier et al., 2016). Additionally, previous studies in the United Kingdom used national survey data to report poor dental attendance rates among "high-risk" groups (Netuveli et al., 2006; Yusof et al., 2006), and these were also in agreement with the results of the current study.

Application of these attendance rates showed that a general dental practitioner would encounter one patient with oral cancer every ten years, one patient with oral cavity cancer every 17 years, and one patient with oropharyngeal cancer every 25 years. If published registration and participation (attendance) rates were applied instead, these numbers

decreased to one patient with oral cancer every 8 years, one patient with oral cavity cancer every 14 years, and one patient with oropharyngeal cancer every 20 years. These results suggest that with greater efforts to fully engage with all patients and increase regular attendance rates, the potential detection rate could markedly increase. No obvious patterns or relationships with deprivation of the practice location were observed, and this could partly be explained by the fact that although there are inequalities in access to NHS primary care services such as general medical practices in Scotland, the distribution of dental practices does not follow this pattern (Audit Scotland, 2012). Therefore, registration rates do not exhibit the typical inequalities skew, although participation (attendance) rates are lower in the more deprived communities (ISD Scotland, 2016b). As a result, this offsets the higher rates of oral cancer in deprived areas as they are distributed among the higher number of dentists in the same areas. Moreover, the linkage study showed no major socioeconomic patterns in dental attendance rates, with the proportions of individuals that made no contact with a GDP in the two years preceding diagnosis being quite similar for the most and least deprived areas of Scotland (55% and 52%, respectively). This lack of a social pattern in dental attendance rates could be explained by possible differences in the SIMD of the patient's residence and that of the practice location they attended, and this was likely facilitated by the existence of a universal health care service such as the NHS. In other words, availability of access to free dental check-ups made it possible for a patient who lived in the most deprived area of Scotland (SIMD 1) to attend a dental practice located in a different SIMD.

Several studies have employed similar methodologies to estimate the number of emergency events that a dentist would likely encounter per year (Fast et al., 1986; Chapman, 1997; Girdler and Smith, 1999); however, none have applied it to estimate the time elapsed before a dentist would encounter a patient with oral cancer. A simple calculation of the headline distribution of patients with oral cancer in relation to the number of

dentists in England, Northern Ireland and Wales suggested there would be one patient per ten dentists per year (Ogden et al., 2015). However, the authors did not provide any information on the definition of oral cancer that was used or the time period under consideration, and also did not take registration rates into consideration.

The results of this study showed considerable differences in the number of patients with oral cavity cancer and oropharyngeal cancer that a general dental practitioner in Scotland could expect to see per year. The main implication of this for GDPs, particularly given the changing background of incidence trends for both subsites, is a need for vigilance and awareness, particularly with regard to signs and symptoms that may be indicative of the subsite involved. For example, although the national guidelines for referral combine the two subsites as oral cancer, certain signs and symptoms such as dysphagia or odynophagia lasting for more than 3 weeks, persistent lump in the throat, and persistent pain in the throat lasting for more than 3 weeks may be indicative of oropharyngeal cancer (NHS Scotland, 2016b). These results also emphasise the importance of including thorough extra- as well as intra-oral examinations in routine dental check-ups, particularly among “high-risk” individuals.

In this study, registration rates included all of the individuals in the general population who were registered with an NHS dentist, while participation (attendance) rates represented the proportion of registered patients who had contacted a general dental practitioner for either examination or treatment (or both) in the past two years (ISD Scotland, 2016b). The latter does not include patients who only visited the dentist occasionally, for emergency treatments only, or attended a private dentist. These published rates were used to estimate the likelihood of a dentist encountering a patient with oral cancer. Furthermore, the linkage study revealed that a sizeable proportion of the patients that were included in this study had not contacted a dentist in the two years preceding diagnosis, and application of these actual attendance rates (which showed even lower contact among those from the most deprived

communities) further reduced the likelihood of encountering a patient with oral cancer.

Another factor that ought to be taken into consideration when interpreting these results is that this study considered the deprivation status of the dental practices, and not that of the patients themselves, to calculate the number of patients per general dental practitioner. The linkage study, on the other hand, considered the SIMD fifth of the patient's area of residence to better elucidate if deprivation had any effect on their likelihood of contacting a general dental practice. This, however, raises the possibility of ecological fallacy as a patient who lives in a particular SIMD fifth may not necessarily attend a dental practice within the same SIMD fifth, just as the registration profile of a practice may not necessarily reflect the SIMD fifth his/her practice is located in.

### 3.5.2 Strengths and Limitations

The main strengths of this study lie in the robust nature of the detailed, routinely collected administrative data used. The Scottish Cancer Registry data have been reported to exhibit high levels of accuracy, completeness, and reliability, particularly in relation to diagnostic and treatment details and demographics (Brewster et al., 1994; Brewster et al., 1997; Brewster et al., 2002). Registration and participation (attendance) rates are also highly accurate, as are data from the MIDAS database, which is the payment system for NHS dental practitioners in Scotland and is, therefore, dependant on practitioners submitting claims for payment.

One data limitation of this study was that headcounts of dentists in a practice were used for all calculations, and the whole-time equivalents of each practitioner was unknown. It would be fair to assume that many of these practitioners were employed part-time, and this may have affected the estimates of likely time to see a patient. The second unknown limitation is in relation to the accuracy and completeness of the data linkage. Kendrick and Clarke (1993) reported that clerical monitoring of

pair-wise linking showed that the false negative rates (the proportion of pairs which the system fails to link) and the false positive rates (the proportion of pairs which are incorrectly linked) were both approximately three percent. Additionally, the completeness of the unique identification number on both the Scottish Cancer Registry and MIDAS databases have been reported to be very high (approximately 99%) (ADLS, 2017; ISD Scotland, 2017e). Therefore, records of patients with oral cancer that did not link to a dental record in MIDAS would be because they did not have a dental contact rather than because their identification numbers did not match or that data linkage was unsuccessful. Thirdly, this study only considered NHS primary care dentists, and did not include those belonging to the private sector. However, the *Dental Workforce Report* showed that only 17% of adults received private treatment only over a 12-month period in 2012 (NHS Education for Scotland, September 2012). Moreover, an analysis of a previous version of this report in 2008 showed that the private sector mainly attracted patients with higher incomes, relatively good oral health, and low future dental care needs (NHS Education for Scotland, 2008). Based on this and the fact that the majority of the patients included in this study were from the most deprived areas of Scotland, it was assumed that non-inclusion of private dentists in this study would have had minimum impact on the results reported. The last limitation of this study was that it only considered a three-year period. The MIDAS data included in this study was requested as a part of a larger PBPP application linking several other datasets together, one of which (the Prescribing Information System) only had data available from 2009 (Chapter 4). As a result, a three-year time-period was selected so as to maintain consistency. Nevertheless, given the changing trends of oral cancer reported in Chapter 2, the results of this study provide a recent estimate of the number of patients a general dental practitioner in Scotland may expect to encounter per year.

Interpretation of the estimates of the time elapsed before a general dental practitioner would encounter a patient with oral cancer has to be

considered in the context of the current guidelines for early detection and referral of head and neck cancer which suggest that identification of mucosal abnormalities require urgent referral (NICE, 2015a; NHS Scotland, 2016b). A recent systematic review and meta-analysis found that the conversion rate, that is, the proportion of patients with oral cancer who were referred within two weeks was approximately 10%, while the detection rate, that is, the proportion of patients with oral cancer who had been referred under the two-week rule was approximately 40% and increasing (Langton et al., 2016). This suggests that approximately 60% of patients with oral cancer are referred out-with the two-week referral pathway. Moreover, there appears to be an increasing number of patients with head and neck conditions, including oral potentially malignant disorders (OPMDs), that are being referred, but fewer patients are being diagnosed with head and neck cancer.

Previous authors have noted that patients with oral cancer do not generally present at general dental (or indeed medical) practices (Gómez et al., 2010). Therefore, the question of whether early detection of oral cancer is feasible has been raised, given the complex range of factors associated with referral pathways into care and definitive diagnosis and treatment. One major factor may be the fact that early oral cavity cancer and oropharyngeal cancer may be asymptomatic or cause subtle mucosal changes. Access to primary dental care or medical services may also be more difficult or limited among those at highest risk, that is, those from poorer socioeconomic circumstances or among older groups (Mercer and Watt, 2007). Other problems associated with early detection and referral delays include professional issues such as limited capability to undertake full clinical examination, training issues, or potential capacity issues (scheduling issues, payment etc.) (Güneri and Epstein, 2014). To this complex mix of factors, the researcher proposes that the underlying burden of disease is an additional factor that needs careful consideration.

## 3.6 Conclusion

In conclusion, despite being a low volume cancer, these results show that the hitherto encountered anecdote that a dentist may come across only two patients with oral cancer in his/her lifetime is not quite true. The original question “is early detection of oral cancer a realistic expectation?” remains somewhat rhetorical. Although the findings confirm that the rarity of the condition compounded by the lower attendance among those who were diagnosed with oral cancer will likely impact on the dentist’s ability to detect oral cancer early, it is worth reiterating that national guidelines do not expect general dental practitioners to make a diagnosis of oral cancer, but rather to identify sustained abnormalities and refer in a timely manner (NICE, 2015a; NHS Scotland, 2016b).

These findings indicate the importance of developing early detection strategies for primary dental care services that consider the changing patterns and rarity of the condition. Moreover, it is important to continue to work to develop and evaluate innovative strategies for dental services to reach out to those who do not attend regularly, to better network dental with other primary care services, and to explore the possibility of early detection strategies in alternative settings.

# 4 Missed opportunities for early detection of oral cancer: the role of primary health care dental and medical services.

## 4.1 Introduction

The literature review presented in Chapter 1 of this thesis discussed the potentially pivotal role of dentists in the early detection and prompt referral of oral cancer through regular patient contact and routine examination of the soft tissues of the mouth. However, this is also largely dependent on patients consulting dentists frequently enough to achieve this. Research from around the world suggests that the proportion of patients with head and neck cancer that had contacted a general dental practitioner regularly was considerably low, thus automatically limiting opportunities for early detection in the dental setting. A case-series analysis that was completed in a tertiary referral centre in the Netherlands reported that only 12% of their study sample (n=306 patients that were diagnosed with head and neck cancer between 2000 and 2002) had contacted a dentist first upon detecting symptoms, and 82% had consulted a general medical practitioner instead (Tromp et al., 2005). This was in agreement with another clinical cohort study that reported that the majority of patients that were diagnosed with oral cavity and oropharyngeal cancer between January 2005 and December 2009 in one teaching hospital in Western Australia did not have regular contact with a dentist (mean duration since last dental visit: 5.6 years) (Frydrych and Slack-Smith, 2011). More locally, two studies used data from the British Household Panel Survey to demonstrate that the "inverse screening law", which suggests that those at the highest risk of developing cancer are also least likely to consult a primary dental care service regularly, was applicable for oral cancer in Britain (Netuveli et al., 2006; Yusof et al., 2006). Chapter 3 of this thesis reported similar results for Scotland, with the majority of patients that were diagnosed with oral cavity and oropharyngeal cancer between 2010 and 2012 having made no contact with a general dental practitioner in the two years prior to diagnosis.

These studies highlighted the role of alternative settings, particularly general practitioners and other specialist practices, in the early detection of head and neck cancer. Prout et al. (1990) first examined 130 patients that were diagnosed with head and neck cancer between September 1st 1985 and March 31st 1988 in Boston, and reported that 94% of them had visited a healthcare provider at least once in the 24 months prior to diagnosis. Moreover, the services contacted were typically those that the subjects considered as their "regular source of care", emphasising the need to integrate these services in strategies for the early detection of cancer. The general consensus of literature from around the world, reviewed previously in Chapter 1, was that the majority of patients with head and neck cancer exhibited poor dental attendance patterns and preferred consulting general practitioners upon self-discovery of symptoms instead (Reid et al., 2004; Paudyal et al., 2014; Ligier et al., 2016).

In the United Kingdom, Crossman et al. (2016) conducted a postal questionnaire study among 200 patients with oral and oropharyngeal cancer randomly selected from the 2010 Cancer Patient Experience Survey (which consisted of 67,713 adults treated for cancer between January and March 2010 at one of the 158 National Health Service hospitals in England), and collected information on all of the health service contacts made by the patients before diagnosis of cancer and the symptoms that had prompted them to do so. They reported that only 32% of the patients had been referred to secondary care by a dentist, while 56% had been referred by a general practitioner instead. The authors concluded that general practitioners played a crucial role in the early detection of oral cancer, and listed common signs and symptoms that could be used for assessment and decision-making. In England, the National Cancer Intelligence Network linked data from the Administrative Hospital Episode Statistics database with Cancer Waiting Times data, cancer screening programme data, and cancer registration data and examined the "Routes to Diagnosis" for patients that were diagnosed with cancer (all sites) between 2006 and 2013 (Elliss-Brookes et al., 2012). Their results showed that 21% of all oral

cavity cancer and 26% of all oropharyngeal cancer diagnoses in England occurred following GP referrals in 2013. Moreover, diagnoses via the "Two-weeks Wait (TWW)" route (defined as including "all urgent GP referrals with a suspicion of cancer") and the "Other Outpatient" route (defined as "an elective route starting with an outpatient appointment") had increased between 2006 and 2013, and there was a possibility that some of the referrals via the latter route ("Other Outpatient") were originally initiated by general practitioners (Elliss-Brookes et al., 2012; NCIN, 2017).

Thus, collectively, the evidence appears to suggest that opportunistic screening for oral cancer, if limited to dental practitioners only, may miss a large fraction of the population at highest risk, and early detection strategies should extend to include general practitioners and specialist services too. However, to date, this has not been tested in a country with very good population dental service coverage such as Scotland.

Lyratzopoulos et al. (2015) defined missed opportunities as "instances where post-hoc judgement indicates that alternative decisions or actions could have led to a more timely diagnosis, that is, something different could have been done or considered under the given circumstances to reach a more prompt diagnosis", and identification of these could inform policy decisions and facilitate identification of areas where health services can be improved. The literature review presented in Chapter 1 discussed some of the available evidence on the existence of missed opportunities and the use of "surrogate markers", including multiple GP consultations before referral (Lyratzopoulos et al., 2012; Lyratzopoulos et al., 2013), emergency attendances (Elliss-Brookes et al., 2012; Mitchell et al., 2013), and abnormal findings (Murphy et al., 2014), to measure them.

Multiple consultations usually indicate prolongation of the time from presentation to referral, often resulting in progression of the clinical stage and a worsening of the outcomes. Evidence shows that their strongest predictors are usually tumour site and prevalence (Lyratzopoulos et al., 2014). A study utilising data from the 2010 National Cancer Patient

Experience Survey, which included 41,299 patients with 24 different types of cancer, reported large variations in the proportions of patients who had visited a general practitioner (GP) three times or more before referral, and that these variations appeared to be associated with the type of cancer diagnosed (lowest for breast cancer and malignant melanoma; highest for multiple myeloma and pancreatic cancer) (Lyratzopoulos et al., 2012). Women, younger patients, and those belonging to ethnic minority groups were more likely to consult a general practitioner more than three times pre-referral, although the variations were less prominent when examined by socioeconomic characteristics, thus providing a certain level of reassurance that a comprehensive coverage system like the National Health Service in the United Kingdom was capable of providing equitable care. The authors concluded that patients that were diagnosed with more well-known cancers were less likely to have had a large number of pre-referral consultations. Similar results were reported by the National Audit of Cancer Diagnosis in Primary Care, conducted in England in 2009/2010, where almost 38% out of 229 patients that were diagnosed with oropharyngeal cancer had consulted their general practitioner two or more times for cancer-related issues before being referred to a specialist for assessment (Rubin et al., 2011).

Several other studies also reported that the frequency of consultations and diagnostic tests increased in the months preceding diagnosis, and these have been reviewed previously in Chapter 1 (Christensen et al., 2012; Hansen et al., 2015). Christensen et al. (2012), in their national registry based case-control study that included all incident cases of cancer diagnosed between 2001 and 2006 and identified from the Danish Cancer Registry together with 1,272,100 gender-matched controls from the general population, reported that the patients with cancer exhibited a modest increase in general practitioner consultations five to six months before diagnosis and that this number peaked one month before diagnosis. The number of hospital visits and diagnostic examinations began to increase approximately three to four months before diagnosis and

escalated steeply two months before diagnosis. However, in contrast to Lyratzopoulos et al. (2012), these studies did not account for a referral period and considered diagnosis to be the end-point. As a result, it was unclear at what point in time these contacts shifted from being missed opportunities for early detection via screening to becoming missed opportunities for early diagnosis that were caused by delays in the diagnostic process itself. Nevertheless, they did highlight the significance of unusual patterns of health service contacts in the identification of opportunities for early detection.

Although these kind of epidemiological data do not provide any information regarding the nature of these consultations and not all of these instances would have necessarily been associated with missed opportunities for early detection of cancer, it did provide a strong indication that there were potential missed opportunities amongst at least some of the patients with cancer (Rubin et al., 2011; Lyratzopoulos et al., 2015). Chapters 2 and 3 of this thesis showed that the incidence burden of oral cancer was relatively low in Scotland and the majority of the patients did not contact a primary dental care service on a regular basis. Therefore, dentists were likely to encounter a limited number of patients in their career, thus limiting opportunities for early detection of oral cancer. Nevertheless, there are several other services (e.g. general medical practices, hospital outpatient and inpatient/day-case services, and pharmacies) through which a cancer patient can enter the health care system, and all of these contacts can be considered as opportunities for early detection. However, currently there are no studies that examine the healthcare service contacts made by patients with oral cancer in Scotland in the two years prior to diagnosis.

Scotland currently has “some of the best administrative and care data in the world” (Pavis and Morris, 2015), with the Information Services Division of National Services Scotland charged with the responsibility of ensuring the quality, completeness, and comparability of the data for over 40 years (ISD Scotland, 2017f). The Scottish national strategy and framework for data linkage, *“Joined-up Data for Better Decisions: A strategy for*

*improving data access and analysis",* was developed with the aim of improving access to data and subsequent analysis through data linkage executed in a legal and ethical manner (The Scottish Government, 2012a). This framework defined data linkage as "the joining of two or more administrative or survey datasets to greatly increase their value for analysis", mainly for research and statistical purposes that help understand groups or populations. Therefore, this study intends to utilise the wealth of routinely collected, administrative health data and data linkage capability in Scotland to link various national administrative databases and examine the healthcare service contacts that were made by patients with oral cancer in the years prior to diagnosis, with the aim of identifying potentially missed opportunities that can be harnessed in the future for early detection efforts.

## 4.2 Aims, hypotheses and objectives

The main ***aim*** of this study was to examine if there was any evidence of potentially missed opportunities for early detection of oral cancer (oral cavity and oropharyngeal cancer) in primary dental care settings, and to also explore the possibility of such opportunities in alternative health care settings in Scotland.

The ***hypotheses*** were:

**Chapter 4 hypothesis (a):** There are a number of potentially missed opportunities for the early detection of oral cancer in dental and other healthcare services.

**Chapter 4 hypothesis (b):** These potentially missed opportunities increase in frequency in the months directly prior to the start of the referral period.

The ***objectives*** were:

**Chapter 4 objective (a):** To create a longitudinal population cohort by linking the available routine administrative health service data including hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescriptions with the Scottish Cancer Registry oral cancer data.

**Chapter 4 objective (b):** To calculate the proportion of patients with oral cancer who had contacted all/any of the healthcare services (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescriptions) in the two years prior to diagnosis, and examine the mean number of contacts made over the same period.

**Chapter 4 objective (c):** To calculate the proportion of patients with oral cancer who had contacted each of the services (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescription) individually over the two years prior to the start of the referral period, examine the mean number of contacts made with each service, and assess any variations by year and six-month periods prior to the start of the referral period in order to identify any alternative opportunities for early detection efforts.

**Chapter 4 objective (d):** To undertake a focused examination of primary dental care service contacts of patients with oral cancer by analysing the frequency and reasons for consultation by year and six-month periods in order to identify any "potentially missed" opportunities for early detection in the dental setting.

**Chapter 4 objective (e):** To examine the nature of contacts made by patients with oral cancer during the one month period directly preceding diagnosis, defined here as the "referral period", in order to assess the feasibility of using this data to examine the routes to diagnosis of oral cancer.

## 4.3 Patients and methods

This section describes the ethical and information governance approval processes of the study, reviews the datasets used and the data requested from them, and clarifies the data linkage process undertaken. It then goes on to set out the data management process undertaken to create the final linked cohort used, and finally discusses the statistical analysis methods used to meet the specific research objectives.

### 4.3.1 Ethical considerations and data access

An application for ethical approval was made to the University of Glasgow, College of Medicine, Veterinary and Life Sciences Ethics Committee, and was approved on 15th December 2015 (Appendix 5).

As the data to be used in this study were generated by the NHS and identifiable, access could only be arranged upon approval from the national information governance committee, the Public Benefit and Privacy Panel for Health and Social Care (PBPP). This application process has been discussed previously in Chapter 3. Briefly, a research protocol that detailed the background, aims and objectives, and the implications of the study to be undertaken was first submitted to the electronic Data Research and Innovation Service (eDRIS), which serves as a single point of contact to assist researchers in navigating the PBPP application process and organising data access in a secure environment (ISD Scotland, 2017g). Thereafter, a research co-ordinator was assigned, who assisted with the PBPP application process including identification of available datasets and relevant variables. The necessary Information Governance training was obtained by completion of an e-learning course (Research Data and Confidentiality e-learning course) conducted by the Medical Research Council on 22nd September 2015 (Appendix 7). The final PBPP application was submitted on 21st January 2016 for consideration at the panel meeting that was held on the 23rd of February 2016. Following several unforeseen time delays, PBPP approval was finally received on the 21st of April 2016 (Appendix 9), and

the application was then forwarded to the relevant teams for processing and uploading of data onto the NHS NSS eDRIS National Safe Haven (remote access). There were further unexpected delays from eDRIS at this stage, and the completed linked datasets were finally uploaded in October 2016.

## 4.3.2 Datasets available and used

The starting point of this study was an oral cancer (defined as C00.3-C00.9, C01-C06, C09-C10, C14) diagnosis that was recorded on the Scottish Cancer Registry, and this was used to "look back" into the health records available. Based on NHS Scotland Health Service data availability (ISD Scotland, 2017f), this study utilised the hospital inpatient/day-case (SMR01— Scottish Morbidity Record 01), hospital outpatient appointments (SMR00 — Scottish Morbidity Record 00), prescriptions (PIS), and primary dental care (MIDAS — Management Information and Dental Accounting System) datasets. Unfortunately, primary care general practitioner data were not available, and prescriptions issued by GPs were used as a proxy for GP contact instead.

### 4.3.2.1 Scottish Cancer Registry

The Scottish Cancer Registry (known as "SMR06"), which was started in 1958, collects and stores information on all Scottish residents that have been diagnosed with malignancies (ISD Scotland, 2017d). The data include a patient's personal, demographic, diagnostic (including site, histology, hospital of diagnosis, tumour behaviour), and geographical information (including socioeconomic status measured by SIMD and Carstairs, NHS area board, and electoral ward). Although tumour stage and grade for certain cancers (namely breast, cervical, and colorectal cancer) have been recorded from 1997 onwards, these data are still unavailable for head and neck cancer. Routine indicators, computer validation, and ad-hoc studies of accuracy and completion are used to monitor the quality of the registry data. In 2016, the level of completeness of data in SMR06 was 96% for patient information and 96.4% for tumour information (UKIACR, 2017). The

average head and neck cancer case ascertainment across NHS boards in Scotland was 95% (ISD Scotland, 2016a).

For the purpose of this study, the data on all patients that were diagnosed with head and neck cancer between 2008 and 2012 were requested (ICD-10 codes C00–C14 & C32; detailed codes requested shown in Appendix 1). The variables included were age at the time of diagnosis, sex, health board of residence, Scottish Index of Multiple Deprivation decile of residence at the time of diagnosis, date of diagnosis, and ICD-10 diagnosis codes.

#### 4.3.2.2 Management Information and Dental Accounting System (MIDAS)

The Management Information and Dental Accounting System (MIDAS) database is the computerised payment system for the General Dental Service in Scotland. It processes and stores information on all individuals that are registered with an NHS dentist in a dynamic fashion, allowing figures to be added daily. Therefore, the number of patients registered changes with time, depending on when the data are extracted. There are approximately 500 treatment fee codes (Items of Service) included in the Statement of Dental Remuneration (SDR), which is the primary dental care contract for NHS Scotland (PSD, 2017). A course of treatment is one where at least one of these Items of Service have been claimed by the primary care dentist on a GP17 payment form and submitted to the Practitioner Services Division of NHS Scotland, who then verifies the claim and pays the list number that the fee-code was claimed under. This dataset contains personal identifiers and geographical information of the practitioner and patient, start and stop dates of treatment, information on treatments received, and financial information (PSD, 2017).

Records of all of the dental contacts that were made by patients with head and neck cancer (as described in section 4.3.2.1) between 2003 and 2012 were requested. The variables included were the patient's sex, age at the time of contact, socioeconomic deprivation level (measured by SIMD v2009), start and stop dates of treatment, and treatment received. Here,

the “start date of treatment” variable was used as an indicator of contact, and each unique date was considered as one contact irrespective of the number of claims made on that date.

#### 4.3.2.3 Hospital inpatient/ day-case admissions (SMR01)

This dataset (known as “SMR01”) collects episode-level data on day-case and hospital inpatient admissions and discharges from acute specialties across Scotland (ISD Scotland, 2017h). Each episode, defined as “an inpatient episode or a day-case episode”, is initiated by a referral (including re-referrals) or admission and is ended by a hospital discharge. This dataset contains patient identifiers as well as information on the location of the episode, the admission type, patient condition, and waiting times. Additionally, geographical information such as SIMD and health board are also included. The diagnosis and treatment fields are mandatory for this dataset and, therefore, are of good quality and have high levels of completeness, (88% and 94% accuracy for diagnosis and treatment, respectively) (ISD Scotland, 2017f).

Records of all of the hospital inpatient/day-case contacts made by patients with head and neck cancer (as described in section 4.3.2.1) between 2003 and 2012 were requested. The variables included were each patient’s sex, age at the time of contact, socioeconomic deprivation level (measured by SIMD v2009), date of admission, date of discharge, and specialty attended. Here, the “date of admission” variable was used as an indicator of contact, and each date was considered as one contact irrespective of the number of procedures undertaken on that date.

#### 4.3.2.4 Hospital outpatient appointments (SMR00)

This dataset (known as “SMR00”) records episode-level data on patients who are attending hospital outpatient clinics in all specialties (ISD Scotland, 2017i). This includes new and recall appointments. It contains patient identifiers (e.g. name, age, and sex), information on the procedures performed, and geographical measures such as SIMD status and

health board. Data on the diagnosis and treatment procedures that were undertaken are limited in this dataset as it is not mandatory to complete these fields (ISD Scotland, 2017j). However, data in relation to patient contact and dates are mandatory due to national requirements to monitor waiting times (ISD Scotland, 2017b).

Records of all hospital outpatient contacts made by the patients with head and neck cancer (as described in section 4.3.2.1) between 2003 and 2012 were requested. The variables included were the patient's sex, age at the time of contact, socioeconomic deprivation level (measured by SIMD v2009), date of attending clinic, specialty attended, and referral source. Here, the "date of attending clinic" variable was used as an indicator of contact, and each unique date was considered to be one contact irrespective of the number of procedures undertaken on that date.

#### 4.3.2.5 Prescribing Information System (PIS)

The Prescribing Information System (labelled "PIS") contains all primary care prescribing and dispensing information at the patient-level, electronic messaging data, as well as various financial items (NHS Scotland, 2017a). The information is supplied by the Practitioner Services Division (PSD) who are responsible for processing and pricing all of the prescriptions that are dispensed in Scotland. The vast majority of these prescriptions (70%) are written by general practitioners, and the remainder are written by other authorised personnel such as dentists and nurses (Audit Scotland, 2013). This dataset contains information on the patient, prescriber, and dispenser as well as data on the items that are prescribed, dispensed, and reimbursed. The PIS dataset only became nationally available in 2009, as the level of capture of patient identifiers before this was low (68% in 2003 as opposed to 87% in 2009) (Alvarez-Madrazo et al., 2016). Although the individual-level data has a high level of completeness, it is influenced by the prescriber (e.g. patient identifier capture was 99% for general practitioners and only 2% for dentists in 2014) as well as the type of medicine prescribed (Alvarez-Madrazo et al., 2016). The low patient

identifier capture for dentists is mainly because they do not have access to the electronic prescribing system, and they only recently gained access to the CHI (Community Health Index) database. However, for the purposes of this study all dental contacts were captured via the MIDAS database.

Records of all of the prescriptions that were issued to patients with head and neck cancer (as described in section 4.3.2.1) between 2009 and 2012 were requested. The variables included were the patient's sex, age at the time of contact, socioeconomic deprivation level (measured by SIMD v2009), date of issue of prescription, prescriber type, and item prescribed. Here, the "date of issue of prescription" variable was used as an indicator of contact, and each unique date was considered to be one contact irrespective of the number of claims that were made on that date. The prescription data were to be used to infer contact with a general practitioner (where it was not a repeat prescription) and a pharmacist. Although the original intention of this study was to request primary care general practitioner contact information, there was a delay of several years in establishing a GP database in Scotland. It has only finally commenced in 2017 and is known as the Scottish Primary Care Information Resource (SPIRE) (ISD Scotland, 2017k).

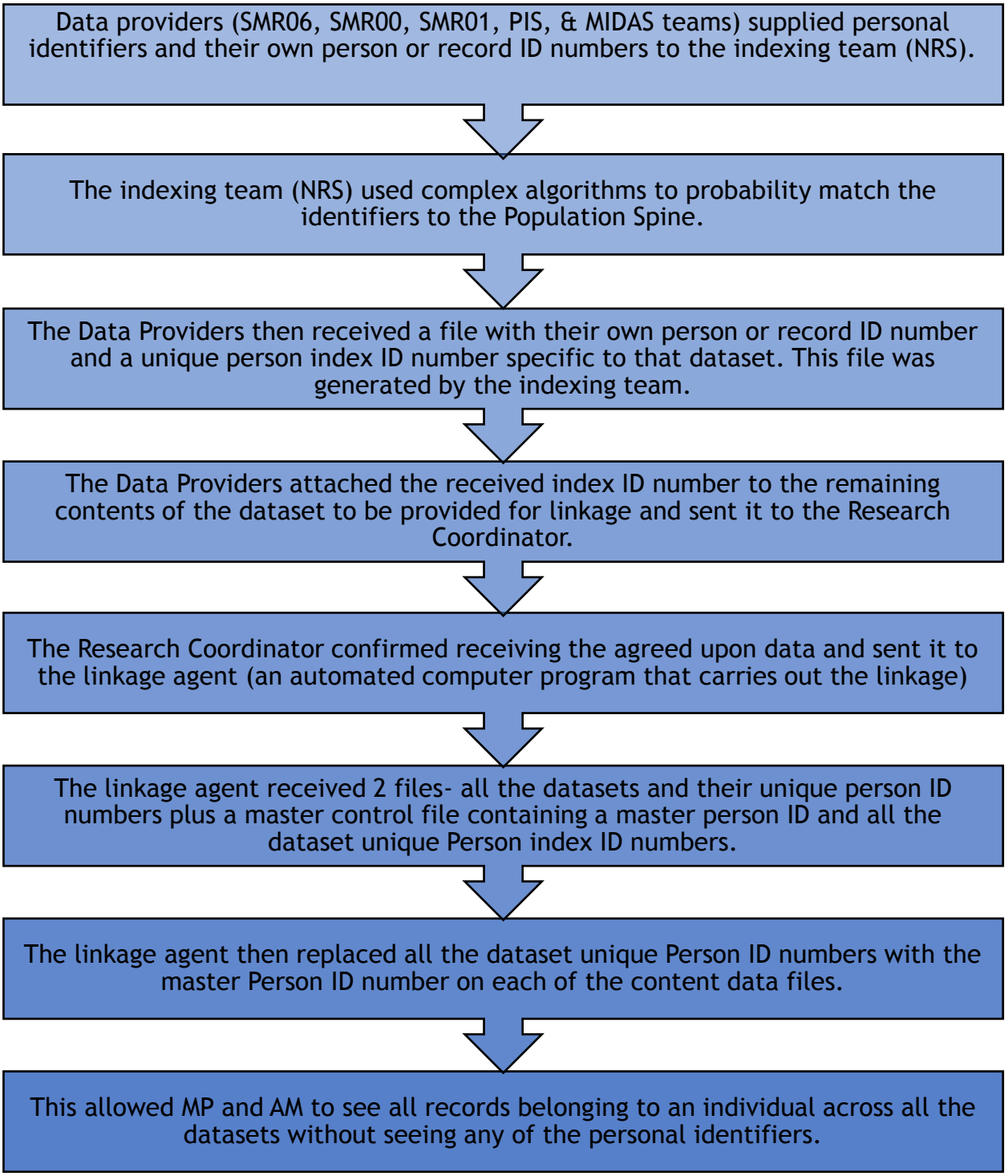
### 4.3.3 Data linkage

Data linkage was performed using probability matching techniques that were based upon the Howard Newcombe principles, and was performed by a third party (University of Edinburgh) on behalf of the electronic Data Research and Innovation (eDRIS, 2017a). After the initiation of the project and the securement of a data sharing agreement (Appendix 10), the Data Controllers (NHS National Services Scotland Information Services Division) prepared the data as per the specifications of the agreement and sent a file containing only personal identifying information to the indexing service, provided by National Records Scotland (NRS). Indexing ensures that all personal information such as names and addresses are kept separate from the rest of the process, thus maintaining anonymity.

Thereafter, NRS matched this file to a “linking population spine” that contained the name, gender, address, and date of birth of all individuals in Scotland who had contacted the NHS to generate a “source key”. This “source key” was sent back to the Data Controllers so that they could replace their own IDs and then pass the data on to National Services Scotland (NSS). NRS also generated a second “linking key” which was sent to NSS to allow them to join the SMR06, SMR00, SMR01, PIS, and MIDAS datasets. Upon receiving the anonymised dataset from the Data Controllers, NSS checked that the file included only the requested data and then used the keys to join the five relevant datasets (SMR06, SMR00, SMR01, PIS, and MIDAS) together. The linking ID was then replaced with a new project ID and the dataset was placed in a Safe Haven that could be accessed for analysis (only by MP and supervisor AM). This step ensured the quality of the data and also made sure that only agreed information was placed in the Safe Haven, thus providing additional security (eDRIS, 2017a; eDRIS, 2017b).

The analysis of this linked dataset was completed within the safe haven, which is a stand-alone secure facility with strictly controlled access. The researchers could only use the software provided within the safe haven to analyse the data, and all of the outputs that were produced were then checked for any potential risk of disclosure of identifiable data before being moved out of the haven. No data could be moved out of the Safe Haven at any point (eDRIS, 2017a; eDRIS, 2017b). Figure 4-1 shows a flowchart of the steps of data linkage that were undertaken.

**Figure 4-1: Data linkage process**



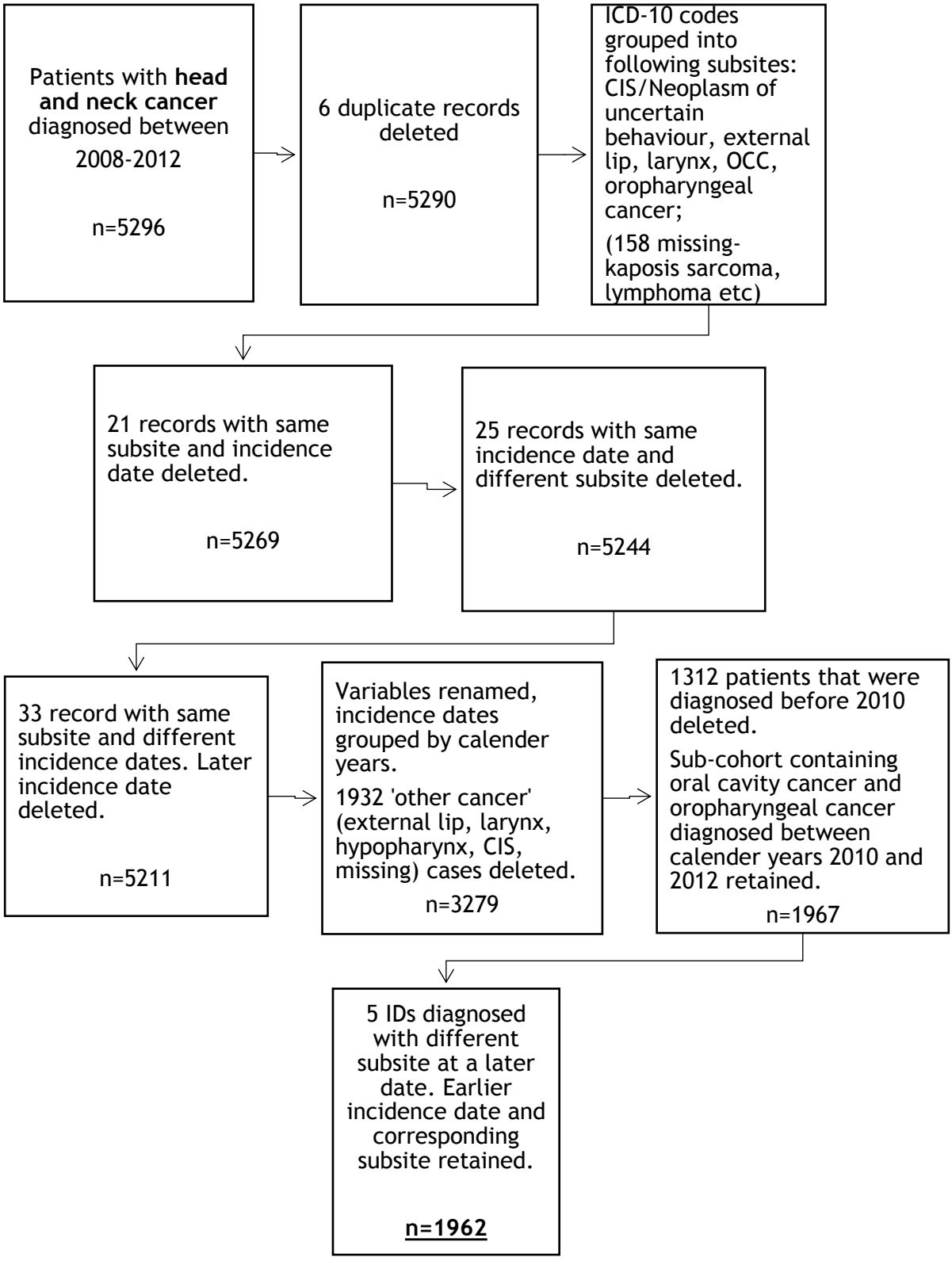

SMR06: Scottish Cancer Registry; SMR00: Hospital outpatient services; SMR01: hospital inpatient/ day-case service; MIDAS: Management Information and Dental Accounting System; PIS: Prescribing Information System; NRS: National Records Scotland.

### 4.3.4 Data management

***Scottish Cancer Registry (SMR06):*** the original linked dataset provided by eDRIS consisted of 5296 records of patients that were diagnosed with primary head and neck cancer (ICD-10 codes requested shown in Appendix 1) between 2008 and 2012 (see flowchart of data management process that yielded the final sample in Figure 4-2). Briefly, after deleting six duplicate records, the remaining 5290 observations were divided into three groups of subsites, namely, oral cavity cancer, oropharyngeal cancer, and other. These subsites of interest were defined as follows: oral cavity cancer — inner lip (C00.3 — C00.9), other and unspecified parts of tongue (C02), gum (C03), floor of mouth (C04), palate (C05), and other and unspecified parts of mouth (C06); oropharyngeal cancer — base of tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), and pharynx (C14); and other — all remaining ICD-10 codes shown in Appendix 1. Thereafter, a total of 84 records with discrepancies in the data were deleted, including 21 records with the same subsite and incidence date and 25 records with different subsites and the same incidence date. Additionally, 33 records with the same subsite and different incidence date, and five records with different subsite and incidence date were found. The earlier incidence date was retained in both cases. For the purposes of this study, only patients that were diagnosed with oral cavity cancer (n=1108) and oropharyngeal cancer (n=854) between 2010 and 2012 (n=1962) were retained, yielding a final sub-cohort of 1962 patients (Figure 4-2). The original plan was to examine the individual subsites separately, in keeping with the rest of the thesis. However, upon commencement of analysis, the numbers for oral cavity cancer and oropharyngeal cancer individually were found to be too small to analyse separately, and a decision was made to combine and examine them as oral cancer instead. Nevertheless, it has been argued that dentists have a potential role in the early detection of both sites and, as stated previously, most of the guidelines for the detection of cancer consider the two subsites together as oral cancer as their signs and symptoms overlap considerably (lump in the neck, problem

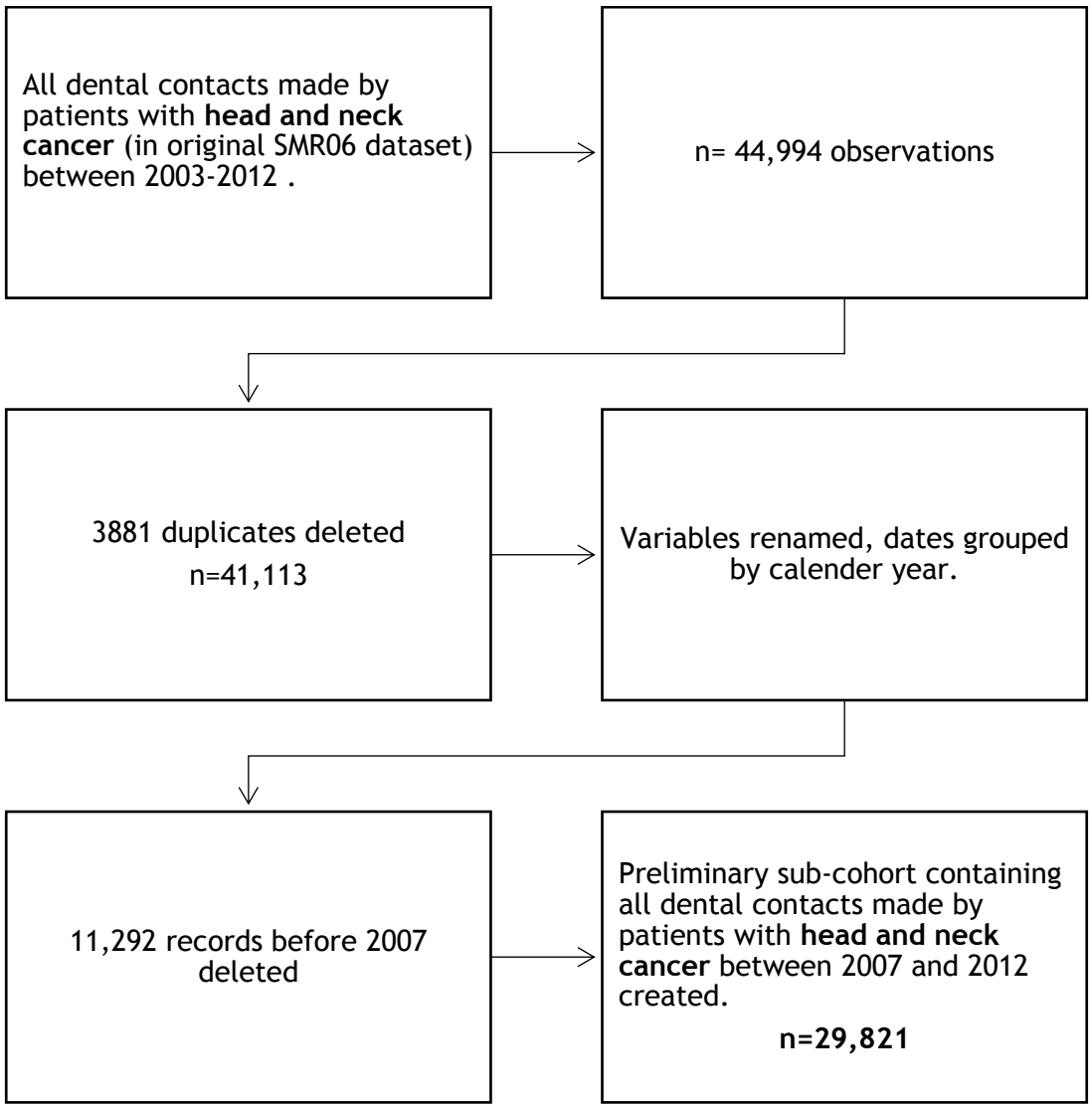
swallowing, lumps or ulcers in the mouth, and hoarseness of voice) (Kreimer, 2014; NICE, 2015a; NHS Scotland, 2016b).

**Figure 4-2: Scottish Cancer Registry — Initial data management:**



***Management Information and Dental Accounting System (MIDAS)***: This dataset contained records of all of the dental contacts that were made by patients with head and neck cancer (diagnosed 2008 — 2012) between 2003 and 2012. The original linked dataset contained 44,994 observations. Upon examination, 3881 duplicate records (records with identical ID number and all other fields) were identified and deleted. The variables were renamed for convenience, and the "start date of treatment" variable was then used to create a new calendar year variable. This variable was then used to retain all contacts between 2007 and 2012. Thus, the preliminary sub-cohort consisted of 29,821 records (Figure 4-3).

**Figure 4-3: Management Information and Dental Accounting System — Initial data management**



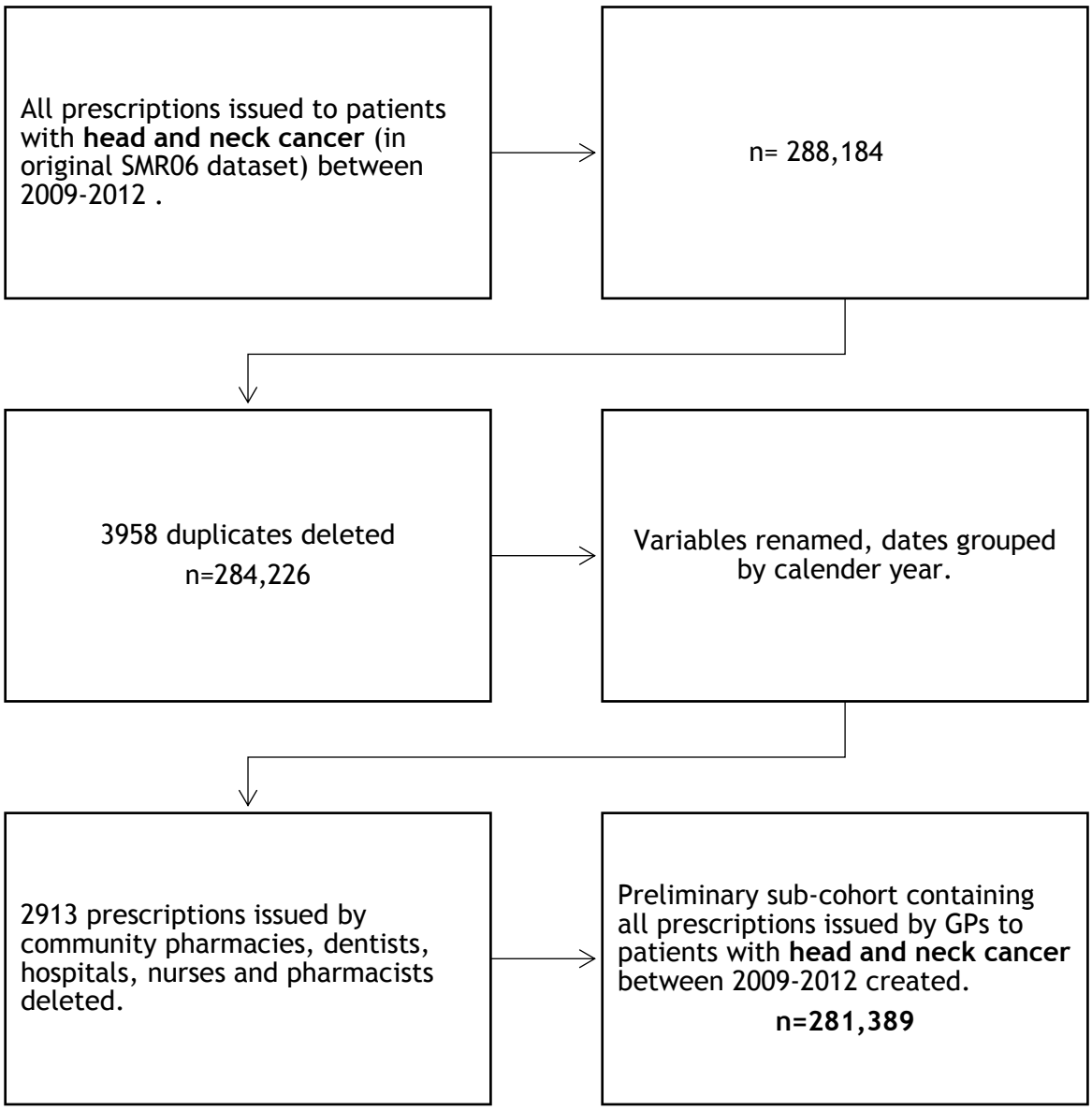
The approach to the analysis was adapted to the Scottish Dental Workforce Report, (NHS Education for Scotland, September 2012) and the treatment code items (n=500) were grouped into broad categories of appointment type, as follows — "Exam & Diagnosis", "Emergency" and "Treatment". Briefly, the "Exam and Diagnosis" group included all assessment and diagnostic codes including examination and radiographs, the "Emergency" group consisted of all treatment codes that indicated emergency intervention, and the "Treatment" group consisted of all procedures (e.g. conservative prosthetic, endodontic, and oral surgery) that could be performed by a dentist (treatment claim codes in each group are shown in Appendix 2). Finally, the number of contacts that were made by the patients over specific periods of time was used to create a new variable to determine the patient's frequency of dental attendance.

***Prescribing Information System (PIS):*** This dataset contained information on all of the prescriptions that were issued to patients with head and neck cancer (diagnosed 2008 — 2012) between the period of 2009 to 2012. The time period that was examined for this dataset differed from the other datasets due to a limited availability of data (with the PIS dataset only becoming nationally available from 2009). The original linked dataset that was received contained 288,184 records. Of these, 3958 were duplicates (records with identical ID number and all other fields) and were deleted, leaving a total of 284,226 records. As stated before, data on general practitioner contacts were unavailable in Scotland, and the PIS system could be considered as a proxy for GP contacts. Therefore, after renaming the variables for convenience, only those prescriptions that were issued by general practitioners were retained, which resulted in a preliminary sub-cohort of 281,389 records (Figure 4-4).

For the purpose of this study, the "date of issue of prescription" variable was considered as an indicator of GP contact and, once again, each date was considered as one contact irrespective of the number of prescriptions issued. Unfortunately, the PIS database does not have a flag for repeat prescriptions, preventing us from identifying and excluding them from the

dataset. No detailed examination of the type of medications that were prescribed was undertaken as this would require expertise in bioinformatics to handle and analyse such large volumes of data, even for this small sample, and this was considered beyond the scope of this study. Thus, PIS data was unfortunately not a "conservative" estimate of general practitioner contact.

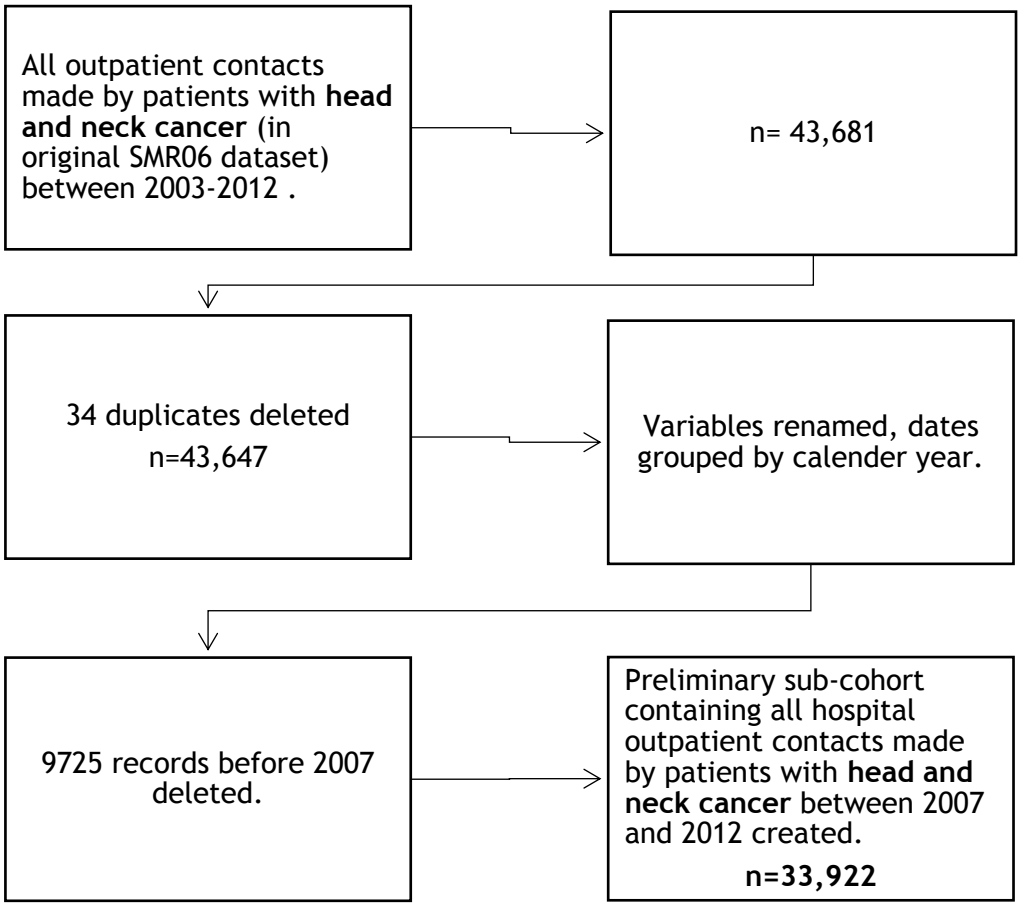
**Figure 4-4:Prescribing Information System — Initial data management**



***Hospital outpatient attendance (SMR00):*** the original linked dataset that was received contained 43,681 records of outpatient contacts made by patients with head and neck cancer (diagnosed between 2008 — 2012) between 2003 and 2012. Of these, only 34 were duplicates (records with identical ID number and all other fields) and were deleted. Thereafter, the variables were renamed for convenience, and the "clinic attendance date" variable was used to create a new calendar year variable. For the purposes of this study, this new variable was then used to retain all records between 2007 and 2012 only, which resulted in a preliminary sub-cohort of 33,922 records (Figure 4-5).

In this case, the "clinic attendance date" was used as an indicator of contact and, once again, each unique date was considered as one contact. This was considered to be a "conservative" estimate of contact.

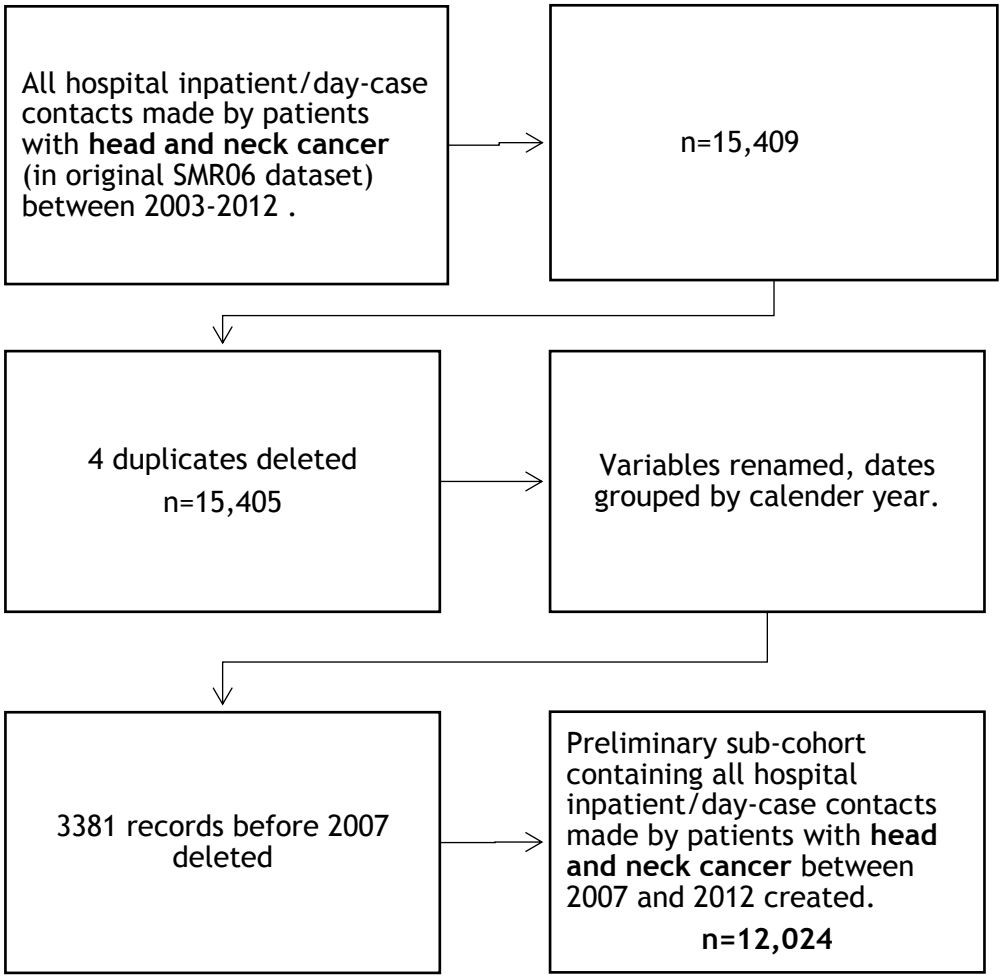
**Figure 4-5: Hospital outpatient attendance — Initial data management**



***Hospital inpatient/ day-case (SMR01):*** the original linked dataset contained 15,409 records of SMR01 contacts made by patients with head and neck cancer (diagnosed between 2008 – 2012) between 2003 and 2012. Of these, only four records were duplicates (records with identical ID number and all other fields) and were deleted. Thereafter, the variables were renamed for convenience, and the "admission date" variable was used to create a new calendar year variable. For the purposes of this study, this new variable was then used to retain all records between 2007 and 2012 only, which resulted in a preliminary sub-cohort of 12,024 records (Figure 4-6).

The "admission date" variable was used as an indicator of contact, and each unique date was considered as one contact. This was considered to be a "conservative" estimate of contact.

**Figure 4-6: Hospital inpatient/ day-case – Initial data management**



## 4.3.5 Final linked cohort

### 4.3.5.1 Creation of the final cohort

The individual datasets received from eDRIS were all linked to one another by means of a unique identification number, the CHI (Community Health Index) number. The Community Health Index is a register of all patients who have used the Scottish National Health Service, and the identification number is usually assigned at the point of first contact with the NHS. In other words, each patient had a unique ID number that remained consistent across all datasets. Upon completion of initial data management, the preliminary sub-cohorts created from the individual datasets were combined using this number to create the final cohort to be used for analysis. The SMR06 dataset created was considered as the master ID file, and only records of patients that were included in this cohort were retained in the final dataset (Figure 4-7). The SIMD decile of the patient's residence, recorded by the Scottish Cancer Registry, was considered to be the master SIMD and was used for all socioeconomic analyses. If a particular ID number did not appear in any one of the databases, it was assumed that the particular patient had made no contact with that service within the study period.

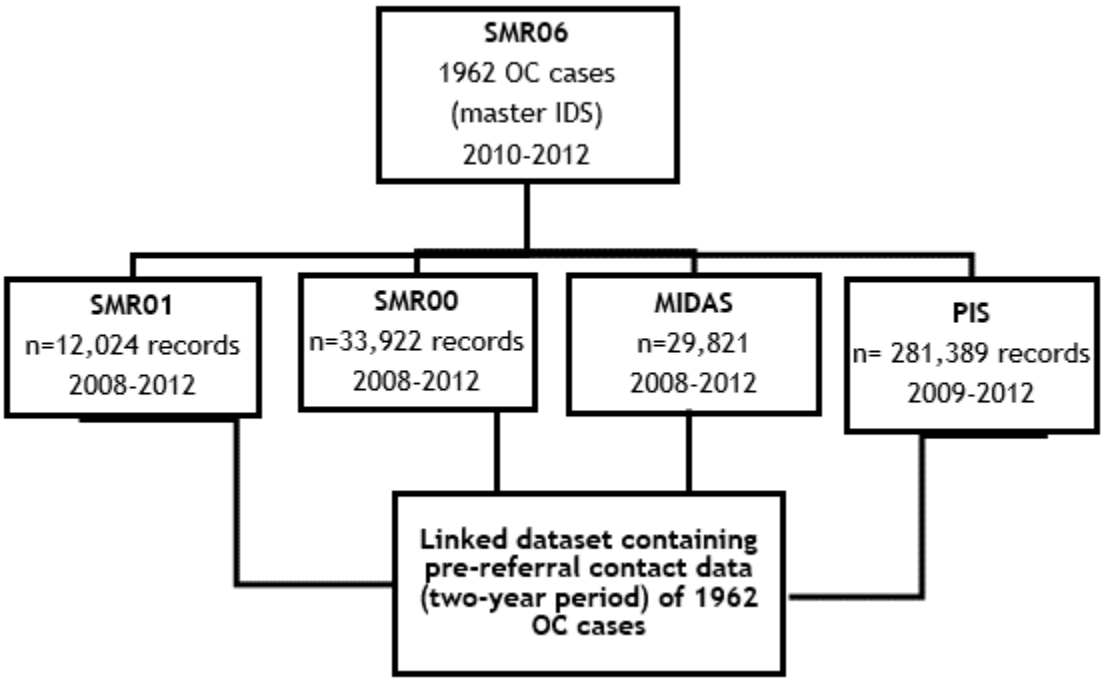
Therefore, the final cohort consisted of all primary dental care, hospital outpatient, and hospital inpatient/ day-case records between 2007 — 2012 and all GP prescription records between 2009 — 2012 for the 1962 patients that were diagnosed with oral cancer between 1st January 2010 and 31st December 2012.

### 4.3.5.2 Definition of oral cancer used

The original aim, as stated in Chapter 3, was to investigate oral cancer, oral cavity cancer, and oropharyngeal cancer separately. However, given the relatively small numbers observed upon linking the datasets, a decision was made that detailed examination by subsite would not be feasible and

was outside the scope of this thesis. Instead, emphasis was given to oral cancer (oral cavity and oropharyngeal cancer combined; ICD10 codes C00.3-C00.9, C01-C06, C09-C10, C14) as dentists have a role in the early detection of both subsites, and most guidelines for the detection of oral cancer consider the two subsites together as their signs and symptoms overlap considerably (hoarseness of voice, lump in the neck, problem swallowing, lumps or ulcers in the mouth) (Kreimer, 2014; NICE, 2015a; NHS Scotland). Therefore, from an early detection perspective, combining the two subsites and examining them as "oral cancer" appeared to be more appropriate.

**Figure 4-7: Creation of final cohort of patients with oral cancer (2010-2012) for analysis**




SMR06: Scottish Cancer Registry; SMR00: Hospital outpatient services; SMR01: hospital inpatient/ day-case service; MIDAS: Management Information and Dental Accounting System; PIS: Prescribing Information System; OC: Oral Cancer.

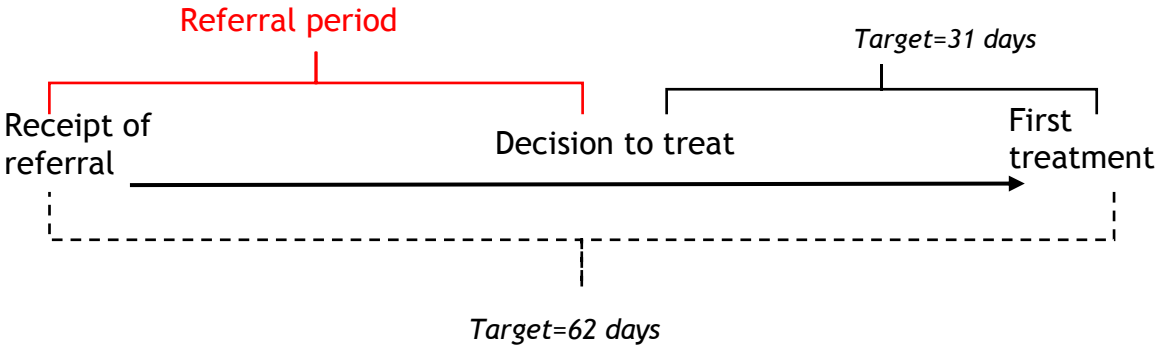
### 4.3.6 Statistical analysis methods

After initial data management and linkage, descriptive analysis was undertaken. Frequency tables (numbers and percentages) showing patient demographics of the cohort were generated.

Unfortunately, the referral date (and source) for patients with oral cancer was unknown from the routine administrative datasets available. However, the cancer waiting time targets of the Scottish Government are 62 days from the receipt of referral to first treatment and 31 days from decision-to-treat to first treatment (ISD Scotland, 2017b). For the purpose of this analysis, the decision to treat was assumed to be the same as the date of diagnosis. Therefore, given that 31 days out of the 62-day target was after the decision to treat (date of diagnosis), the referral period was unlikely to be more than 30 days. Based on this, a 30-day referral period (defined as the period from the receipt of referral up to the decision to treat) was selected for this analysis (Figure 4-8), and all healthcare service contacts made by the patients during this period were assumed to be part of the referral process. This was considered the appropriate cut-off for Scottish data given the referral guidelines (NHS Scotland, 2016b).

However, this would not be appropriate in case of patients who did not meet the national waiting time targets and, therefore, an additional sensitivity analysis that considered a two-month (60 days) referral period was also undertaken. This was similar to the approach adopted by Ligier et al. (2016), who adopted a more conservative and longer two-month referral period for their study.

**Figure 4-8: Visual representation of Waiting Time targets and definition of the referral period**

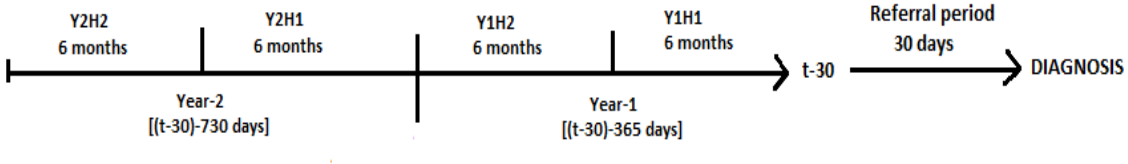



Thereafter, frequency tables showing the proportion of patients who had contacted any of the four services examined (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescription) in the two years prior to the start of the referral period (t–30) were generated. Additionally, the mean number of contacts made with each service over the entire pre-referral two-year period, individual years, and six-month periods were also calculated. A one-sample t-test was used to test the statistical significance of differences in the mean number of contacts between the different time periods, and also to provide a 95% confidence interval for the mean difference

For the purpose of this analysis, Year–1 was defined as the most recent 365-day period prior to the start of the referral period (t–30), while Year–2 represented the 365-day period preceding that (Figure 4-9).

In a similar way, Y1H1 was defined to be the most recent six months prior to the start of the referral period, Y1H2 represented the six-months preceding that, and so on until Y2H2 which represented the six-month period furthest away from the start of the referral period (Figure 4-9).

**Figure 4-9: Visual representation of cohort time periods leading up to oral cancer diagnosis.**




[t: date of diagnosis; Y1H1: Year—1 half 1; Y1H2: Year—1 half 2; Y2H1: Year—2 half 1; Y1H1: Year—2 half 2]

Additionally, a detailed analysis of the nature of all dental contacts in the two years preceding the start of the referral period was undertaken. Frequency tables including number and percentage by reason for contact were generated. McNemar's test was used to examine the statistical significance of within-person differences. This test was chosen as the dataset consisted of paired data.

Contacts made within the one-month referral period were also analysed separately. Particularly, the mean number of contacts made within this period overall and by each service was calculated. As mentioned previously, a sensitivity analysis investigating the two-month period preceding diagnosis ("t–60 days") was also undertaken to assess whether the referral period was a distinct period including high levels of hospital contacts. Additionally, the last service contacted before the start of the referral period was also examined. All data analyses were undertaken using SAS 9.4 on the National Safe Haven.

## 4.4 Results

At this stage, it is essential to draw attention back to the fact that the current study focuses on oral cancer and, unlike the previous chapters, does not consider the individual subsites (oral cavity cancer and oropharyngeal cancer). This decision was made based primarily on the numbers observed (oral cavity cancer=1108, oropharyngeal cancer=854)

upon commencement of analysis, and this has been discussed further in Section 4.3.4.

### 4.4.1 Cohort description - patient demographics

This study included 1962 patients that were diagnosed with oral cancer between 1st January 2010 and 31st December 2012 and registered with the Scottish Cancer Registry. Nearly two-thirds of these patients were males (n=1269, 65%), were above the age of 45 years (n=1846, 94%), and were from the most deprived areas of Scotland (SIMD 1: n=650, 33%) (Table 4-1).

Of these 1962 patients, the vast majority (95%, n=1867) had contacted at least one of the four services (hospital inpatient/ day-case, hospital outpatient, GP prescription, and primary dental care) in the two years prior to the start of the referral period (t–30) ("Ever" group), while only a very small proportion (5%, n=95) had not contacted any of the four services over the same period ("Never" group) (Table 4-1). A comparison of the patient profile of the two groups showed no major differences, with the majority of the "Ever" and "Never" groups being male (64% and 73%, respectively), above 45 years of age (94% and 95%, respectively), and from the most deprived areas of Scotland (SIMD 1: 33% and 32%, respectively) (Table 4-1).

**Table 4-1: Demographics of all patients with oral cancer diagnosed between 2010-2012 by contact with any healthcare service in the two years prior to the start of the referral period.**

| | All patients N (%) | Ever N (%) | Never N (%) |
|---|---|---|---|
| **Total** | **1962 (100.00)** | **1867 (95.16)** | **95 (4.84)** |
| **Sex** | | | |
| **Males** | 1269 (64.68) | 1200 (64.27) | 69 (72.63) |
| **Females** | 693 (35.32) | 667 (35.73) | 26 (27.37) |
| **Age** | | | |
| **0 - 25** | 10 (0.51) | 9 (0.48) | 1 (1.05) |
| **26 - 35** | 21 (1.07) | 17 (0.91) | 4 (4.21) |
| **36 - 45** | 85 (4.33) | 85 (4.55) | 0 (0.00) |
| **46 - 55** | 407 (20.74) | 374 (20.03) | 33 (34.74) |
| **56 - 65** | 630 (32.11) | 593 (31.76) | 37 (38.95) |
| **66 - 75** | 489 (24.92) | 473 (25.33) | 16 (16.84) |
| **76 - 85** | 263 (13.40) | 259 (13.87) | 4 (4.21) |
| **>86** | 57 (2.91) | 57 (3.05) | 0 (0.00) |
| **SIMD** | | | |
| **1 (most deprived)** | 650 (33.13) | 620 (33.21) | 30 (31.58) |
| **2** | 410 (20.90) | 396 (21.21) | 14 (14.74) |
| **3** | 412 (21.00) | 390 (20.89) | 22 (23.16) |
| **4** | 335 (17.07) | 318 (17.03) | 17 (17.89) |
| **5 (least deprived)** | 142 (7.24) | 130 (6.96) | 12 (12.63) |
| Frequency Missing = 13 (0.66%) | | | |
| **Health board region** | | | |
| **East** | 701 (35.88) | 669 (35.97) | 32 (34.04) |
| **North** | 333 (17.04) | 320 (17.20) | 13 (13.83) |
| **West** | 920 (47.08) | 871 (46.83) | 49 (52.13) |
| Frequency Missing = 8 (0.40%) | | | |

### 4.4.2 Patient contact with healthcare services

This section examines the proportion of patients with oral cancer (n=1962) that had contacted all or any of the healthcare services (hospital outpatient appointments, hospital inpatient/day-case admissions, GP prescriptions, and primary dental care) in the two years prior to the start of the referral period, calculates the mean number of contacts made, and explores any variations over time.

A greater proportion of patients contacted all or any of the four services in the most recent year prior to the start of the referral period (Year–1) compared to the year preceding that (Year–2) (93% vs 86%, respectively); however, this difference was quite small (Table 4-2). The mean number of contacts [16.9, standard deviation (S.D) 14.4] was higher in the most recent year prior to the start of the referral period (Year–1) compared to the year preceding that (Year–2) (10.9, S.D 11.7) (Table 4-2). The mean difference in the number of contacts was 6.0 [one-sample t-test p=<0.0001, 95% confidence interval (C.I) = 5.5-6.5] and this was statistically significant (Table 4-3). This increase was also clinically significant, with patients with oral cancer making 6 more contacts with all or any of the four healthcare services in the most recent year prior to the start of the referral period compared to the year preceding that.

The proportion of patients that had contacted all or any of the four services at least once in six months increased from 74% (n=1459) in the six-month period furthest away from the start of the referral period (Y2H2) to 91% (n=1778) in the most recent six months prior to the start of the referral period (Y1H1) (Table 4-2). The mean difference in the number of contacts between the most recent six months prior to the start of the referral period (Y1H1) and the six months preceding that (Y1H2) was 1.0 (one-sample t-test p=<0.0001, 95% C.I = 0.8–1.1) (Table 4-3). The mean difference in the number of contacts between the most recent six months prior to the start of the referral period (Y1H1) and the six-month period

furthest away from the start of the referral period (Y2H2) was 3.0 (one-sample t-test p=<0.0001, 95% C.I = 2.7-3.2) (Table 4-3).

**Table 4-2: All or any healthcare service contacts over time for patients with oral cancer diagnosed between 2010-2012 (n=1962)**

| | Never contacted healthcare service n (%) | Ever contacted healthcare services n (%) | Minimum number of contacts | Maximum number of contacts | Mean number of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| **Year-2 (least recent)** | 274 (13.97) | **1688 (86.03)** | 0 | 90.00 | **10.90** | **11.78** |
| **Year-1 (most recent)** | 143 (7.29) | **1819 (92.71)** | 0 | 108.00 | **16.96** | **14.40** |
| | | | | | | |
| **Y2H2 (least recent)** | 503 (25.64) | **1459 (74.36)** | 0 | 48.00 | **5.00** | **6.12** |
| **Y2H1** | 388 (19.78) | **1574 (80.22)** | 0 | 45.00 | **5.89** | **6.38** |
| **Y1H2** | 270 (13.76) | **1692 (86.24)** | 0 | 41.00 | **7.00** | **6.64** |
| **Y1H1 (most recent)** | 184 (9.38) | **1778 (90.62)** | 0 | 51.00 | **8.02** | **6.91** |

**Table 4-3: One-sample t-test comparing time periods by mean number of service contacts**

| One-sample t-test comparing time periods by service contacts | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Year-1 vs. Year-2 | | | Y1H1 vs. Y1H2 | | | Y1H1 vs. Y2H1 | | | Y1H1 vs. Y2H2 | | |
| Service contacted | Mean difference in number of contacts | 95% CI | P value | Mean difference in number of contacts | 95% CI | P-value | Mean difference in number of contacts | 95% CI | P value | Mean difference in number of contacts | 95% CI | P value |
| All/Any service contacts | 6.05 | 5.59-6.51 | **<0.0001** | 1.01 | 0.83-1.19 | **<0.0001** | 2.12 | 1.89-2.34 | **<0.0001** | 3.01 | 2.75-3.27 | **<0.0001** |
| Hospital inpatient/day-case service contacts | 0.27 | 0.15-0.39 | **<0.0001** | 0.01 | -0.03-0.05 | 0.6168 | 0.05 | 0.01-0.09 | 0.0177 | 0.04 | -0.01-0.09 | 0.0925 |
| Hospital outpatient service contacts | 0.08 | 0.01-0.15 | <0.0198 | 0.20 | 0.12-0.27 | **<0.0001** | 0.24 | 0.16-0.32 | **<0.0001** | 0.23 | 0.14-0.32 | **<0.0001** |
| GP prescription service contacts | 3.68 | 3.35-4.01 | **<0.0001** | 0.74 | 0.60-0.88 | **<0.0001** | 1.76 | 1.57-1.94 | **<0.0001** | 2.67 | 2.44-2.89 | **<0.0001** |
| Primary dental care service contacts | 2.02 | 1.77-2.27 | **<0.0001** | 0.07 | 0.04-0.10 | **<0.0001** | 0.08 | 0.04-0.11 | **<0.0001** | 0.08 | 0.05-0.11 | **<0.0001** |

### 4.4.3 Hospital inpatient/day-case (SMR01)

A greater proportion of patients had contacted a hospital inpatient/day-case service in the most recent year prior to the start of the referral period (Year–1) compared to the year preceding that (Year–2) (25% vs 23%, respectively); however, this difference was also quite small (Table 4-4). The mean number of hospital inpatient/day-case contacts was 0.5 (S.D 1.5) in the most recent year prior to the start of the referral period (Year–1) and 0.4 (S.D 1.2) in the year preceding that (Year–2) (Table 4-4). The mean difference in the number of contacts was 0.2 and, although this was statistically significant (one-sample t-test p = <0.0001, 95% C.I 0.1–0.3), it was unlikely to have any clinical significance as the difference in number of hospital inpatient/day-case contacts between the two years was less than one contact (Table 4-3).

The proportion of patients that had contacted a hospital inpatient/day-case service at least once in six months marginally increased from 14% (n=271) in the six-month period furthest away from the start of the referral period (Y2H2) to 17% (n=331) in the most recent six months prior to the start of the referral period (Y1H1) (Table 4-4). The mean number of hospital outpatient contacts was 0.9 (S.D 1.9) in the most recent six months prior to the start of the referral period (Y1H1), 0.7 (S.D 1.64) in the six months preceding that (Y1H2), 0.7 (S.D 1.61) in the six months preceding Y1H2, and 0.7 (S.D 1.68) in the six-month period furthest away from the start of the referral period (Y2H2) (Table 4-4). The mean difference in the number of contacts between the most recent six months prior to the start of the referral period (Y1H1) and the six-month period preceding that (Y1H2) was 0.01 (one-sample t-test p=0.6168, 95% C.I = –0.03–0.05) (Table 4-3). The mean difference in the number of contacts between the most recent six months prior to the start of the referral period (Y1H1) and the six-month period furthest away from the start of the referral period (Y2H2) was 0.04 (one-sample t-test p=0.0925, 95% C.I = –0.01–0.09) (Table 4-3). These differences were neither statistically nor clinically significant.

**Table 4-4: Hospital inpatient/ day-case service (SMR01) contacts over time for patients with oral cancer diagnosed between 2010-2012 (n=1962)**

| | Never contacted hospital inpatient/ day-case service n (%) | Ever contacted hospital inpatient/ day-case service n (%) | Minimum number of contacts | Maximum number of contacts | Mean number of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| **Year–2 (least recent)** | 1505 (76.71) | **457 (23.29)** | 0 | 19.00 | **0.49** | 1.29 |
| **Year–1 (most recent)** | 1468 (74.82) | **494 (25.18)** | 0 | 30.00 | **0.57** | 1.56 |
| | | | | | | |
| **Y2H2 (least recent)** | 1691 (86.19) | **271 (13.81)** | 0 | 28.00 | **0.74** | 1.68 |
| **Y2H1** | 1700 (86.65) | **262 (13.35)** | 0 | 29.00 | **0.73** | 1.61 |
| **Y1H2** | 1674 (85.32) | **288 (14.68)** | 0 | 26.00 | **0.77** | 1.64 |
| **Y1H1 (most recent)** | 1631 (88.13) | **331 (16.87)** | 0 | 27.00 | **0.97** | 1.92 |

### 4.4.4 Hospital outpatient appointments (SMR00)

A greater proportion of patients had contacted hospital outpatient services in the most recent year prior to the start of the referral period (Year–1) compared to the year preceding that (Year–2) (50% vs 44%, respectively) (Table 4-5). The mean number of hospital outpatient contacts was 1.74 (S.D 3.13) in the most recent year prior to the start of the referral period (Year–1) and 1.46 (S.D 2.95) in the year preceding that (Year–2) (Table 4-5). The mean difference in the number of contacts between the two years was 0.08 and this was neither statistically nor clinically significant (one-sample t-test p <0.0198, 95% C.I = 0.01–0.15) (Table 4-3).

The proportion of patients that had contacted a hospital outpatient service at least once in six months increased from 32% (n=634) in the six-month period furthest away from the start of the referral period (Y2H2) to 40% (n=781) in the six-month period closest to the start of the referral period (Y1H1) (Table 4-5). The mean number of hospital inpatient/day-case contacts in the most recent six months (Y1H1) was 0.2 (S.D 0.83) and this was very similar to the mean number of contacts in all of the other six-month periods (Y1H2: mean=0.2, S.D = 0.9; Y2H1: mean=0.2, S.D = 0.8; Y2H2: mean=0.2, S.D = 0.8) (Table 4-5). The one-sample t-test showed that the mean difference in the number of contacts between the most recent six months prior to the start of the referral period (Y1H1) and the six months preceding that (Y1H2) was 0.2 (p <0.0001, 95% C.I 0.1–0.2); between the six-month period closest to the start of the referral period (Y1H1) and Y2H1 was 0.2 (p <0.0001, 95% C.I 0.1–0.3); and between the most recent six months prior to the start of the referral period (Y1H1) and the six-month period furthest from start of the referral period (Y2H2) was also 0.2 (p <0.0001, 95% C.I 0.1–0.3) (Table 4-3). Once again, despite statistical significance, the differences in the number of contacts between two six-month periods were consistently less than one contact, suggesting limited clinical significance.

**Table 4-5: Hospital outpatient service (SMR00) contacts over time for patients with oral cancer diagnosed between 2010-2012 (N=1962)**

| | Never contacted hospital outpatient service n (%) | Ever contacted hospital outpatient service n (%) | Minimum number of contacts | Maximum number of contacts | Mean number of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| **Year-2 (least recent)** | 1103 (56.22) | **859 (43.78)** | 0 | 57.00 | **1.46** | 2.95 |
| **Year-1 (most recent)** | 973 (49.59) | **989 (50.41)** | 0 | 53.00 | **1.74** | 3.13 |
| | | | | | | |
| **Y2H2 (least recent)** | 1328 (67.69) | **634 (32.31)** | 0 | 19.00 | **0.25** | 0.85 |
| **Y2H1** | 1325 (67.53) | **637 (32.47)** | 0 | 11.00 | **0.24** | 0.81 |
| **Y1H2** | 1293 (65.90) | **669 (34.10)** | 0 | 17.00 | **0.28** | 0.96 |
| **Y1H1 (most recent)** | 1181 (60.19) | **781 (39.81)** | 0 | 13.00 | **0.29** | 0.83 |

### 4.4.5 Prescribing Information System (PIS)

The proportion of patients that had been issued a prescription by a general practitioner had increased in the most recent year prior to the start of the referral period compared to the year preceding that (Year–1: 89%, Year–2: 73%). The mean number of GP prescriptions issued was 12 (S.D 10.9) in the most recent year prior to the start of the referral period (Year–1) and 8.3 (S.D 10.0) in the year preceding that (Year–2) (Table 4-6). The mean difference in the number of contacts between the two years was 3.6 and this was statistically significant (one-sample t-test p<0.0001, 95% C.I = 3.3-4.0) (Table 4-3). This increase was also clinically significant, with 3.6 more prescriptions being issued by general practitioners in the most recent year prior to the start of the referral period.

The proportion of patients that had been issued a prescription by a general practitioner had increased drastically from 57% (n=1113) in the six-month period furthest away from the start of the referral period (Y2H2) to 85% (n=1663) in the six-month period closest to the start of the referral period (Y1H1) (Table 4-5). The mean number of GP prescriptions issued was 6.4 (S.D 5.8) in the six-month period closest to the start of the referral period (Y1H1), 5.7 (S.D 5.5) in the six months preceding that (Y1H2), 4.6 (S.D 5.44) in the six months preceding Y1H2 (Y2H1), and 3.7 (S.D 5.22) in the six-month period furthest away from the start of the referral period (Y2H2) (Table 4-6). The mean difference in the number of contacts between the six-month period closest to the start of the referral period (Y1H1) and the six months preceding that (Y1H2) was 0.7 (p <0.0001, 95% C.I 0.6–0.8); between the six-month period closest to the start of the referral period (Y1H1) and Y2H1 was 1.7 (p <0.0001, 95% C.I 1.5–1.9), and between the six-month period closest to the start of the referral period (Y1H1) and the six-month period furthest away from the start of the referral period (Y2H2) was 2.6 (p <0.0001, 95% C.I 2.4–2.8) (Table 4-3).

**Table 4-6: GP prescription service (PIS) contacts over time for patients with oral cancer diagnosed between 2010-2012 (n=1962)**

| | Never contacted GP prescription service n (%) | Ever contacted GP prescription service n (%) | Minimum number of contacts | Maximum number of contacts | Mean number of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| Year-2 (least recent) | 539 (27.47) | **1423 (72.53)** | 0 | 72.00 | **8.36** | **10.06** |
| Year-1 (most recent) | 224 (11.42) | **1738 (88.58)** | 0 | 73.00 | **12.04** | **10.97** |
| | | | | | | |
| Y2H2 (least recent) | 894 (43.27) | **1113 (56.73)** | 0 | 36.00 | **3.72** | **5.22** |
| Y2H1 | 609 (31.04) | **1353 (68.96)** | 0 | 41.00 | **4.64** | **5.44** |
| Y1H2 | 381 (19.42) | **1581 (80.58)** | 0 | 37.00 | **5.65** | 5.57 |
| Y1H1 (most recent) | 299 (15.24) | **1663 (84.76)** | 0 | 42.00 | **6.39** | 5.86 |

## 4.4.6 Dental service contacts

This section presents the results of a focused examination of all primary dental care service contacts made by the patients with oral cancer in the two years prior to the start of the referral period, with the aim of identifying any potentially missed opportunities for opportunistic screening in the primary dental care setting.

### 4.4.6.1 Patient demographics by primary dental care service contact status

Just over half of the patients with oral cancer had made no contact with a primary dental care service in the two years prior to the start of the referral period ("Never- dental" group: n= 1086, 55%; "Ever-dental" group: n=876, 45%) (Table 4-7), thus automatically limiting opportunities for early detection. It is vital to bear in mind that these numbers represent patients who had or had not made contact with a primary dental care service in the two years preceding the start of the one-month referral period (t–30) and, therefore, represent a more refined analysis compared to that presented in Chapter 3 which considered the two-year period directly preceding the date of diagnosis. Therefore, while 911 (46%) patients with oral cancer had contacted a primary dental care service in the two years prior to diagnosis (t) (shown in Chapter 3 Table 3-3), a slightly smaller number of 876 patients with oral cancer had consulted a general dental practitioner in the two years prior to the start of the one-month referral period (t-30 days) (Table 4-7).

A comparison of the patient profile of the two groups showed no major differences, with a majority of the patients with oral cancer in the "Ever-dental" and "Never-dental" groups being male (65% for both), above 45 years of age (92% and 96%, respectively), and from the most deprived areas of Scotland (SIMD 1: 31% and 35%, respectively) (Table 4-7). In contrast, only 36% of the "Ever-dental" group were females, 8% were below 45 years of age, and 8% were from the least deprived areas of Scotland (SIMD 5). Similarly, only 35% of the "Never-dental" group were females, 4% were

below 45 years of age, and 7% were from the least deprived areas of Scotland (SIMD 5) (Table 4-7).

**Table 4-7: Patient demographics by dental service contact in the two years prior to the start of the referral period.**

| | Total n (%) | Ever-dental n (%) | Never-dental n (%) |
|---|---|---|---|
| **Total** | **1962 (100.00)** | **876 (44.65)** | **1086 (55.35)** |
| **Sex** | | | |
| **Males** | 1269 (64.68) | 565 (64.50) | 704 (64.83) |
| **Females** | 693 (35.32) | 311 (35.50) | 382 (35.17) |
| **Age** | | | |
| **0 - 25** | 10 (0.51) | 7 (0.80) | 3 (0.28) |
| **26 - 35** | 21 (1.07) | 11 (1.26) | 10 (0.92) |
| **36 - 45** | 85 (4.33) | 56 (6.39) | 29 (2.67) |
| **46 - 55** | 407 (20.74) | 200 (22.83) | 207 (19.06) |
| **56 - 65** | 630 (32.11) | 299 (34.13) | 331 (30.48) |
| **66 - 75** | 489 (24.92) | 191 (21.80) | 298 (27.44) |
| **76 - 85** | 263 (13.40) | 91 (10.39) | 172 (15.84) |
| **>86** | 57 (2.91) | 21 (2.40) | 36 (3.31) |
| **SIMD** | | | |
| **1 (most deprived)** | 650 (33.13) | 273 (31.16) | 377 (34.71) |
| **2** | 410 (20.90) | 179 (20.43) | 231 (21.27) |
| **3** | 412 (21.00) | 189 (21.58) | 223 (20.53) |
| **4** | 335 (17.07) | 157 (17.92) | 178 (16.39) |
| **5 (least deprived)** | 142 (7.24) | 70 (7.99) | 72 (6.63) |
| Frequency Missing = 13 (0.66%) | | | |
| **Region of Residence** | | | |
| **East** | 701 (35.88) | 349 (38.89) | 352 (32.62) |
| **North** | 333 (17.04) | 113 (12.91) | 220 (20.39) |
| **West** | 920 (47.08) | 413 (47.20) | 507 (46.99) |
| Frequency Missing = 8 (0.41%) | | | |

#### 4.4.6.2 Frequency of primary dental care service contacts

The proportion of patients that had contacted a dental service did not differ between the most recent year prior to the start of the referral period and the year preceding that (Year–1: 32%, Year–2: 32%). However, the mean number of contacts made in the most recent year prior to the start of the referral period was considerably higher than that observed in the year preceding it (Year–1: mean 2.6, S.D 5.9; Year–2: mean 0.5, S.D 1.0) (Table 4-8). The mean difference in the number of contacts between the two years was 2.0 contacts and this was statistically significant (one-sample t-test p<0.0001, 95% C.I 1.7–2.2) (Table 4-3). Moreover, this was also clinically significant, with two more primary dental care service contacts being observed in the year prior to the start of the referral period compared to the year furthest away from the start of the referral period.

The proportion of patients that had contacted a primary dental care service at least once in six months increased from 23% (n=447) in the six-month period furthest away from the start of the referral period (Y2H2) to 29% (n=566) in the six-month period closest to the start of the referral period (Y1H1) (Table 4-8). The mean number of dental service contacts was 0.3 (S.D 0.57) in the most recent six-month period prior to the start of the referral period (Y1H1), and this was slightly higher than all of the other six-month periods examined (Y1H2: mean=0.3, S.D = 0.5; Y2H1: mean=0.2, S.D = 0.6; Y2H2: mean=0.2, S.D = 0.6) (Table 4-8). The mean difference in number of contacts between the most recent six-month period prior to the start of the referral period (Y1H1) and the six months preceding that (Y1H2) was 0.07 (one-sample t-test p< 0.0001, 95% C.I = 0.04–0.1); between the most recent six-month period prior to the start of the referral period (Y1H1) and Y2H1 was 0.08 (one-sample t-test p <0.0001, 95% C.I = 0.04–0.1); and between the most recent six-month period prior to the start of the referral period (Y1H1) and the six-month period furthest away from the start of the referral period (Y2H2) was 0.08 (one-sample t-test p <0.0001, 95% = C.I 0.05 — 0.1) (Table 4-3). While these differences were

statistically significant, they were unlikely to have any clinical significance as the differences were less than one contact every six months

**Table 4-8: Dental service (MIDAS) contacts over time for patients with oral cancer diagnosed between 2010-2012 (n=1962)**

| | Never n (%) | Ever n (%) | Minimum number of contacts | Maximum number of contacts | Mean number of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| **Year-2 (least recent)** | 1338 (68.20) | **624 (31.80)** | 0 | 9.00 | **0.58** | 1.04 |
| **Year-1 (most recent)** | 1344 (68.50) | **618 (31.50)** | 0 | 49.00 | **2.61** | 5.98 |
| | | | | | | |
| **Y2H2 (least recent)** | 1515 (77.22) | **447 (22.78)** | 0 | 6.00 | **0.29** | 0.60 |
| **Y2H1** | 1510 (76.96) | **452 (23.04)** | 0 | 6.00 | **0.29** | 0.61 |
| **Y1H2** | 1483 (75.59) | **479 (24.41)** | 0 | 4.00 | **0.30** | 0.59 |
| **Y1H1 (most recent)** | 1396 (71.15) | **566 (28.85)** | 0 | 5.00 | **0.37** | 0.67 |

#### 4.4.6.3 Nature of primary dental care service contacts

This section carries out a detailed exploration of the reasons for primary dental care service contact by focusing on the "Ever-dental" contact group (n=876), that is, patients who had contacted a primary dental care service in the two years prior to the start of the referral period.

Upon analysing the reasons for contact, the majority (n=713, 81%) of the "Ever-dental" contact group were seen to have undergone at least one "Exam and/or Diagnosis" category procedure during their visit in the two years prior to the start of the referral period. However, only 12% (n=105) of the patients had attended for a "Treatment" procedure only, and a smaller proportion of 7% (n=58) had attended for "Emergency" purposes only (Table 4-9).

For a more detailed examination by individual year, the patients were classified into the following groups: a) "1-2 contacts" — those who had one to two contacts with a general dental practitioner per year, and b) ">2 contacts" — those who had more than two contacts with a general dental practitioner per year. One to two appointments per year (one every six months) were considered to be "routine" (regular), as per the current SDR-primary dental care contract regulation (NHS Scotland, 2017b). Of the 876 (45%) patients with oral cancer who had consulted a primary dental care service in the two years preceding the start of the referral period (Table 4-9), 252 (29%) had made zero contact in Year–2 and 258 (29%) had made zero contact in Year–1 (Table 4-9). The proportion of patients that had made *routine* contact (one to two contacts) decreased drastically from 57% in the year furthest from the start of the referral period (Year–2) to 18% in the most recent year prior to the start of the referral period (Year–1) (Table 4-9). Therefore, just over half of the patients (n=456, 52%) had made *non-routine* frequency of contact (more than two contacts) in the most recent year prior to the start of the referral period (Year–1), and this was considerably larger than the proportion seen in the year preceding that (Year–2) (n=121, 14%) (Table 4-9).

With regard to the reasons for contact, 41% (n=363) of the patients exhibited higher than the usual *routine* frequency of contacts (more than two contacts) for "Exam and Diagnosis" purposes in the most recent year prior to the start of the referral period (Year–1) compared to only 8% (n=70) in the year preceding that (Year–2). In other words, the proportion of patients that had more than just a *routine* number of contacts, particularly for exam and diagnosis purposes, had risen in the most recent year prior to the start of the referral period. A similar pattern was observed with regard to the other categories, that is, the proportion of patients that had more than a *routine* number of contacts with a dental service for "Treatment" or "Emergency" purposes only was greater in the most recent year prior to the start of the referral period (Year–1) compared to the year preceding that (Year–2) (Table 4-9). These differences were seen to be statistically significant (McNemar's test $p<0.0001$). Therefore, the results suggest that a) a greater proportion of patients with oral cancer (52.05%) that were included in the "Ever-dental" group had increased their frequency of attending a dental service (i.e. more than the routine one to two contacts per year) in the year prior to the start of the referral period, and b) the patients appeared to have mainly undergone some form of examination and/or diagnostic procedures during these contacts.

The number of dental service contacts made by the patients was then examined by six-month periods in a similar way, with Y1H1 representing the most recent six months prior to the start of the referral period, Y1H2 being the six months preceding that, and so on until Y2H2 which was the six-month period furthest away from the start of the referral period (Figure 4-9). Here, one contact per six months (i.e. two contacts per year) was considered to be "routine". The patients with oral cancer were classified into the following groups: a) "1 contact" — for those who had one contact with a dental service over a six-month period, and b) ">1 contact" — for those who had more than one contact with a dental service over a six-month period.

**Table 4-9: Frequency of dental service contact of "Ever-dental" group (n=876) by reason for contact.**

| Time period | No of contacts | Reason for contact | | | |
|---|---|---|---|---|---|
| | | Exam & Diagnosis N (%) | Emergency N (%) | Treatment N (%) | Total N (%) |
| **Two-year period prior to the start of referral** | | **713 (81.39)** | **58 (6.62)** | **105 (11.99)** | **876 (100)** |
| **Examination by individual year** | | | | | |
| **Year-2** | **0 Contacts** | – | – | – | 252 (28.77) |
| | **1-2 Contacts** | 437 (49.89) | 23 (2.63) | 43 (4.91) | 503 (57.42) |
| | **>2 Contacts** | 70 (7.99) | 8 (0.91) | 43 (4.91) | **121 (13.81)** |
| **Year-1** | **0 Contacts** | – | – | – | 258 (29.45) |
| | **1-2 Contacts** | 133 (15.18) | 19 (2.17) | 10 (1.14) | 162 (18.49) |
| | **>2 Contacts** | 363 (41.44) | 24 (2.74) | 69 (7.88) | **456 (52.05)** |
| **Examination by six-month periods** | | | | | |
| **Y2H2** | **0 Contacts** | – | – | – | 429 (48.97) |
| | **1 Contact** | 306 (34.93) | 11 (1.26) | 31 (3.54) | 348 (39.73) |
| | **>1 Contact** | 48 (5.48) | 12 (1.37) | 39 (4.45) | **99 (11.30)** |
| **Y2H1** | **0 Contacts** | – | – | – | 424 (48.40) |
| | **1 Contact** | 312 (35.62) | 13 (1.48) | 30 (3.42) | 355 (40.53) |
| | **>1 Contact** | 57 (6.51) | 6 (0.68) | 34 (3.88) | **97 (11.07)** |
| **Y1H2** | **0 Contacts** | – | – | – | 397 (45.32) |
| | **1 Contact** | 327 (37.33) | 17 (1.94) | 43 (4.91) | 387 (45.32) |
| | **>1 Contact** | 63 (7.19) | 7 (0.80) | 22 (2.51) | **92 (10.50)** |
| **Y1H1** | **0 Contacts** | – | – | – | 310 (35.39) |
| | **1 Contact** | 378 (43.15) | 24 (2.74) | 49 (5.59) | 451 (51.48) |
| | **>1 Contact** | 76 (8.68) | 13 (1.48) | 26 (2.97) | **115 (13.13)** |

Of the 876 patients with oral cancer who had contacted a primary dental care service in the two years before the start of the referral period, only 35% (n= 310) had made zero contacts in the most recent six-month period prior to the start of the referral period (Y1H1). This was considerably lower than the number of patients who had made zero contact in all of the remaining six-month periods examined (Y1H2: n=397, 45%; Y2H1: n= 424 48%; Y2H2: n= 429, 49%) (Table 4-9). A somewhat downward trend appeared to exist, with the number of patients with no contact with a dental service decreasing from the six-month period furthest away from the start of the referral period (Y2H2) to the six-month period closest to the start of the referral period (Y1H1).

The number of patients that had contacted a primary dental care service once over a six-month period appeared to exhibit a somewhat upward trend closer to the start of the referral period (Table 4-9). More specifically, only 40% (n=348) of patients had contacted the dental service once in Y2H2 (the six-month period furthest away from the start of the referral period), and this proportion had increased to just over half (51%, n=451) in the most recent six-months prior to the start of the referral period (Y1H1). This is important as even one contact could be considered as an opportunity for early detection of oral cancer.

When examining for *non-routine* patterns of contact (i.e. more than one contact per six-month period), 13% (n=115) of the patients had made more than one contact with a dental service in the most recent six-month period (Y1H1) prior to the start of the referral period. This proportion was slightly, but not significantly, greater than that seen in the remaining six-month periods examined, with the corresponding proportions being 11% (n=92) in the six-month period preceding the most recent one (Y1H2), 11% (n=97) in the more recent six-month period of the year furthest away from the start of the referral period (Y2H1), and 11% (n=99) in the six-month period furthest away from the start of the referral period (Table 4-9).

Lastly, when examining the reasons for contact with a dental service, 9% (n= 76) of the patients were seen to have had more than one contact for some form of examination or diagnostic procedure in the most recent six-months (Y1H1) prior to the start of the referral period. This proportion was slightly greater than that seen in the remaining six-month periods examined, with the corresponding proportions being 7% (n=63) in the six-month period preceding the most recent one (Y1H2), 7% (n=57) in the more recent six-month period of the year furthest away from the start of the referral period (Y2H1), and 5% (n=48) in the six months furthest away from the start of the referral period (Table 4-9). The number of patients who had one or more contact with a general dental practitioner for some form of examination and diagnosis procedure, albeit still low, appeared to increase closer to the start of the referral period (Table 4-9). The difference between the two halves of the most recent year prior to the start of the referral period was statistically significant (McNemar's test comparing Y1H1 AND Y1H2: p-value <0.005). Moreover, the proportions of patients who had attended a primary dental care service for "Emergency" and "Treatment" purposes only in the most recent six months prior to the start of the referral period were 1% (n=13) and 3% (n=26), respectively. Although these numbers were much smaller, these contacts could potentially be additional opportunities for the early detection of cancer.

Therefore, the results show that a) the number and proportion of patients contacting a primary dental care service at least once increased closer to the start of the referral period; b) the number and proportion of patients with *non-routine* contacts (more than one contact per six-month period) increased closer to the start of the referral period; and c) a larger proportion of the cohort underwent some form of examination and/or diagnostic procedure in the most recent six months prior to the start of the referral period (Y1H1) compared to the earlier six-month periods examined.

## 4.4.7 Route to diagnosis

### 4.4.7.1 Service contacted last before the start of the referral period

The last service contacted by patients with oral cancer before the start of the referral period was examined as a potential proxy for referral. The two most common services that were contacted were GP prescription (n=48% n=932) and hospital outpatient (22%, n=437), with only 16% (n=314) of the "referrals" appearing to have come from dental services (Table 4-10). While this was a very superficial exploration and there was no actual referral data available, the results seem to indicate that the route to diagnosis was largely from services other than dental. This chimes with the earlier findings that a large proportion of patients with oral cancer were not attending primary dental care services routinely.

**Table 4-10 Last service contacted before the start of the referral period**

| Last service contacted | Frequency | Percent |
|---|---|---|
| **Hospital inpatient/day-case** | 279 | 14.22 |
| **Hospital outpatient** | 437 | 22.27 |
| **GP prescription** | 932 | 47.50 |
| **Primary dental care** | 314 | 16.00 |

### 4.4.7.2 Contacts made during the one-month referral period

The referral period was defined as the 30-day period prior to diagnosis, and it was assumed that all contacts made during this period were part of the referral process. The vast majority of the patients (98%, n=1925) had made contact with at least one of the four services examined within the referral month, and the mean number of contacts was 3.5 (S.D 2.4) (Table 4-11).

Of the 1925 patients with oral cancer who had contacted a service within the referral period, the majority had contacted hospital outpatient (86%, n=1685) and GP prescription (74%, n=1449) services (Table 4-11). In contrast, considerably smaller proportions had contacted primary dental care and hospital inpatient/day-case services (primary dental care: 13%, n=251; hospital inpatient/day-case: 33%, n= 644) (Table 4-11). The mean number of contacts was 0.3 (S.D 0.6) for hospital inpatient/day-case services, 1.1 (S.D 0.8) for hospital outpatient, 1.5 (S.D 1.4) for GP prescription, and 0.4 (S.D 1.6) for primary dental care services.

**Table 4-11: Ever/never and mean number of contacts with hospital outpatient, hospital inpatient/ day-case, primary dental care and GP prescription services during referral period**

| Service | Contact | n (%) | Minimum no. of contacts | Maximum no. of contacts | Mean no. of contacts | Standard deviation |
|---|---|---|---|---|---|---|
| **All/Any service** | **Ever** | **1925 (98.11)** | 0 | 17 | 3.56 | 2.42 |
| | **Never** | **37 (1.89)** | | | | |
| **Hospital inpatient/ day-case** | **Ever** | **644 (32.82)** | 0 | 8 | 0.38 | 0.62 |
| | **Never** | 1318 (67.18) | | | | |
| **Hospital outpatient** | **Ever** | **1685 (85.88)** | 0 | 7 | 1.19 | 0.81 |
| | **Never** | 277 (14.12) | | | | |
| **GP prescription** | **Ever** | **1449 (73.85)** | 0 | 9 | 1.54 | 1.46 |
| | **Never** | 513 (26.15) | | | | |
| **Primary dental care** | **Ever** | **251 (12.79)** | 0 | 15 | 0.46 | 1.61 |
| | **Never** | 1711 (87.21) | | | | |

Further examination of the hospital inpatient/day-case and hospital outpatient specialties contacted during the referral period showed that the vast majority of the patients with oral cancer that were included in this study were visiting the ENT (hospital outpatient: 36%, hospital inpatient/day-case: 55%), Oral and Maxillofacial Surgery (hospital outpatient: 23%, hospital inpatient/day-case: 21%), and hospital outpatient General Surgery departments (33%) (Table 4-12).

**Table 4-12: Hospital outpatient and hospital inpatient/day-case specialties contacted during referral period (30 days)**

| Hospital outpatient specialty contacted | N (%) | Hospital inpatient/day-case specialty contacted | N (%) |
|---|---|---|---|
| **Ear, nose & throat** | **609 (36.14)** | **Ear, nose & throat** | **356 (55.28)** |
| **General surgery** | **564 (33.47)** | **Oral & maxillofacial surgery** | **136 (21.12)** |
| **Oral surgery **** | **395 (23.44)** | **General medicine** | **53 (8.23)** |
| **Oral medicine** | 27 (1.60) | **Oral surgery** | **44 (6.83)** |
| **Clinical oncology** | 16 (0.95) | **General surgery** | 7 (1.09) |
| **Plastic surgery** | 12 (0.71) | **Plastic surgery** | 7 (1.09) |
| **Gastroenterology** | 8 (0.47) | **Clinical oncology** | 5 (0.78) |
| **Dermatology** | 7 (0.42) | **Geriatric medicine** | 5 (0.78) |
| **Haematology** | 7 (0.42) | **Cardiology** | 4 (0.62) |
| **Trauma & orthopaedics** | 6 (0.36) | **Ophthalmology** | 4 (0.62) |
| **Ophthalmology** | 5 (0.30) | **Respiratory medicine** | 3 (0.47) |
| **Urology** | 4 (0.24) | **Trauma & orthopaedics** | 3 (0.47) |
| **Endocrinology** | 3 (0.18) | **Gastroenterology** | 2 (0.31) |
| **General medicine** | 3 (0.18) | **GP without obstetrics** | 2 (0.31) |
| **General psychiatry** | 2 (0.12) | **Haematology** | 2 (0.31) |
| **Geriatric medicine** | 2 (0.12) | **Palliative medicine** | 2 (0.31) |
| **Gynaecology** | 2 (0.12) | **Acute medicine** | 1 (0.16) |
| **Medical oncology** | 2 (0.12) | **Anaesthetics** | 1 (0.16) |
| **Renal medicine** | 2 (0.12) | **Dermatology** | 1 (0.16) |
| **Restorative dentistry** | 2 (0.12) | **Infectious diseases** | 1 (0.16) |
| **Cardiology** | 1 (0.06) | **Paediatrics** | 1 (0.16) |
| **Clinical radiology** | 1 (0.06) | **Rehabilitation medicine** | 1 (0.16) |
| **Neurology** | 1 (0.06) | **Rheumatology** | 1 (0.16) |
| **Palliative medicine** | 1 (0.06) | **Urology** | 1 (0.16) |
| **Psychiatry of old age** | 1 (0.06) | **Vascular surgery** | 1 (0.16) |
| **Respiratory medicine** | 1 (0.06) | | |
| **Rheumatology** | 1 (0.06) | | |

** This includes Oral and Maxillofacial Surgery as, at the time of this study being conducted, outpatient Oral and Maxillofacial Surgery clinics were being mis-coded as "dental oral surgery" clinics (Wales, 2018).

#### 4.4.7.3 Contacts made during the two-month referral period (sensitivity analysis)

A preliminary sensitivity analysis was also undertaken where the referral period was increased to 60 days ("t–60 days"), and all hospital outpatient and hospital inpatient/day-case contacts made during this period were examined. The services contacted most frequently during the 60-day referral period were the same as those contacted during a 30-day referral period (ENT, oral and maxillofacial surgery, and general surgery).

It was hypothesised that if the number and proportion of patients who had contacted these services over a 60-day referral period increased drastically from that observed in the 30-day referral period analysis, the additional patients would likely have made these contacts in the 30 days preceding the start of the 30-day referral period (t–30). However, the results showed that the number and proportion of patients with oral cancer contacting these services over a 60-day referral period did not differ drastically from the number that contacted these services over a 30-day referral period.

To explain this further, the difference between the number of patients who contacted a hospital outpatient ENT service over a 60-day referral period and a 30-day referral period was only 22 (60–day referral period: n= 631, 36%; 30–day referral period: n=609, 36%). Therefore, only 22 patients had contacted a hospital outpatient ENT in the 30 days preceding the start of the 30-day referral period, while 609 had contacted the same over the 30-day referral period ("t-30 days"). Similar results were observed for the other services, with the additional number of patients that made contact in the 30 days preceding the start of the 30-day referral period being 0 for hospital inpatient/day-case ENT, three for hospital outpatient oral surgery, two for hospital inpatient/day-case oral surgery and so on.This suggests that a referral period of 30-days was a reasonable assumption as the results of the sensitivity analysis would have exhibited a greater increase in the number and proportion of patients contacting these services if patients had indeed been referred earlier (Table 4-13).

**Table 4-13: Sensitivity analysis - Hospital outpatient and hospital inpatient/day-case specialties contacted during referral period (60 days) (**

**

| Hospital outpatient specialty contacted | N (%) | Hospital inpatient/day-case specialty contacted | N (%) |
|---|---|---|---|
| Ear, Nose & Throat | **631 (36.31)** | Ear, Nose & Throat | **356 (52.28)** |
| General surgery | **576 (33.14)** | Oral & maxillofacial surgery | **136 (19.97)** |
| Oral surgery ** | **398 (22.90)** | General medicine | **66 (9.69)** |
| Oral medicine | 27 (1.55) | Oral surgery | **46 (6.75)** |
| Clinical Oncology | 19 (1.09) | General surgery | 13 (1.91) |
| Plastic surgery | 12 (0.69) | Geriatric medicine | 7 (1.03) |
| Dermatology | 9 (0.52) | Plastic surgery | 7 (1.03) |
| Haematology | 9 (0.52) | Cardiology | 6 (0.88) |
| Gastroenterology | 8 (0.46) | Gastroenterology | 6 (0.88) |
| Trauma & Orthopaedics | 7 (0.40) | Clinical oncology | 5 (0.73) |
| General medicine | 5 (0.29) | Ophthalmology | 5 (0.73) |
| Ophthalmology | 5 (0.29) | Respiratory medicine | 4 (0.59) |
| Endocrinology | 4 (0.23) | Trauma & orthopaedics | 4 (0.59) |
| Gynaecology | 4 (0.23) | GP without obstetrics | 3 (0.44) |
| Urology | 4 (0.23) | Acute medicine | 2 (0.29) |
| Cardiology | 2 (0.12) | Haematology | 2 (0.29) |
| General psychiatry | 2 (0.12) | Palliative medicine | 2 (0.29) |
| Geriatric medicine | 2 (0.12) | Urology | 2 (0.29) |
| Medical oncology | 2 (0.12) | Vascular surgery | 2 (0.29) |
| Renal medicine | 2 (0.12) | Anaesthetics | 1 (0.15) |
| Restorative dentistry | 2 (0.12) | Dermatology | 1 (0.15) |
| Clinical radiology | 1 (0.06) | Gynaecology | 1 (0.15) |
| Infectious diseases | 1 (0.06) | Infectious diseases | 1 (0.15) |
| Neurology | 1 (0.06) | Paediatrics | 1 (0.15) |
| Palliative medicine | 1 (0.06) | Rehabilitation medicine | 1 (0.15) |
| Psychiatry of old age | 1 (0.06) | Rheumatology | 1 (0.15) |
| Respiratory medicine | 1 (0.06) | | |
| Rheumatology | 1 (0.06) | | |

This includes Oral and Maxillofacial Surgery as, at the time of this study being conducted, outpatient Oral and Maxillofacial Surgery clinics were being mis-coded as "dental oral surgery" clinics (Wales, 2018).

**Table 4-14: Summary table- All service contacts over time of patients with oral cancer diagnosed between 2010-2012 (n=1962)**

| Service contacted | No. of contacts | Contact by year | | Contact by six-month periods | | | | Contact during referral period |
|---|---|---|---|---|---|---|---|---|
| | | Year– 2 | Year–1 | Y2H2 | Y2H1 | Y1H2 | Y1H1 | t-30 days |
| All/Any Service contacts | Never n (%) | 274 (13.97) | 143 (7.29) | 503 (25.64) | 388 (19.78) | 270 (13.76) | 184 (9.38) | 37 (1.89) |
| | Ever n (%) | **1688 (86.03)** | **1819 (92.71)** | **1459 (74.36)** | **1574 (80.22)** | **1692 (86.24)** | **1778 (90.62)** | **1925 (98.11)** |
| | Min. no of contacts | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Max. no. of contacts | 90.00 | 108.00 | 48.00 | 45.00 | 41.00 | 51.00 | 17.00 |
| | Mean no. of contacts | **10.90** | **16.96** | **5.00** | **5.89** | **7.00** | **8.02** | 3.56 |
| | STD | 11.78 | 14.40 | 6.12 | 6.38 | 6.64 | 6.91 | 2.42 |
| Hospital inpatient/ day-case service contacts | Never n (%) | 1505 (76.71) | 1468 (74.82) | 1691 (86.19) | 1700 (86.65) | 1674 (85.32) | 1631 (88.13) | 1325 (67.53) |
| | Ever n (%) | **457 (23.29)** | **494 (25.18)** | **271 (13.81)** | **262 (13.35)** | **288 (14.68)** | **331 (16.87)** | **637 (32.47)** |
| | Min. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Max. | 19.00 | 30.00 | 28.00 | 29.00 | 26.00 | 27.00 | 8.00 |
| | Mean | **0.49** | **0.57** | **0.74** | **0.73** | **0.77** | **0.97** | **0.38** |
| | STD | 1.29 | 1.56 | 1.68 | 1.61 | 1.64 | 1.92 | 0.62 |
| Hospital outpatient service contacts | Never n (%) | 1103 (56.22) | 973 (49.59) | 1328 (67.69) | 1325 (67.53) | 1293 (65.90) | 1181 (60.19) | 277 (14.12) |
| | Ever n (%) | **859 (43.78)** | **989 (50.41)** | **634 (32.31)** | **637 (32.47)** | **669 (34.10)** | **781 (39.81)** | **1685 (85.88)** |
| | Min. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Max. | 57.00 | 53.00 | 19.00 | 11.00 | 17.00 | 13.00 | 7.00 |
| | Mean | **1.46** | **1.74** | **0.25** | **0.24** | **0.28** | **0.29** | **1.19** |
| | STD | 2.95 | 3.13 | 0.85 | 0.81 | 0.96 | 0.83 | 0.81 |
| GP prescription service contacts | Never n (%) | 539 (27.47) | 224 (11.42) | 849 (43.27) | 609 (31.04) | 381 (19.42) | 299 (15.24) | 527 (26.86) |
| | Ever n (%) | **1423 (72.53)** | **1738 (88.58)** | **1113 (56.73)** | **1353 (68.96)** | **1581 (80.58)** | **1663 (84.76)** | 1435 (73.14) |
| | Min. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Max. | 72.00 | 73.00 | 36.00 | 41.00 | 37.00 | 42.00 | 9.00 |
| | Mean | **8.36** | **12.04** | **3.72** | **4.64** | **5.65** | **6.39** | **1.54** |
| | STD | 10.06 | 10.97 | 5.22 | 5.44 | 5.57 | 5.86 | 1.46 |
| Primary dental care service contacts | Never N (%) | 1338 (68.20) | 1344 (68.50) | 1515 (77.22) | 1510 (76.96) | 1483 (75.59) | 1396 (71.15) | 1711 (87.21) |
| | Ever N (%) | **624 (31.80)** | **618 (31.50)** | **447 (22.78)** | **452 (23.04)** | **479 (24.41)** | **566 (28.85)** | **251 (12.79)** |
| | Min. no of contacts | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Max. no. of contacts | 9.00 | 49.00 | 6.00 | 6.00 | 4.00 | 5.00 | 15.00 |
| | Mean no. of contacts | **0.58** | **2.61** | **0.29** | **0.29** | **0.30** | **0.37** | **0.46** |
| | STD | 1.04 | 5.98 | 0.60 | 0.61 | 0.59 | 0.67 | 1.61 |

# 4.5 Discussion

## 4.5.1 Key points, comparison with other work, and potential explanations

This study attempted to identify potentially missed opportunities for early detection of oral cancer by examining how patients made contact with healthcare services in the two years preceding referral using routine administrative linked data. It also included an exploratory analysis of the routes to diagnosis of oral cancer during the one-month referral period. This section summarises some of the key findings of this study, compares it to existing evidence, and draws together previous literature to discuss possible explanations for the results observed.

The findings of this study showed that nearly all of the patients (95%) had contacted at least one of the four services (hospital inpatient/day-case, hospital outpatient, primary dental care, GP prescription) in the two years prior to the start of the referral period. These results were corroborated by Ligier et al. (2016) who reported that 88% of the patients with head and neck cancer (n=342) from a high-incidence region in France included in their study had contacted a health professional (GP, dentist, ENT specialist, non-ENT specialist) at least once in the two to 12-month period preceding diagnosis. However, under half (45%) of the patients with oral cancer that were included in the current study had contacted a primary dental care service in the two years preceding the start of the referral period. These results were in agreement with several other studies conducted in France, The Netherlands, and Western Australia that also reported poor dental attendance patterns in the majority of patients with head and neck cancer, oral cancer, and oropharyngeal cancer (Tromp et al., 2005; Frydrych and Slack-Smith, 2011). Ligier et al. (2016) also reported similar results, with approximately 80% of patients with head and neck cancer (n=342; defined as including the anatomic subsites oral cavity, oropharynx, hypopharynx, and larynx) that were included in their study showing no evidence of having consulted a dentist in the two to twelve months prior to diagnosis. Examination of the profile of patients with no primary dental care service contact in the two years prior to the start of the referral period showed that the majority of them

were males, aged above 45 years, and from the most deprived areas of Scotland, and this was in keeping with the "inverse screening law", proposed by Netuveli et al. (2006), which stated that "high-risk" individuals were less likely to attend healthcare practices frequently enough to benefit from early detection efforts.

These results suggest that there are potential opportunities for early detection of oral cancer, but they do not all lie within primary dental care services. This study looked at novel contacts for early detection of oral cancer in hospital/secondary care settings (both hospital inpatient/day-case and hospital outpatient), but found limited evidence of it. However, it did identify considerable potential in other primary care settings, particularly the GP and pharmacy, with 89% of patients with oral cancer that were included in this study being issued a GP prescription in the most recent year prior to the start of the referral period. Although a large proportion of these were likely to be repeat prescriptions, almost all of them would have been dispensed at the pharmacy. Therefore, pharmacists may have a role to play in the early detection of oral cancer as they are in an ideal position to provide smoking and alcohol cessation advice; increase awareness regarding the signs, symptoms, and risk factors of oral cancer; and refer patients exhibiting the warning signs of oral cancer (e.g. persistent mouth lesions that have not healed with medication) to a dentist in a timely fashion (Weinberg, 2006). However, there is also a possibility that some of these dispensing contacts did not involve actual face-to-face contact between the pharmacist and the patient (e.g where the prescriptions were delivered to the patient's home), and this would eliminate any opportunities for early detection in GP or pharmacy settings altogether. Future studies exploring dispensing contacts in further detail should take this into consideration when interpreting results.

The proportion of patients contacting each of the four services increased over the two -year period prior to the start of the referral period, irrespective of the service. The mean number of contacts with each of these services also exhibited an upward trend, although the differences between the individual years had more clinical significance than those between the six-month periods. The frequency of primary dental care service contacts (mean difference in number of contacts between Year-1 and Year-2: 2 contacts) and GP prescription contacts

(mean difference in number of contacts between Year-1 and Year-2: 3.6 contacts) appeared to have significantly increased in the most recent year prior to the start of the referral period compared to the previous year. When examined by six-month periods, the differences in the number of hospital outpatient, hospital inpatient/day-case, and primary dental care service contacts, although statistically significant, were consistently less than one and therefore unlikely to have any clinical significance. The only noteworthy difference was in the number of GP prescriptions issued in the most recent six months before the start of the referral period, compared to the six-month period furthest away from the start of the referral period (mean difference in number of GP prescriptions issued: 2.6). Therefore, not only were more patients contacting these services closer to the start of the referral period, their frequency of contact, particularly with the primary dental care and GP prescription services, had also increased.

This study considered two contacts with dental services per year to be "routine" in accordance with The Statement of Dental Remuneration, which is the primary dental care contract that permits a dentist to make only one examination claim every six months (NHS Scotland, 2017b). Of those who had contacted a primary dental care service (n=876), 52% (n=456) had made an unusual number of contacts (exceeding "routine", that is, two contacts per year) in the most recent year prior to the start of the referral period, and 41% (n=363) of these contacts were for examination and diagnostic purposes. When considering the most recent six-month period prior to the start of the referral period, 51% (n=451) had made at least one contact with a primary dental care service, of which 43% (n=378) were for examination and diagnosis purposes. Moreover, 13% (n=115) had made more than one contact, of which 9% (n=76) were associated with examination and diagnostic procedures. Finally, the proportion of patients making an unusual number of contacts, particularly for examination and diagnosis purposes, exhibited an upward trend throughout the examination period. Therefore, not only were the patients with oral cancer that were included in this study contacting primary dental care services more frequently closer to the start of the referral period, they were also undergoing examination and diagnostic procedures at these visits.

Lyratzopoulos et al. (2015) previously reported that unusual pre-referral health service contacts could be indicative of missed opportunities for early diagnosis of cancer in at least some of the cases. Several other studies (Christensen et al., 2012; Lyratzopoulos et al., 2012; Ahrensberg et al., 2013; Hansen et al., 2015) have also previously used unusual pre-referral consultation patterns as a "surrogate marker" for missed opportunities for early diagnosis and as an indicator of patient experience. Based on this, and given that oral cancer is frequently preceded by potentially malignant disorders (van der Waal, 2009), the increasing frequency of pre-referral contacts with health services that was observed in this study could represent missed opportunities for early detection, appointments with potential oral cancer concerns, or potential further opportunities for earlier detection and referral.

Lastly, a superficial exploration of contacts made just before and during the one-month referral period was also undertaken as a proxy for the routes to diagnosis of patients with oral cancer. The two most common services that were contacted last before the start of the referral period were GP prescription and hospital outpatient. Although not definitive, there was a possibility that these consultations were the sources of referral, suggesting that the majority of patients with oral cancer that were included in this study were referred by GPs or were emergency presentations, and only 16% of them had been referred by a dentist. This was in keeping with the study conducted by Elliss-Brookes et al. (2012) where they examined the "Routes to Diagnosis" of cancer in England and reported that the most common ones were "Emergency" and "GP referrals". Another study conducted in Ireland reported that 19% of oral cancer referrals came from hospital sources and only one in six patients were referred by a dentist (O'Sullivan, 2001). Although the numbers observed in the current study were slightly higher (approximately 36% from hospital sources and 16% from dentists), the overall implication that the majority of the referrals were coming from hospitals and the contribution of dentists was minimal in comparison remained the same.

The vast majority (98%) of the patients that were included in the current study had contacted at least one of the four services during the one-month referral period, and the most commonly contacted services were hospital outpatient and

GP prescription. In comparison, very few patients had consulted primary dental care or hospital inpatient/day-case admission services during the same period. Moreover, the hospital outpatient and hospital inpatient/ day-case specialties that were contacted most frequently within this one-month referral period were ENT, general surgery, and oral and maxillofacial surgery, suggesting that, as suspected, these contacts were likely to be already associated with the symptoms and signs of oral cancer. There was also a possibility of the hospital outpatient service being the referral destination for a large proportion of the patients included in this study. These results were in agreement with those of Ligier et al. (2016) who also reported that ENTs were the most common specialists consulted by patients with head and neck cancer post-referral.

### 4.5.2 Strengths and limitations

The main strength of this study lay in the use of big, high-quality, robust, routinely collected national data that allowed examination of a population representative cohort spanning several years. These data were readily available. The Scottish Cancer Registry has high levels of completeness of data (96% for patient information and 96% for tumour information in 2016) (UKIACR, 2017). Additionally, 85% of the patients registered on SMR06 are confirmed microscopically and only 2% are Death Certificate Only registrations (Parkin et al., 2005; UKIACR, 2017). There was also considerable evidence on the high, and continually developing, levels of case-ascertainment (Brewster et al., 1994; Brewster et al., 1997; Brewster et al., 2002). The hospital inpatient/day-case database has an accuracy rate of 88% and 94% for main condition and main operation/procedure, respectively. With regard to the prescription database, 95% of the records on PIS at the end of 2014 included unique identifiers that allowed it to be easily linked to other datasets. Rigorous quality checks are executed on the raw data before they are submitted to the prescription database and made publicly available, and it was reported to have high-levels of completeness with regard to individual-level data, although this was found to be influenced by the type of health care practitioner (Alvarez-Madrazo et al., 2016).

The presence of unique identifiers in the various databases permitted data linkage which, in turn, allowed examination of the medical consultation histories of patients over a period of several years. The quality of data linkage in Scotland is quite high, and Kendrick and Clarke (1993) reported that clerical monitoring of pair-wise linking showed that the false negative rates (the proportion of pairs which the system fails to link) and the false positive rates (the proportion of pairs which are incorrectly linked) were both approximately three percent. The use of data linkage lowered the risk of selection bias, allowed access to detailed longitudinal trajectories that permitted testing of various novel hypotheses, and was cost-effective. The advantages and disadvantages of data linkage have been discussed in detail in Chapter 5.

The limitations of this study are mainly related to the individual databases and the restrictions imposed by the unavailability of data. The first main limitation was the lack of availability of general practitioner data in Scotland. This study used prescriptions issued by GPs as a proxy for GP contact. However, there is a possibility that at least some of these would have been repeat prescriptions which would not require face-to-face contact with a general practitioner. Harris and Dajda (1996) first examined the scale of repeat prescribing using data from 115 practices identified from the IMS MediPlus database over a period of one year. They reported that repeat prescriptions accounted for 75% of all prescriptions issued, and approximately 48% of all patients that were included in their study (n= 750,390) had been issued a repeat prescription. Moreover, the percentage of repeat prescriptions were seen to increase with age. More recently, in their cross-sectional study examining repeat prescriptions issued by 29 general practices in one Primary Care Trust in England, Petty et al. (2014) reported that approximately 77% of all prescriptions issued in 2011 were repeat prescriptions, with the mean number of repeat items per individual being 1.87. Moreover, approximately 43% of the population in the United Kingdom had received at least one repeat prescription in the year of study. The authors stated that their results were largely “typical of the UK” as their study included both small and large practices that covered a wide socioeconomic and cultural range of population. Although the proportion of repeat prescriptions issued in Scotland is currently not measured, personal communication with the principle pharmacist at the Information Services Division Scotland, revealed that the

generally accepted assumption was that approximately 80% of all prescriptions issued in Scotland were repeat prescriptions (McTaggart, 2018). Therefore, this must be taken into consideration when interpreting the results of this thesis as it may have led to an overestimation of contacts with general practitioners.

The Prescribing Information System (PIS) database has several limitations of its own. In 2009, the PIS database achieved 87% completeness with regard to patient identifiers. However, this number fell to only 68% in 2008 and continued to decrease up to less than 1% in 2003 (Alvarez-Madrazo et al., 2016). It was therefore recommended that longitudinal studies requiring individual-level prescription data, such as the current one, should only go as far back as 2009 (Alvarez-Madrazo et al., 2016). This meant that information on "GP contacts" was only available for a period of one year before diagnosis for patients that were diagnosed in 2010. This may have biased the results slightly as the duration examined did not remain the same for all of the patients that were included in the study. Another limitation was that this database does not record the diagnosis or indication for prescription, and this information would have allowed us to ascertain whether or not the contacts were cancer-related. No detailed examination of the medications prescribed to the patients was undertaken as this would require expertise in bioinformatics, even for such a small cohort, and was therefore considered to be beyond the scope of this thesis. Further analysis in this area would have provided a clearer picture of the health care contacts that were cancer-related. Lastly, the PIS database also does not flag repeat prescriptions, making it impossible to decipher if the prescriptions issued by general practitioners were one-off or a part of a course of treatment. Although examination of the items and dates prescribed would have allowed identification of repeat prescriptions, this was considered to be beyond the scope of this thesis.

As mentioned earlier, small numbers prevented examination of pre-referral health service contacts of patients with oral cancer by individual subsites (oral cavity cancer and oropharyngeal cancer). This limited the researcher from teasing out any differences in opportunities for early detection by subsite, which would have been useful from an epidemiological and primary prevention perspective. However, dentists have a role in the early detection of both sites,

and most guidelines for detection of cancer consider the two subsites together as oral cancer as their signs and symptoms overlap considerably (hoarseness of voice, lump in the neck, problem swallowing, lumps or ulcers in the mouth) (Kreimer, 2014; NICE, 2015a; NHS Scotland). Therefore, from an early detection perspective, combining the two subsites and examining them as "oral cancer" appeared to be more appropriate.

The Management Information and Dental Accounting System only provides information on treatments undertaken, with no record of the diagnosis or indication for the same. Once again, this information would have allowed us to determine whether the contacts with primary dental care services were cancer-related. Another limitation of the MIDAS database was that it only provided access to records of patients registered with a General Dental Practitioner (registration rate less than 80% in 2012), and patients attending private dental practices were excluded. This may have resulted in an underestimation of the number of contacts with a primary dental care service.

Furthermore, this study used the "start date of treatment" variable as an indicator of contact with a dental service. This was a conservative measure of "contact" because while many of the "end date of treatment" were on the same date as the "start date of treatment" (n=1380, 70%), a good number (n=582, 30%) of treatment courses would have been spread over several weeks and even months. Similarly, the "admission date" variable was used as an indicator of contact with hospital inpatient/ day-case services, and contacts over the period between "admission date" and "discharge date" were not considered. This may have resulted in an underestimation of the number of contacts made with health care services.

Additionally, there was no information on the stage of cancer at the time of diagnosis, and this would have helped develop a better understanding of the impact of missed opportunities for early detection/diagnosis. Moreover, referral data was also not available and this information would have permitted elucidation of the "routes to diagnosis". There was also limited information on the nature of the contacts with health care services, particularly hospital and GP contacts. Although the patient may have been present at the service, there was

a possibility that the reason for contact was unrelated to the diagnosis of cancer and, therefore, examination of the oral cavity was unnecessary. This may have resulted in an overestimation of the opportunities for early detection.

Lastly, Bohensky et al. (2010) undertook a structured narrative review of factors that affected the quality of data linkage as these may introduce systemic bias in the outcomes reported. They found that several elements including age, sex, race, setting, health and socioeconomic status were associated with a risk of incomplete data linkage, although the evidence on the association between some of these factors and the probability of incomplete linkage occurring was inconsistent. The authors categorised the various reasons for incomplete linkage occurring into three broad groups, namely: governance issues such as the need for consent, method of linkage employed, and accuracy and completeness of the original datasets used for linkage. Additionally, factors such as a lack of a standardised definition for data or inconsistencies in coding practices may further complicate matters. These factors may introduce a certain level of bias in the results of the study and, therefore, must be kept in mind when interpreting outcomes. The authors developed a framework to aid researchers in reporting data linkage studies, and this tool was used as a guide during the formulation of this thesis. The main goals of this framework were to attain a certain level of consistency in the reporting of data linkage studies, create an awareness of the limitations of such studies among clinicians and policy-makers, and assist them in interpreting the outcomes while bearing the potential for bias in mind.

## 4.6 Conclusion

In conclusion, although dentists are in an ideal position to detect oral cancer early, the reality is that the majority of the patients simply do not consult dentists frequently enough to permit this. Therefore, there is a need to focus on motivating individuals, particularly those from the most socioeconomically deprived areas, to attend dental practices more frequently. Moreover, the results of this study suggested that there were opportunities for early detection of oral cancer in alternative healthcare services such as GPs and pharmacies, and early detection strategies should target these settings in the future.

# 5 Discussion

## 5.1 Introduction

This final chapter of the thesis summarises the principle findings of the three studies that were undertaken (Chapter 2-4), highlights the contributions to the literature by comparing the results to existing work, and discusses the results in the context of the thesis hypotheses. It then draws on existing literature, some of which has been reviewed previously in Chapter 1, to discuss possible explanations for the findings; recognises some of the methodological strengths and limitations of the study; discusses some of the further work that can be undertaken; and finally makes recommendations that are based on the results observed.

## 5.2 Summary of results, contributions to the literature, and fulfilment of study hypotheses

The overarching aim of this thesis was to identify opportunities for early detection of oral cancer in Scotland by: a) examining the incidence burden and sociodemographic profile of patients with head and neck cancer in Scotland by individual subsite; b) investigating whether early detection of oral cancer in dental settings was a realistic expectation, given the current burden and sociodemographic risk profile of the disease and the location and distribution of general dental practices; and c) identifying any potentially missed opportunities for early detection of oral cancer in dental and alternative healthcare settings. This section first summarises the principle findings of the thesis, highlights the contributions to the literature, and finally discusses the results in the context of the individual study hypotheses.

### 5.2.1 Summary of the results and contributions to the literature

#### 5.2.1.1 Summary of the results

***Chapter 2*** of this thesis, a different version of which was published in *Oral Oncology* in 2016 (Purkayastha et al., 2016), was the first national descriptive

epidemiological study to use routine administrative data to examine the incidence trends of head and neck cancer in Scotland between 1975 and 2012 by individual subsites and various sociodemographic determinants. Although the original plan for this study was to examine the trends for the United Kingdom as a whole, the results for England were examined and published by colleagues in London and Birmingham (Louie et al., 2015) while the current study was still in the process of discussing and sequencing the UK-wide Cancer Registry data from the National Cancer Intelligence Network. Moreover, analysis by area-based socioeconomic deprivation across the UK also proved to be difficult due to the lack of availability of a uniform measure of deprivation (i.e. the Scottish Index of Multiple Deprivation and the English and Welsh Indices of Multiple Deprivation were not standardised). Therefore, a decision was made to focus on the trends of head and neck cancer over time by various subsites and sociodemographic characteristics in Scotland exclusively. The literature review presented in Chapter 1 first resolved some of the issues around the definitions of oral cavity cancer and oropharyngeal cancer and clarified distinct groupings of ICD-10 codes for this study as this was essential for understanding the burden of head and neck cancer by subsite. Analysis of incidence trends over time showed that the rates of head and neck cancer had risen between 1975 and 2012, and that this appeared to be largely driven by a dramatic increase in the rates of oropharyngeal cancer. Moreover, this burden of incidence was expected to continue to rise up to 2025, with the rates of oropharyngeal cancer surpassing the rates of oral cavity cancer, which was expected to exhibit only a modest increase. Males, patients above 60 years of age, and those from the most deprived areas of Scotland consistently exhibited the highest incidence rates of cancer, irrespective of subsite. Moreover, a dose-effect relationship between the incidence burden and deprivation was seen to exist, with the risk of developing cancer increasing as the level of deprivation increased. These results were in agreement with Louie et al. (2015) who also reported a rise in the incidence rates of head and neck cancer (1995-2011) that appeared to be driven by a dramatic increase in the burden of oropharyngeal cancer in England.

***Chapter 3*** was the first study to examine the feasibility of early detection of oral cancer, oral cavity cancer, and oropharyngeal cancer in dental settings, given the relatively low volume of the disease in Scotland. It examined the distribution of the incidence burden that was reported in Chapter 2 in relation to the location and socioeconomic status of general dental practices, and accurately estimated the proportion of patients that had contacted a primary care dentist in the two years preceding diagnosis. A different version of this chapter was submitted to the *British Dental Journal* for publication. The principle finding of this study was that just over half (approximately 54%) of the patients with oral cancer that were included in this study had made no contact with a dentist in the two years prior to diagnosis, thus automatically limiting opportunities for early detection in a dental setting. Application of published registration and participation (attendance) rates at NHS dental practices showed that a dentist would encounter one case of oral cancer every 8 years. However, application of the actual attendance rates that were calculated using data linkage showed that this number was more likely to be approximately one case of oral cancer every ten years. No socioeconomic inequality was observed in the number of patients with oral cancer a dentist could expect to see per year due to the relatively equal distribution of NHS dental practices in Scotland (Audit Scotland, 2012).

***Chapter 4*** of this thesis explored potentially missed opportunities for early detection of oral cancer in primary dental care and other healthcare services, and undertook an initial exploratory analysis of the possible routes to diagnosis. The results showed that just under half of the patients had contacted a primary dental care service in the two years prior to the start of the referral period, but nearly all (95%) of them had contacted at least one of the four services examined (hospital outpatient, hospital inpatient/day-case, primary dental care, and GP prescription) over the same period. These results suggested that there were several potential opportunities for the early detection of oral cancer, but they were not necessarily within primary dental care services. Moreover, the proportions of patients contacting the four services increased closer to the start of the referral period, as did the mean

number of contacts made with each service. This implies that there was an existence of delays in the diagnostic process as any contact with the four services over the study period could be considered as a potentially missed opportunity for early detection of oral cancer. The two services that were most commonly contacted before the start of the referral period were GP prescription and hospital outpatient services. Although it was not that definitive, there was a possibility that these consultations were the sources of referral, suggesting that most of the patients with oral cancer that were included in this study were referred by GPs or via alternative routes as emergency presentations. Almost all of the patients (98%) had contacted at least one of the four services during the one-month referral period, and the most commonly contacted services were GP prescription and hospital outpatient. In comparison, very few patients had consulted primary dental care or hospital inpatient/day-case services during the same period. The hospital outpatient specialties most commonly contacted were ENT, oral surgery, oral and maxillofacial surgery, and general surgery, confirming that these consultations within the one-month referral period were indeed cancer-related.

#### 5.2.1.2 Contributions to the literature

As discussed previously in Chapter 1, the World Health Organisation's *Cancer Control: Knowledge into Action, WHO Guide for Effective Programs* was a six-part series that provided practical advice for policy-makers and programme managers on ways to plan and implement cancer control programs effectively (WHO, 2017b). This report suggested three key steps to developing a successful cancer control program, and made recommendations with regard to actions that would help accomplish them. These have been discussed in detail previously in Chapter 1, and this section will only consider the specific action recommendations that are relevant to this thesis.

The first recommended step of planning an effective cancer control program was answering the question "where are we now?" by conducting a "situation analysis". This included assessment of a) the burden of cancer amenable to

early detection, and b) the existing early detection plan and current population coverage of services. The findings presented in Chapters 2 and 3 contributed to a "situation analysis" of early detection of oral cancer in Scotland by a) exploring the incidence rates of head and neck cancer over time by subsite, thus identifying the burden of cancer amenable to early detection, and b) examining the distribution of this burden in relation to the location of general dental practices, hence clarifying the population coverage of current dental services in Scotland.

The second recommended step of building an effective cancer control program was answering the question "where do we want to be?". The WHO suggested several actions that would help answer this question, and the ones that were most relevant to this thesis were a) identification of the target population for early detection of cancer, b) assessment of feasibility of early detection interventions, c) identification of gaps in early detection services, and d) choosing between early diagnosis and screening approaches.

The descriptive epidemiological study presented in Chapter 2 assessed the risk profile of oral cancer in Scotland and found that males, patients above 60 years of age, and those from the most deprived areas consistently exhibited the highest incidence burden and, therefore, also represented the target "high-risk" population for early detection efforts. Moreover, the estimation of the proportion of patients with oral cancer that had contacted a general dental practice in the two years prior to the start of the referral period (Chapter 3) showed that there was a section of the population that simply did not contact GDPs on a regular basis and, therefore, required further targeted efforts that provided additional support and motivation. Chapter 3 of this thesis examined the feasibility of early detection of oral cancer in primary dental care services by exploring the distribution of the incidence burden in relation to the location and socioeconomic status of general dental practices in Scotland, and also calculating the number of patients with oral cancer that a dentist could expect to see per year. Finally, Chapter 4 contributed to the identification of gaps in early detection services by showing that patients with oral cancer exhibited increasing frequency of consultations with healthcare

services prior to referral, indicating poor patient experience and avoidable delays in the diagnostic process (Lyratzopoulos et al., 2012). Moreover, the findings of this study also contributed to Step 2 (d) to a certain extent by examining potentially missed opportunities for early detection of oral cancer over a period of two years prior to referral. Consideration of this extended period of time meant that these opportunities could be suitable for either screening or early diagnosis based on when they occurred. In other words, contacts further away from referral could be considered as potential opportunities for opportunistic screening, while those closer to referral could be considered as missed opportunities for early diagnosis as patients would probably have started exhibiting the signs and symptoms of oral cancer by then.

Therefore, the findings of this thesis showed that although the rates of oral cancer are rising in Scotland, early detection in primary dental care services may not be entirely feasible given the relatively low overall incidence burden in Scotland and the large proportion of patients that do not contact a general dental practitioner on a regular basis. However, there do seem to be opportunities for early detection of oral cancer in alternative healthcare settings, with nearly all of the patients having contacted one of the four services examined (hospital outpatient, hospital inpatient/ day-case, primary dental care, and GP prescription) in the two years prior to the start of the referral period and the majority of the referrals appearing to have come from hospital outpatient or GP prescription services. Lastly, the increasing frequency of contacts with these services nearer to the start of the referral period suggest that there were avoidable delays in the diagnostic process, and minimising these could contribute towards the improvement of early detection of oral cancer.

### 5.2.2 Thesis hypotheses

This section discusses the results of this thesis in the context of the individual study hypotheses. The overarching ***aim*** of this thesis was to investigate

opportunities for early detection of oral cancer in Scotland. The hypotheses for the individual studies have been listed below.

**Chapter 2 hypothesis (a):** The trends of head and neck cancer are increasing and are projected to continue to do so.

**Chapter 2 hypothesis (b):** This increase in incidence rates of head and neck cancer will largely be driven by an increase in the rates of oropharyngeal cancer.

**Chapter 2 hypothesis (c):** The patient profile of oropharyngeal cancer will differ from other subsites, particularly in relation to socioeconomic status.

**Chapter 2 hypothesis (d):** In relation to the socioeconomic distribution of head and neck cancer, there will be a clear stratification of "high-risk" areas in the more deprived communities that could be utilised to target early detection initiatives.

**Chapter 3 hypothesis (a):** The number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) a general dental practitioner in Scotland can expect to see will be low.

**Chapter 3 hypothesis (b):** Dentists working in more deprived areas will expect to see a greater number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) compared to dentists working in relatively less deprived areas.

**Chapter 4 hypothesis (a)** There are a number of potentially missed opportunities for early detection of oral cancer in dental and other healthcare services.

**Chapter 4 hypothesis (b)** These potentially missed opportunities increase in frequency in the months directly prior to the start of the referral period.

#### 5.2.2.1 Chapter 2 hypothesis (a): The trends of head and neck cancer are increasing and are projected to continue to do so.

This hypothesis was confirmed by the results of Chapter 2 which showed that the incidence rates of head and neck cancer had risen between 1975 and 2012 and were expected to continue to do so up to 2025. These findings were generally in agreement with the trends observed globally as well as more locally in the United Kingdom, and the literature review that has been presented in Chapter 1 has discussed some of this existing evidence in detail. Specifically, Louie et al. (2015) undertook a detailed cancer registry analysis in England and reported that the incidence rates of head and neck cancer had increased by 59% between 1995 and 2011, although they did not show any evidence of having examined the socioeconomic distribution of this burden. Similar trends were also observed in the current study in Scotland, although the increase observed over the same period (1995-2011) was lower at approximately 32%.

#### 5.2.2.2 Chapter 2 hypothesis (b): This increase in the incidence rates of head and neck cancer will largely be driven by an increase in the rates of oropharyngeal cancer.

This hypothesis was also supported by the findings of Chapter 2. The increase in the incidence rates of head and neck cancer appeared to be largely driven by the rates of oropharyngeal cancer, which exhibited a dramatic rise between 1975 and 2012 (RR 3.45, 95% CI 2.66-4.48) and almost doubled between 2001 and 2012 (RR 1.85, 95% CI 1.53-2.25). These rates were also projected to continue to rise at a rapid rate up to 2025 and even surpass the rates of oral cavity cancer, which were expected to have only a relatively modest increase.

Once again, these results were in general agreement with the previous global evidence discussed in the literature review in Chapter 1. More locally, similar results were observed in England where the increase in the incidence burden of head and neck cancer was largely driven by a rise in the rates of oropharyngeal cancer (Louie et al., 2015). The authors also predicted that the rates of oropharyngeal cancer would continue to increase up to 2025, and this

too was in agreement with the findings of the study presented in Chapter 2 of this thesis.

#### 5.2.2.3 Chapter 2 hypothesis (c): The patient profile of oropharyngeal cancer will differ from other subsites, particularly in relation to socioeconomic status.

The current study demonstrated a gender and socioeconomic inequality in the incidence burden of head and neck cancer, with males and those from the most deprived areas of Scotland consistently exhibiting the highest rates of cancer, irrespective of subsite. Moreover, a dose-effect relationship was also seen, with the rates of cancer increasing as the level of deprivation increased.

The risk profile of oropharyngeal cancer was very similar to this, with males and those from the most deprived areas consistently exhibiting the greatest incidence burden. The peak age of incidence of oropharyngeal cancer was slightly lower (5-10 years) than that of the other subsites examined in this thesis. These findings were in agreement with a previous retrospective analysis conducted in the United States (Gillison et al., 2012b) that also reported an increased burden of oropharyngeal cancer among males, as well as a brief presentation in Scotland which reported that this was the fastest increasing cancer (particularly in men) (Junor et al., 2010). Dahlstrom et al. (2015), in their study examining 356 patients that were diagnosed with oropharyngeal cancer at the University of Texas MD Anderson Cancer Centre, reported that the patients included in their study exhibited high levels of education, income, and overall socioeconomic status. This was in contradiction to the findings of this thesis which showed a socioeconomic inequality in the distribution of the incidence burden of oropharyngeal cancer, with those from the most deprived areas consistently exhibiting the highest incidence rates.

Therefore, this hypothesis was rejected as, despite being slightly younger, the overall patient profile of oropharyngeal cancer did not differ considerably from the other subsites, particularly with regard to socioeconomic status.

#### 5.2.2.4 Chapter 2 hypothesis (d): in relation to the socioeconomic distribution of head and neck cancer (oral cavity and oropharyngeal cancer), there will be a clear stratification of "high-risk" areas in the more deprived communities that could be utilised to target early detection initiatives.

This hypothesis was confirmed by the findings of Chapter 2 which showed that the most deprived areas of Scotland consistently exhibited the highest incidence rates of cancer, irrespective of subsite, thus representing "high-risk" areas that could be utilised to target early detection efforts. Additionally, this socioeconomic inequality between the most and least deprived areas of Scotland exhibited a dose-effect relationship, with the rates of cancer rising as the levels of deprivation increased.

These findings were in general agreement with the global evidence presented previously in Chapter 1. More locally, these results were corroborated by Conway et al. (2006), who also reported higher incidence rates of oral cancer in the most deprived areas of Scotland.

#### 5.2.2.5 Chapter 3 hypothesis (a): The number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) a general dental practitioner in Scotland can expect to see per year will be relatively low.

This hypothesis was confirmed by the findings of Chapter 3 which showed that the number of patients with oral cancer (oral cavity and oropharyngeal cancer) a primary dental care practitioner in Scotland could expect to see per year was quite low. Upon application of published dental service registration and participation (attendance) rates, it was estimated that a primary dental care practitioner could expect to see one case of oral cancer every 8 years, one case of oral cavity cancer every 14 years, and one case of oropharyngeal cancer every 20 years. However, this study also used data linkage to calculate the actual proportion of patients that had contacted a general dental practitioner in the two years prior to diagnosis and, upon using these calculated attendance rates, the numbers were seen to increase to ten years for oral cancer, 17 years for oral cavity cancer, and 25 years for oropharyngeal cancer.

Although several studies had used this methodology previously to examine the distribution of childhood cancer and medical emergencies in relation to the location of health practitioners (Feltbower et al., 2004; Muller et al., 2008), there was only one other study that had focused on patients with oral cancer by undertaking a simple calculation of the headline distribution of the patients in relation to the number of dentists in England, Northern Ireland, and Wales (Ogden et al., 2015). The authors suggested that there would be one case of oral cancer for every ten dentists per year, and the current thesis reported similar, albeit slightly lower, numbers (using published rates), with one case of oral cancer for every 8 dentists per year. However, Ogden et al. (2015) did not provide any information on the definition of oral cancer used and the time period considered, and also did not take registration rates into consideration.

#### *5.2.2.6* Chapter 3 hypothesis (b): Dentists working in more deprived areas will expect to see a greater number of patients with oral cancer (oral cavity cancer and oropharyngeal cancer) compared to dentists working in relatively less deprived areas.

This hypothesis was rejected as examination of the distribution of patients with oral cancer, oral cavity cancer, and oropharyngeal cancer in relation to the location of general dental practices in Scotland by deprivation showed no obvious patterns or relationships. This could partly be explained by the fact that although there are inequalities in access to NHS primary care services such as general medical practices in Scotland, the distribution of dental practices does not follow this pattern (Audit Scotland, 2012). Therefore, registration rates do not exhibit the typical skew of inequality, although participation (attendance) rates are lower in the more deprived communities (ISD Scotland, 2016b). As a result, this offsets the higher incidence rates of oral cancer in deprived areas as they are distributed among the higher number of dentists in these same deprived areas.

No other studies could be identified to date that have examined the influence of socioeconomic status on the distribution of patients with oral cancer, oral cavity cancer, and oropharyngeal cancer in relation to the location of general

dental practices. Therefore, the findings reported in Chapter 3 were novel and could not be compared with any other studies.

#### 5.2.2.7 Chapter 4 hypothesis (a): There are a number of potentially missed opportunities for early detection of oral cancer in dental and other healthcare services.

Chapter 4 showed that nearly all (95%) of the patients that were included in this study had contacted at least one of the four healthcare services examined (hospital outpatient, hospital inpatient/ day-case, primary dental care, and GP prescription) in the two years prior to the start of the referral period, while just under half (45%) had contacted a primary dental care service over the same period. This suggested that there were potential opportunities for early detection, but they were not all within primary dental care services. These results were, to a certain extent, in agreement with Ligier et al. (2016) who reported that 88% of the patients with head and neck cancer (n=342) from a high-incidence region in France included in their study had contacted a health professional (GP, dentist, ENT specialist, non-ENT specialist) at least once in the 2- to 12-month period preceding diagnosis, while the majority (80%) of them had not consulted a dentist over the same period.

Chapter 4 also looked at novel contacts for early detection of oral cancer in hospital/secondary care settings (both hospital inpatient/ day-case and hospital outpatient), but found limited evidence of it. Instead, it identified considerable potential in other primary care settings, particularly GP and pharmacy, with 89% of patients with oral cancer that were included in this study being issued a GP prescription in the most recent year prior to the start of the referral period. Although a large proportion of these were likely to have been repeat prescription (Harris and Dajda, 1996; Petty et al., 2014), almost all of them would have been dispensed at the pharmacy. Therefore, there is a possibility that the pharmacy may have a role to play in the early detection of oral cancer, and this could be an interesting setting for further work.

Therefore, the findings of this study were in support of the hypothesis that there were numerous potentially missed opportunities for early detection of oral cancer in primary dental care as well as other healthcare settings.

#### 5.2.2.8 Chapter 4 hypothesis (b): These potentially missed opportunities increase in frequency in the months directly prior to the start of the referral period.

This hypothesis was also confirmed by the findings of Chapter 4 which showed that the patients that were included in the current study had increased their frequency of contact with hospital outpatient, hospital inpatient/ day-case, primary dental care, and GP prescription services in the most recent year and, particularly, the most recent six months prior to the start of the referral period. Moreover, the proportion of patients contacting these services had also increased over the same time period. Lyratzopoulos et al. (2015) previously reported that unusual pre-referral health service contacts could be indicative of missed opportunities for early detection of cancer and, based on this logic, the increasing frequency of contacts with health services observed in this study could be interpreted as missed opportunities in at least some of the cases or as potential opportunities that can be harnessed for further early detection efforts.

## 5.3 Interpretation of results and possible explanations

This section discusses the interpretations of some of the major findings of this thesis, and uses the previous literature to draw conclusions regarding possible explanations.

The descriptive epidemiological study presented in Chapter 2 of this thesis showed that the rates of head and neck cancer were rising in Scotland, and this appeared to be largely driven by a dramatic increase in the rates of oropharyngeal cancer between 1975 and 2012. Moreover, these rates were predicted to continue to rise up to 2025, with the rates of oropharyngeal cancer bypassing the rates of oral cavity cancer, which were expected to exhibit a more modest increase. These results were in keeping with Louie et

al. (2015) who reported that the increasing burden of head and neck cancer in England between 1995 and 2011 appeared to be largely driven by the incidence rates of oropharyngeal cancer. Moreover, they predicted that oropharyngeal cancer would account for one third of the projected burden of head and neck cancer by 2025. Human papilloma virus infections have been shown to play an aetiological role in oropharyngeal cancer (Gillison, 2004; D'Souza et al., 2009), and Hashibe and Sturgis (2013) proposed that the changing profile of head and neck cancer incidence could be explained by the controlling of a "tobacco epidemic while a human papillomavirus epidemic emerges". This statement was supported by Louie et al. (2015) when they demonstrated that the increasing rates of oropharyngeal cancer were paralleled by a rise in sexually transmitted infections (used as a proxy for HPV infection in their study). They suggested that these results "highlighted changing sexual behaviours", based on the evidence that HPV infections may be transmitted via oral sexual behaviours (Hemminki et al., 2000; D'Souza et al., 2009), and made an urgent call for primary prevention through administration of the HPV vaccine in males and females in England.

Although many countries have exhibited a dramatic decrease in the rates of oral cavity cancer in the recent past (Chaturvedi et al., 2013), the results of this thesis showed an increase in incidence rates between 1975 and 2012 in Scotland. Similar escalating trends were also observed in the Netherlands, Brazil, and Denmark (Chaturvedi et al., 2013), as well as in England (Louie et al., 2015). However, this increase could not be attributed to smoking, based on the decreasing rates of lung cancer observed in England and Scotland (ISD Scotland, 2015; Louie et al., 2015), and the role of HPV in the aetiology of oral cavity cancer is still unclear (Hübbers and Akgül, 2015). Possible alternative explanations could be an increase in alcohol consumption, known to act synergistically with tobacco, in more recent birth cohorts (Franceschi et al., 2000; Chaturvedi et al., 2013); a greater prevalence of smokeless tobacco consumption among the growing South-Asian Community in Scotland (Herrero et al., 2003; Lambert et al., 2011; The Scottish Government, 2017a);

and the migration of populations from regions with high incidence of head and neck cancer (Warnakulasuriya et al., 1999; Mangtani et al., 2010).

The differences in incidence rates between the sexes possibly reflected the greater prevalence of HPV infections and tobacco and alcohol consumption among men compared to women (IARC, 2007; ScotPHO, 2008; Chaturvedi et al., 2011; Gillison et al., 2012b; Hashibe and Sturgis, 2013). Although the difference in smoking rates between males and females in Scotland was quite low (22% in males vs 20% in females) (ScotPHO, 2015), the prevalence of hazardous drinking (defined by the Scottish Government as being over the recommended 14 units of alcohol per week) among males (36%) was more than double the rates observed in women (17%) (The Scottish Government, 2015). A previous meta-analysis reported that males were more likely to indulge in "risky behaviours" such as smoking, drinking, and unprotected sex, and this gender gap in behavioural tendencies varied with age (Byrnes et al., 1999). The authors explained these differences using three theoretical models. The first was the self-regulatory model proposed by Byrnes (1998) which suggested that the gender gap was a result of "double standards with respect to parenteral monitoring" that resulted in women and girls encountering greater restrictions while growing up, lack of knowledge regarding "self-correcting strategies" among men, and overconfidence among men and boys. The second biopsychosocial theory was proposed by Lipsitt and Mitnick (1991) and suggested that periodic changes in a number of factors such as self-perception, biological maturation, risk perceptions, personal values, cognitive scope, and perceptions of the social environment affected men and women in different ways and at different times, resulting in a gender gap that varied with age. The last theory was Wigfield and Eccles (1992) expectancy-value model which suggested that gender differences in behaviour were a result of variations in the expectations of men and women. However, Byrnes et al. (1999) clarified that they had isolated these three models to explain the gender differences in behavioural factors as they were the most relevant to the findings of their meta-analysis and, in reality, there were several other models that could also explain aspects of the gender gap.

The socioeconomic determinants of health inequalities have been a key focus of research over the last century. In the United Kingdom, evidence of a social pattern in disease distribution was first reported by Sir Douglas Black in the influential *Black Report* where he divided the British population into six social classes and reported that members of the lowest class exhibited mortality rates that were approximately double that exhibited by the highest social class (Black, 1982). Although this report had several limitations, it formed the foundation for a subsequent explosion of research in the field of socioeconomic determinants of health. Notably, the Whitehall study of British civil servants used grade of employment as a marker of socioeconomic status and reported a social gradient for all major causes of death (Marmot et al., 1984).

The WHO International Agency for Research on Cancer proposed that socioeconomic factors could affect inequalities in health through a number of pathways including access to medical care health selection, factors operating in early life, health-related behaviours, material factors, and psychosocial factors (Pearce, 1997). The epidemiological study of this thesis demonstrated a socioeconomic inequality in the distribution of head and neck cancer in Scotland, with the most deprived areas exhibiting higher rates of cancer compared to the least deprived areas, irrespective of the subsite considered. This socioeconomic gap could be explained to a certain extent by an inequality in the distribution of risk factors. The Whitehall study II (Marmot et al. 1991) demonstrated a clear link between socioeconomic position and several established behavioural and biological risk factors, with lower social classes consistently exhibiting higher prevalence of smoking, poor diet, obesity, and lack of physical activity. In keeping with this, the prevalence of smoking was seen to be much higher in the most deprived areas (36%) of Scotland compared to the least deprived areas (10%) in 2012 (ASH Scotland, 2014). Moreover, the number of cigarettes smoked per day was also higher in the most deprived areas (15.3) compared to the least deprived areas of Scotland (12.6) (ASH Scotland, 2014). A similar inequality was also observed with regard to alcohol consumption, with the number of people (per 100,000)

being admitted to hospital for alcohol-related reasons being eight times higher in the most deprived areas compared to the least deprived areas (ISD Scotland, 2017l). A cross-sectional analysis examining the relationship between deprivation and alcohol and tobacco outlet density in Scotland reported that the most deprived areas had the greatest densities of both (Shortt et al., 2015), and this social gradient in the supply of tobacco and alcohol would likely be reflected in the consumption rates and, subsequently, the incidence rates of tobacco and alcohol related diseases. Moreover, previous studies have suggested that higher socioeconomic position may have resulted in a reinforcement of healthy behaviours such as maintenance of oral hygiene and regular physical exercise (Liberatos et al., 1988; Ross and Wu, 1995), while education and higher-level occupations were often associated with better access to health services and reduced exposure to occupational risk factors of head and neck cancer (Riechelmann, 2002). With regard to HPV infections, a previous small clinical series conducted at the University of Texas MD Anderson Cancer Centre examined the socioeconomic characteristics of oropharyngeal cancer by HPV status and reported that patients with HPV-positive oropharyngeal cancer usually exhibited higher levels of income and education (Dahlstrom et al., 2015). Moreover, within this group, non-smokers tended to have the highest socioeconomic status. Gillison et al. (2008), in their case-control analysis, reported that patients with HPV-negative head and neck cancer were more likely to have high school degrees and were also less likely to earn $50,000 or more compared to the cancer-free controls. However, neither of these studies considered population-level data, and instead focused on a very small sample of patients with oropharyngeal cancer. The findings of the current thesis contrasted with these studies, with the most deprived areas of Scotland exhibiting the highest rates of head and neck cancer irrespective of subsite. The dataset used did not contain information on HPV status and tobacco and alcohol consumption thereby preventing exploration of any variations in trends by risk factors in the Scottish context, and this could be an interesting setting for further work.

Another possible explanation for socioeconomic inequalities in health was the theory of health selection (Black, 1988), the essence of which was that health determined social position instead of vice versa. This selection could occur at different stages of life, and could be explained by one of the two following ideas: a) that the "sick drifted down the social hierarchy", producing an accumulation of individuals at a higher risk of disease in the lower social groups, or b) where selection occurred at an earlier age between childhood and introduction to the labour market, that is, the health status in childhood ultimately determined the social status of an adult. Common background factors operating in early life may also lead to inequalities in health, and this was termed as 'indirect selection' (Wilkinson, 1986). These include genetic factors, early life experiences that led to biological changes, and various social, psychological, cultural and educational factors. Ben-Shlomo and Davey-Smith (1991) stated that early life influences shaped the lives people led as adults and the social environments in which they existed, and these conditions, in turn, could be related to ill health. Lastly, psychosocial factors associated with job strain, low control, and low social support may also increase the risk of disease. For example, a perceived 'lack of control over health' among individuals in lower socioeconomic strata may have led to the adoption of health behaviours such as smoking or poor diet, which increased the risk of developing disease (Pearce, 1997).

The descriptive epidemiological study (Chapter 2 of this thesis) was undertaken bearing secondary prevention of oral cancer in mind, with the focus on trends from a socioeconomic perspective aiming to identify target "high-risk" subgroups of the population for further early detection efforts. The two strategies for early detection, namely, screening and early diagnosis, have been discussed previously in Chapter 1. To reiterate, the goal of screening was to identify pre-cancerous lesions in an apparently healthy population, while that of early diagnosis was to detect the signs and symptoms of cancer in a timely manner so as to achieve diagnosis at an earlier stage when the prognosis was better (WHO, 2006). The overarching aim of this thesis was to identify opportunities for early detection of oral cancer in

various healthcare settings. However, the cohort for this study was identified based on a diagnosis of oral cancer, and this automatically biased the results in favour of opportunities for early diagnosis rather than screening. Given that the difference between the two strategies essentially lies in the clinical stage progression of the disease, there was a possibility that some of these healthcare service contacts occurred before the clinical signs and symptoms of oral cancer had become apparent, and further research with regard to OPMDs would help clarify whether these contacts could represent missed opportunities for opportunistic screening instead. Therefore, although interpretation of the opportunities identified in this thesis was not as straightforward as expected and screening and early diagnosis differ fundamentally in terms of logistics and resources (WHO, 2006), the findings did contribute towards identification of the subgroup of the population and the alternative healthcare services that could be utilised to target further early detection efforts.

Dental health services are provided across a range of settings in Scotland, and the dental care team typically consists of dentists, dental nurses, hygienists, therapists, receptionists/managers, and dental technicians. The majority of general dental services are provided by general dental practitioners who are independent contractors that provide services on behalf of the various NHS Health Boards. Public Dental Service dentists are those that are employed by the NHS Health Boards, and their main function is to provide dental services to those with special care needs and those living in geographical areas where it may be difficult to access a general dental practitioner, while the Hospital Dental Services in Scotland accepts patient referrals from medical and dental practitioners and primarily provide secondary care services. Recently, the Scottish Government's Oral Health Improvement Plan, published in January 2018, set the direction for tackling oral health inequalities to reorientation of services from the simple oral health focus to a wider, more prevention-based approach (The Scottish Government, 2018). It also recommended community engagement and development activities, and specifically mentioned oral cancer risk assessment and preventive pathways. Early detection of oral

cancer in primary dental care services is largely dependent on patients consulting general dental practitioners on a regular basis, and the results of this thesis showed that a bulk of the patients with oral cancer in Scotland simply did not do so. There could be several possible explanations for this, some of which have been discussed previously in Chapter 1. Netuveli et al. (2006) in their study using data from the Health Survey for England (2001) and the British Household Panel Survey reported that the "inverse screening law" was applicable to patients with oral cancer, with those at the highest risk of developing cancer being the least likely to contact dental services on a regular basis. The authors suggested that this could be because "risk behaviours tend to cluster in the same individuals", with heavy smokers and drinkers more likely to avoid risk-aversion behaviours such as regular dental attendance. Another possible explanation proposed was the role of psychological factors in a patient's decision to seek help. Hackett et al. (1973) suggested that delay in seeking help was often a conscious and deliberate act on the part of the patient, and this was often fuelled by underlying psychosocial factors such as fear and perceptions of social accountability. Moreover, worry, though a complex variable, was seen to be inversely proportional to the duration of delay, with those worrying about a particular symptom often exhibiting reduced delay (Hackett et al., 1973). This was supported by a recent extensive review that examined the components and possible solutions for late stage diagnosis of oral cancer and found that factors such as fear, denial, worry, and perceptions of social responsibilities often caused patients to delay seeking medical help upon observing symptoms (Güneri and Epstein, 2014). Conversely, a considerably older study suggested that the most common determinant of delay was cancer knowledge (Antonovsky and Hartman, 1974), and this was corroborated by a case-series analysis in the Netherlands that used self-reported questionnaires to examine delays in seeking medical help and reported that patients were more likely to visit a healthcare provider sooner after self-discovery of symptoms if they had prior knowledge and a higher level of awareness of cancer (Tromp et al., 2005).

This thesis also examined whether early detection of oral cancer in primary dental care services was a realistic expectation, given the relatively low incidence burden in Scotland. The results showed that the number of patients with oral cancer per dentist was very low, and a general dental practitioner in Scotland could expect to encounter only one patient with oral cancer every ten years or, in other words, only four patients over a career spanning 40 years. Further exploration showed that this situation worsened if individual subsites were considered, with a general dental practitioner in Scotland expecting to see only one case of oral cavity cancer every 17 years and one case of oropharyngeal cancer every 25 years. However, these results do not intend to "over-burden" general dental practitioners in Scotland by creating an expectation for early detection of oral cavity cancer and oropharyngeal cancer separately. Instead, the purpose of this additional exploration by subsites was to highlight the need for vigilance and the importance of conducting extra- and intra-oral examinations during routine dental check-ups. Moreover, awareness of certain signs and symptoms that could suggest involvement of a particular subsite is also necessary. For example, dysphagia or odynophagia lasting for more than three weeks, a persistent lump in the throat, and persistent pain in the throat lasting for more than three weeks could be indicative of oropharyngeal cancer, while ulceration or unexplained swellings of the oral mucosa persisting for more than three weeks and/or all red or mixed red and white patches of the oral mucosa persisting for more than three weeks could suggest oral cavity cancer (NHS Scotland, 2016b).

Therefore, the results of Chapter 3 of this thesis suggest that the consequence of limiting early detection efforts for oral cancer to primary dental care services only was that a large section of the population would be neglected. However, almost all (95%) of the patients included in this thesis had contacted one of the four services (hospital outpatient, hospital inpatient/ day-case, primary dental care, and GP prescription) examined in the two years prior to the start of the referral period, suggesting that there were opportunities for early detection in alternative healthcare services. This was in agreement with Ligier et al. (2016) who reported that 88% of the 342 patients with head and

neck cancer that were included in their study had contacted a health professional at least once in the 2- to 12-month period preceding referral. Paudyal et al. (2014), in their systematic review examining patient acceptance of oral cancer screening in non-dental settings, reported that most patients preferred to contact a general medical practitioner upon detecting symptoms primarily because of ease of access, familiarity with the practitioner, local nature and relevance in case of a health-related intervention. “Lack of trust of a dentist” was cited as another reason why patients preferred general medical practitioners over dentists, and this was rooted in the belief that dentists were “teeth specialists” and did not have the same power as a general medical practitioner to write prescriptions and refer patients. Financial costs may also have had a role to play as, under the National Health Service in the United Kingdom, all contacts with general medical practitioners are free of charge while only check-up and examination contacts with general dental practitioners are free. All other treatments by a general dental practitioner are chargeable. Given that a large proportion of the patients with oral cancer that were included in this study were from the most deprived areas of Scotland, there was a possibility that this factor influenced their decision to approach alternative healthcare services upon self-discovery of symptoms. Lastly, difficulty in access and lack of availability of appropriate dental services may also have affected a patient’s decision to contact alternative healthcare services instead.

Another key finding of this thesis was that the patients with oral cancer that were included in this study had increased their frequency of contacts with health care services in the one year and, specifically, the six-month period prior to the start of the referral period. Although not all of these contacts were necessarily cancer-related, these results do suggest that there may have been missed opportunities for earlier diagnosis and referral in at least some of these cases. Multiple consultations before referral are usually associated with delays in the diagnostic process (Lyratzopoulos et al., 2014), and factors contributing to patient, professional, or system delays have been discussed in detail in the literature review in Chapter 1. Briefly, patient factors that may

have contributed to multiple pre-referral appointments and delays in the diagnostic process include “no show” events, failure to follow up on results, and psychosocial factors (Lyratzopoulos et al., 2015). Professional factors that may have played a role include the failure of dental and medical practitioners to recognise malignant lesions of the oral cavity due to the non-specific appearance and potentially insidious nature of these lesions (Güneri and Epstein, 2014); vague or unspecific clinical signs (Bruun, 1976); lack of experience/unfamiliarity with the disease (Guggenheimer et al., 1989); low index of suspicion (Holland, 1975); deficient clinical examination (Robbins et al., 1950); and presence of co-morbidities (Allison et al., 1998). System delays could be caused by factors such as limited accessibility and affordability of healthcare services, availability of specific treatments, and difficulties in scheduling appointments (Güneri and Epstein, 2014). To this mix of factors, this thesis adds the additional issues of relatively low volume of oral cancer in Scotland and poor dental attendance patterns (despite universal population coverage) among the target population.

## 5.4 Methodological strengths and limitations

This section reviews some of the strengths and limitations of this thesis, particularly in relation to the nature of the data used and the methodology employed. The strengths and limitations of each study have been considered in the discussion sections of the relevant chapters, and this section mainly summarises those relevant to this thesis in its entirety.

### 5.4.1 Routine administrative data

Grzeskowiak et al. (2013) stated that it was almost an ethical obligation on the part of researchers to exploit routinely collected health data if they would help develop a better understanding of the disease and its risk profile. The main strength of this thesis lay in the use of robust, routinely collected administrative health data with full population coverage, and such data has several advantages. Firstly, this study used individual-level data that covered the entire population of Scotland, resulting in a relatively large sample size

that increased the generalisability, accuracy, and precision of the results and minimised the risk of several types of bias including selection bias and recall bias. Secondly, the data were routinely collected as part of clinical and/or administrative procedures and were therefore readily available, allowing exploration of the various research questions in a timely and cost-efficient manner. Thirdly, the data collection process was standardised and unobtrusive, and enabled examination of the various elements of a patient's healthcare service contact history over several years. Fourthly, as discussed in detail previously, the quality of the data that was collected and maintained in Scotland was extremely high, which further increased the strength of the evidence (Brewster et al., 1994; Brewster et al., 1997; Brewster et al., 2002). Lastly, routinely collected administrative data had the additional advantage of allowing linkage of several databases. In Scotland, it was estimated that approximately 96.5% to 99.9% of the population had a Community Health Index (CHI) number, which is a register of all patients who have used the Scottish National Health Service, and this unique identification number allowed linkage of all healthcare records of a particular individual across time and location (Pavis and Morris, 2015). The specific advantages and disadvantages of the data linkage process have been discussed in further detail in the next section.

Routinely collected data also has several limitations, and these are mainly related to their availability. Firstly, data from general practitioners were unavailable in Scotland and this restricted a detailed exploration of contacts made by the patients. Instead, this thesis considered prescriptions issued by GPs as a proxy for contact with a general practitioner, based on the assumption that all prescriptions were associated with a face-to-face contact with a GP hence creating an opportunity for the early detection of oral cancer. However, in reality, a large proportion of these were likely to have been repeat prescriptions, and introduction of the electronic prescription service in Scotland meant that many of these could have been dispensed online and did not require actual contact with a general practitioner (Digital Health, 2017). A recent cross-sectional study examining repeat prescriptions

issued by 29 general practices in one Primary Care Trust in England reported that approximately 77% of all prescriptions issued in 2011 were repeat prescriptions, with the mean number of repeat items per individual being 1.87 (Petty et al., 2014). Approximately 43% of the population in the United Kingdom had received at least one repeat prescription in the year of study, and the authors stated that their results were largely "typical of the UK" as their study included both small and large practices that covered a wide socioeconomic and cultural range of population. Although the proportion of repeat prescriptions issued in Scotland is currently not measured, personal communication with the principle pharmacist at the Information Services Division Scotland revealed that the generally accepted assumption was that approximately 80% of all prescriptions issued in Scotland were repeat prescriptions (McTaggart, 2018). This must be taken into consideration when interpreting the results of this thesis as it may have led to an overestimation of contacts with a GP.

Data on the severity of the disease (stage of cancer at the time of diagnosis) were unavailable, and this information would have allowed further examination of the impact of missed opportunities for early detection on prognosis and determination of whether pre-referral contact with a healthcare service could result in a shift to an earlier stage of cancer at the time of diagnosis. Lack of data on the HPV status of patients and behavioural factors such as smoking and alcohol consumption prevented exploration of the driving factors of the trends seen in Chapter 2, and also restricted the development of a clearer risk factor profile of patients. There was a potential for misclassification of the primary neoplasm and subsequent errors in the ICD code assigned. This may have influenced the results, particularly where additional exploration by subsite was performed. Lastly, data on the source of referral were also unavailable, and this information would have allowed accurate estimation of the proportion of patients with oral cancer that had consulted and been referred by alternative healthcare services.

### 5.4.2 Data linkage

The data linkage process aims to match routinely collected health data of the same individual across various databases using a unique identification number or various personal identifiers such as name, age, and sex. Scotland currently has some of the best administrative health data in the world, with approximately 96.5% to 99.9% of the Scottish population having a Community Health Index number, and linkage of this data would allow researchers to "unleash, at scale, the power of health service and wider administrative data" (Pavis and Morris, 2015). The Scottish Government's strategy for data linkage, "*Joined up data for better decisions: A strategy for improving data access and analysis*", acknowledges that the advantages of this process are numerous and summarises them into five key benefits (The Scottish Government, 2012a). Firstly, it allows provision of a high-quality cross-sectoral evidence base that can be used for policy planning and strategic development, which in turn speeds up the process of service improvement. Secondly, linking various existing, routinely collected healthcare databases enhances the quality and consistency of the data itself through deletion of duplicate records in the system and correction of data artefacts. Moreover, it maximises the potential of the data by allowing researchers to develop reliable methods of producing statistics and examine complex issues affecting society in a non-intrusive manner. Thirdly, it allows longitudinal research, both retrospective and prospective, to be executed easily and in a cost-efficient manner. Fourthly, it increases the capacity to accurately evaluate public sector programs by providing the means to answer sophisticated research questions and reducing the cost of carrying out surveys instead. Lastly, feedback loops focusing on linkage activities allows monitoring of the quality and consistency of the data.

As discussed previously, the quality of data linkage in Scotland is also quite high, and Kendrick and Clarke (1993) reported that clerical monitoring of pair-wise linking showed that the false negative rates (the proportion of pairs which the system fails to link) and the false positive rates (the proportion of pairs which are incorrectly linked) were both approximately three percent

only. In this thesis, data linkage allowed examination of the patient's past medical history in terms of their utilisation of health care services in a cost-efficient, complete, and non-intrusive manner. It also lowered the risk of selection bias and permitted testing of various novel hypotheses. Providing access to the de-identified, linked research datasets through a federated network of "safe havens" also eliminated the need for individual patient consent, and instead relied on consent from the legal data controllers following a rigorous assessment of the research protocol (Pavis and Morris, 2015).

However, data linkage also has several limitations. In Scotland, this is achieved by using the probabilistic matching method which accounts for discrepancies in personal identifiers (discrepancy rate of three percent) that may lead to approximately 15% of true links being missed (Kendrick and Clarke, 1993). There is a certain level of uncertainty associated with this method, particularly when performing longitudinal or cross-generational matching of records as there may be changes in name or address, typographical errors, or individuals lost to follow-up because of a change in country or state of residence (Grzeskowiak et al., 2013). A systematic review examining the accuracy (the proportion of records that were truly linked) and specificity (proportion of truly unmatched records) of probabilistic data linkage found that it ranged from 74% to 98% and from 99% to 100%, respectively (Pinto da Silveira and Artmann, 2009). The authors also mentioned that these figures were largely dependent on the quality and number of fields available for linkage.

Moreover, as discussed previously, Bohensky et al. (2010), in their structured narrative review of factors that affected the quality of data linkage, reported that age, sex, race, setting, health, and socioeconomic status were usually associated with a risk of incomplete data linkage, although the evidence on the association between some of these factors and the probability of incomplete linkage occurring was inconsistent. Additionally, they also suggested that this incomplete linkage could be caused by factors such as governance issues including the need for consent, method of linkage

employed, and accuracy and completeness of the original datasets used for linkage. Additionally, factors such as lack of a standardised definition for data or inconsistencies in coding practices may further complicate matters by introducing a certain level of systemic bias in the results of the study and, therefore, must be kept in mind when interpreting outcomes.

Therefore, in relation to the data linkage research executed in this thesis (Chapter 3 and 4), although on one hand there were real strengths in collating all the data on patients that were diagnosed with oral cancer in Scotland, there were also some limitations in terms of missing linkages which must be considered when interpreting the results. However, the impact of missing linkages would lead to an under- rather than an over-ascertainment of opportunities for early detection, and hence the findings of this thesis were generally conservative.

### 5.4.3 Measurement of socioeconomic status

Miech and Hauser (2001) defined socioeconomic status as “a broad concept that refers to the placement of persons, families, households and census tracts or other aggregates with respect to the capacity to create or consume goods that are valued in our society". There are two main approaches to measuring socioeconomic status, namely, the compositional approach which takes into account the characteristics of the individual and the contextual approach which considers the characteristics of the individual’s environment (Kaplan, 1999). Both of these approaches have their own strengths and limitations. For example, a compositional measure such as education has several advantages such as ease of measurement; reasonable stability beyond early adulthood; increased possibility of capturing aspects of lifestyle and behaviour; less likely to be influenced by disease than income or occupation; and higher levels of education usually predict better jobs and, consequently, better working conditions, housing, and neighbourhood. However, it also has several limitations such as the fact that it has different social meaning and consequences in different populations and at different times; increases in years of education are not always accompanied by a consistent increase in

SES; and the economic returns of education may vary with race/ethnicity and gender. Similarly, occupation as an SES measure provides a structural link between education and income, captures the environmental and working conditions of an individual, and is less volatile than income. However, there is difficulty associated with classification of homeowners and retirees, it cannot always be measured precisely, it does not take into account racial or gender differences in the benefits that arise from employment in the same occupation, and occupational class usually includes a range of heterogeneous occupations which may vary considerably in terms of the education required and the associated income and prestige. Contextual measures, on the other hand, usually include ecologic measures that capture the social and economic conditions that affect all individuals living in a particular geographic area (Shavers, 2007). Their accuracy is influenced by factors such as the amount of time elapsed since the data was collected and the dynamic nature of the area including gentrification, variations in industry and employment rates, and movements in and out of the area.

The Scottish Index of Multiple Deprivation is a composite measure of socioeconomic status that takes into account 38 indicators in seven domains which include both compositional (income, employment, health, education) and contextual measures (geographic access, crime, and housing) (Donnelly, 2009). The main advantage of using such a measure is that it incorporates both individual-level and area-level factors which may provide additional insight. Moreover, it may also be useful for area-wide planning. However, the main limitation of such an index is that aggregation of SES may result in confounding brought about by a measure of area-level SES that is difficult to interpret (Shavers, 2007). The influence of individual measures of SES on the results of epidemiological studies are dependent on the research question and population being examined (Shavers, 2007). However, consideration of the effects of the individual measures included in the Scottish Index of Multiple Deprivation on the findings of the studies presented in Chapters 2, 3, and 4 was considered to be beyond the scope of this thesis.

An essential issue to consider while interpreting the results of this thesis is the phenomenon of "ecological fallacy", caused by the use of geographic area-based measures of socioeconomic status as surrogate individual measures. Such deprivation indices assign individuals living within a certain area the same socioeconomic status, and this can result in individual-level inferences being made from area-level relationships (Berkman and Macintyre, 1997; Macintyre and Ellaway, 2000). For example, Chapter 3 of this thesis considered the deprivation status of the dental practices, and not that of the patients themselves, to calculate the number of patients per dentist. The linkage study, on the other hand, considered the SIMD fifth of the patient's area of residence to better elucidate if deprivation had any effect on their likelihood of attending a dentist. This may have resulted in ecological fallacy as a patient who lives in a particular SIMD fifth may not necessarily attend a dental practice within the same SIMD fifth, just as the registration profile of a practice may not necessarily reflect the SIMD fifth his/her practice is located in.

However, such ecological interpretation also has several advantageous in terms of indicating the social and physical environment or circumstances, for example, adequate access to health care services. Additionally, it also helps better understand small area diseases, plan ways to tackle them based on availability of health services, and monitor population level inequalities. Ideally, a combination of individual and area-based socioeconomic measures would be utilised in order to take account of individual and area effects

## 5.5 Further work

The findings of this study and the limitations imposed by data availability, time, and resources made it evident that additional research in the field of potential or missed opportunities for the early detection of oral cancer was necessary. This section summarises some of the further work that could be undertaken.

One of the key limitations of the current thesis was the unavailability of general practitioner data in Scotland, necessitating the use of prescriptions issued by GPs as a proxy for contact instead. However, the Scottish Primary Care Information Resource (SPIRE) was introduced in May 2017 and, although not a national database that collects data on a routine basis, this service will collect some information from general practitioner practice records for further use in research, efforts to improve care, and the planning of services (ISD Scotland, 2017k). Future research should utilise data from this resource to further explore missed opportunities and the role of general medical practices in the early detection of oral cancer. Moreover, as mentioned previously, an estimated 80% of the GP prescriptions issued to the patients with oral cancer that were included in this study were likely to be repeat prescriptions and, therefore, did not necessarily require face-to-face contact with a general practitioner (McTaggart, 2018). However, the majority of these patients would have come in contact with a pharmacist at the time of dispensing the prescribed medications, and future studies could explore these prescription-dispensing contacts in order to further clarify the role of pharmacies in early detection strategies for oral cancer.

A key finding of this thesis was that the majority of the patients diagnosed with oral cancer were older males from the most deprived areas of Scotland who exhibited low levels of engagement with dental services. Moreover, although this data was unavailable in the current study, previous evidence suggests that these individuals were also likely to exhibit higher prevalence of risky health behaviours such as smoking and alcohol consumption. Therefore, future studies could focus on these individuals and attempt to understand their motivations for engaging in such risky health behaviours and the extent to which they felt supported when attempting cessation. Additionally, emphasis could also be laid on trying to understand ways in which to support these individuals in the management of risk and motivate them to engage with healthcare services on a more frequent basis.

Further risk stratification of the communities in relation to the location of alternative healthcare services such as general practitioners and pharmacies

could be undertaken to allow estimation of the expected number of patients with oral cancer that would be seen per year by these services. This would inform further early detection strategies in alternative healthcare settings.

The findings of this thesis also showed that the patients with oral cancer had significantly increased their frequency of contacts with the GP prescription services in the most recent months prior to diagnosis. However, the proportion of these contacts that were actually cancer-related was unknown, and a future study could carry out a detailed exploration of the nature of the prescriptions issued by the general practitioners in order to develop a better understanding of this.

Another limitation of the current thesis was the utilisation of head counts of dentists to explore the distribution of the incidence burden of the disease in relation to the location of general dental practitioners in Scotland. Unfortunately, whole-time equivalent data for GDPs were unavailable, and future studies could consider utilising national workforce reports and activity data as a proxy measure of this to derive an even more accurate estimation of the number of patients a general dental practitioner could expect to see per year.

Unfortunately, data on the source of referral were currently unavailable at the national level in Scotland, and this thesis performed a superficial exploration of the routes to diagnosis by considering the last service contacted before the start of the referral period as a proxy for the referral source. It would take considerable effort to collate data on the sources of referral from all of the local clinical IT systems, and this could be another area of focus for future studies as it would permit exploration of the routes to diagnosis of oral cancer accurately.

The introduction of President Barack Obama's *The Precision Medicine Initiative* in the United States, and NHS England's *Improving Outcomes Through Personalised Medicine* strategy shifted the focus of research from the prevalent "one size fits all" approach, which developed strategies and made

recommendations bearing an “average person” in mind, to the “precision medicine” approach which tailored prevention strategies and treatments to subgroups of patients at the highest risk of developing a particular disease (The White House, 2015; NHS England, 2016). In Scotland, the Stratified Medicine Scotland Innovation Centre, introduced in 2013, aimed to accelerate the adoption of precision medicine by bringing together researchers, industry innovators, and clinicians to link together Scotland’s domain expertise, data assets, and delivery capability. The descriptive epidemiological study included in this thesis explored the trends of head and neck cancer in Scotland by various socio-demographic determinants, bearing early detection and the principles of precision medicine in mind. The broad goal of such an examination was to identify the subgroups of “high-risk” individuals that should be the focus of targeted early detection efforts. Although the findings of this thesis accomplished that to a certain extent, further risk stratification is necessary. Future studies could utilise nationally available data on HPV status and the stage of cancer at the time of diagnosis to examine variations in incidence trends. Additionally, further analyses of the existing data taking the Scottish Government’s Urban Rural Classification (The Scottish Government, 2016) into consideration can be undertaken as this will allow further risk stratification of patients based on their area of residence and, subsequently, their access to various healthcare services.

Although the results of this thesis can be generalised to other countries with similar universal healthcare settings such as the NHS, caution must be taken when interpreting the results in the context of other countries with different health and population infrastructures. Gallagher et al. (2018) recently reported that the majority (69%) of the world’s 1.6 million dentists were distributed in Europe and America, leaving the majority of the global population in developing countries such as India with approximately 30% of the available workforce. Therefore, the methodology and findings of the current thesis can be used to guide similar analyses in such countries where the distribution of a considerably higher burden of cancer among a lower volume of dentists would likely provide a different picture of opportunities for

early detection. Such analyses could also take availability of resources and the infrastructure of alternative healthcare services in such countries into consideration.

## 5.6 Conclusions and recommendations

Kingdon (2011), a political scientist from the United States, suggested that in order to achieve any significant change in population health, it was essential to consider three main issues, namely, "communicate the nature of the problem to be solved, identify appropriate evidence based policies, and engage with politics to achieve the desired change". This section discusses the thesis in this context by summarising the main findings to describe the nature of the problem identified, and then utilising these results to make policy and practice recommendations for the prevention of oral cancer at the community and healthcare service levels.

### 5.6.1 Thesis conclusions

The findings of this thesis showed that the burden of head and neck cancer had increased in Scotland between 1975 and 2012, and this appeared to be largely driven by a rapid rise in the incidence of oropharyngeal cancer in recent decades. Moreover, this burden of incidence was projected to continue to rise up to 2025, with the rates of oropharyngeal cancer surpassing the rates of oral cavity cancer, which were expected to exhibit only a relatively modest increase. Socioeconomic inequality in the distribution of head and neck cancer was also observed, with those from the most deprived areas of Scotland being at the highest risk of developing cancer. This pattern was consistent for all subsites, with oropharyngeal cancer being no exception, as had been previously suggested by Dahlstrom at al. (2015). Moreover, an almost dose-like effect appeared to exist, with the burden of cancer increasing with worsening levels of deprivation. The burden of incidence of cancer was higher among men than women, and among older age groups, although the peak age of incidence of oropharyngeal cancer (61-65 years) was only slightly lower than that of oral cavity cancer (71-75 years). Thus, overall

the sociodemographic profile of the various subsites of head and neck cancer appeared to be largely similar.

The overarching aim of this thesis was to identify opportunities for the early detection of oral cancer, and it was anticipated that the sociodemographic profile of the patients would inform community-based risk stratification that could target efforts and initiatives to improve early detection. The World Health Organisation (2006) recently clarified and made distinct the two main strategies for early detection, namely, screening and early diagnosis of cancer, with the key difference between the two being the stage of clinical progression of the disease. While the aim of screening was to identify pre-cancerous lesions in an apparently healthy population, the latter aimed to achieve a "stage shift" (to an earlier stage) through timely detection of the signs and symptoms of cancer and prompt referral and treatment (WHO, 2006). This thesis primarily focussed on opportunities for early detection through early diagnosis, grounded in the fact that the main cohort analysed in Chapter 4 was based on patients who had been diagnosed with oral cancer (rather than including data on oral potentially malignant disorders). There was a possibility that some of the healthcare service contacts examined as opportunities for early detection could have occurred before the clinical signs and symptoms of oral cancer had become apparent. This should be taken into consideration when interpreting the results of this thesis, and further research with regard to OPMDs would help clarify whether these contacts could represent missed opportunities for opportunistic screening.

Despite the increasing trends, the overall incidence rates of oral cancer were relatively low in Scotland, and this thesis was among the first to question the feasibility of early detection in a dental setting in the light of this low disease volume. Examination of the distribution of the oral cancer burden in relation to the location of general dental practices in Scotland showed that a dentist would encounter one case of oral cancer every ten years, one case of oral cavity cancer every 17 years approximately, and one case of oropharyngeal cancer every 25 years. At the outset, it was anticipated that this time frame would be markedly reduced in the deprived communities because of the high

incidence of oral cancer. However, due to the even distribution of NHS dental practices and practitioners, which do not exhibit an unequal or skewed distribution in Scotland, specific locations or practices could not be identified for targeting further support, training, or pathways. This was further complicated by the fact that the majority of patients with oral cancer that were included in this study had made no contact with a general dental practitioner in the two years preceding diagnosis, thus further limiting opportunities for early detection

However, approximately 95% of the patients with oral cancer that were included in this study had contacted NHS hospital services (either hospital outpatient or hospital inpatient/day-case), clinics for GP prescriptions, or primary dental care services in the two years prior to the start of the referral period, suggesting that there were potential opportunities for early detection in alternative healthcare services. Although no novel settings (e.g. specific clinical specialities) for early detection in hospital or secondary care settings were identified, this thesis did recognise considerable potential in other primary care settings, particularly GP and pharmacy. Approximately 89% of the patients with oral cancer that were included in this study had been issued with a GP prescription in the most recent year prior to the start of the referral period and, although a significant proportion (possibly up to 80%) of these were likely to be repeat prescriptions (McTaggart, 2018), they would have all been dispensed in a pharmacy. This suggests that pharmacists may have a role to play in the early detection of oral cancer as they are in an ideal position to provide preventive advice on smoking and alcohol cessation, increase awareness about the risk factors and signs and symptoms of oral cancer, monitor changes in medications and attendance patterns, and refer patients exhibiting the warning symptoms and signs of oral cancer (e.g. persistent mouth lesions that have not healed with medication) in a timely fashion (Weinberg, 2006).

The proportion of patients contacting each of the four services increased over the two -year period prior to the start of the referral period, as did the mean number of contacts with each of these services. However, the differences

between the individual years had more clinical significance than those between six-month periods. The frequency of primary dental care service and GP prescription contacts significantly increased in the most recent year prior to the start of the referral period compared to the previous year. Of those who had contacted a primary dental care service, more than half (52%) had made an unusual number of contacts (exceeding “routine”, that is, two contacts per year) in the most recent year prior to the start of the referral period, and 41% of these contacts were for examination and diagnostic purposes. When considering the most recent six-month period prior to the start of the referral period, 51% of the patients with oral cancer that were included in this study had made at least one contact and 13% had made more than one contact with a primary dental care service. Additionally, the proportion of patients making an unusual number of contacts, particularly for examination and diagnosis purposes, exhibited an upward trend throughout the period examined. Therefore, not only were more patients contacting these services closer to the start of the referral period, their frequency of contact, particularly with the dental and GP prescription services, had also increased. Moreover, the contacts with the primary dental care services were mainly associated with examination and diagnostic procedures. All of these contacts could represent potential or missed opportunities for early detection, appointments with potential oral cancer concerns, or potential further opportunities for earlier detection and referral.

Lastly, a preliminary exploration of healthcare service contacts made just before and during the one-month referral period was also undertaken, in an attempt to assess the feasibility of utilising this data to examine the routes to diagnosis. The findings showed that the two most common services contacted most recently before the start of the referral period were GP prescription and hospital outpatient, suggesting that there was a possibility that these consultations were the sources of referral. However, unavailability of data on the referral source and time made further exploration of the routes to diagnosis unfeasible. The findings of this analysis also showed that almost all of the patients (98%) included in the current study had contacted at least one

of the four services during the one-month referral period, and the most commonly contacted services were hospital outpatient and GP prescription. In comparison, very few patients had consulted dental or hospital inpatient/ day-case services during the same period. Moreover, the hospital outpatient and hospital inpatient/ day-case specialties contacted most frequently within this period were ENT, general surgery, oral and maxillofacial surgery, and oral surgery, suggesting that, as suspected, these contacts were likely to be already associated with the symptoms and signs and referral for oral cancer. There was also a possibility of the hospital outpatient service being the referral destination for a large proportion of the patients included in this study.

Therefore, this thesis identified several areas, particularly with regard to subgroups of the population at the highest risk of developing cancer and alternative healthcare services, that future early detection efforts can and should target.

The findings of this thesis were used to develop recommendations in relation to improving early detection of oral cancer, and these have been discussed in the following section.

### 5.6.2 Recommendations

The 70th World Health Assembly recently adopted a draft resolution, "*Cancer prevention and control in the context of an integrated approach*" (WHO, 2016), the broad consensus of which was that cancer was a growing global public health concern and required prioritization and funding. It clarified that a more concerted approach for the prevention and management of cancer was necessary in order to achieve the Sustainable Development Goals by 2030, particularly the target to decrease premature mortality from non-communicable diseases (NCDs) including cancer by one third, and the target which endeavoured to achieve universal health coverage to improve cancer care and outcomes (WHO, 2016).

The findings of this thesis could inform development of policy and practice in primary and secondary prevention of oral cancer, including a focus on the potential role of risk stratification of communities to better target early detection efforts at the community and healthcare service levels. The recommendations made in section have been developed taking the Behaviour Change Wheel (BCW), proposed by Michie et al. (2011), into consideration. Following an extensive review and synthesis of 19 behaviour change frameworks from a wide range of disciplines, the BCW was formulated with the goal of aiding development of interventions and policies to change behaviour. The core of the wheel was formed by a 'behaviour system', which was composed of the three basic components of behaviour change including capability, opportunity, and motivation. The middle layer of the wheel included nine intervention functions that could be used to target any deficits in the core, while the outermost layer was formed by seven policy actions that could enable the interventions necessary for behavioural change.

#### 5.6.2.1 Recommendations for the primary prevention of oral cancer

Primary prevention aims to minimise the incidence burden of a particular disease by decreasing the prevalence of its key risk factors in the general population. Sheiham and Watt (2000) suggested the utilisation of a "common risk factor approach" to achieve this. The basis of this approach was that health improvement activities targeting a small number of risk factors would, in the long run, affect a larger number of diseases at a lower cost and with greater efficiency and effectiveness, compared to measures targeting a single specific disease. The strategy also aimed to improve health by minimising the prevalence or clustering of multiple risk factors such as tobacco and alcohol, which are both known to play an aetiological role in a number of diseases, by creating supportive environments for cessation and facilitating behavioural changes.

In keeping with this, the Scottish Government, in their reports titled *Changing Scotland's Relationship with Alcohol: A Framework for Action* and *Tobacco Control Strategy - Creating a Tobacco-Free Generation,* developed and

recommended strategies aiming to reduce the consumption of tobacco and alcohol in Scotland, provide support to families and communities, create positive public attitudes that encourage positive choices, and improve treatment and support (The Scottish Government, 2009; The Scottish Government, 2013). Additionally, Scotland has also led the world in upstream policy legislation to address smoking and alcohol – including the ban on smoking in public spaces (The Scottish Government, 2005) and the recently introduced Alcohol Minimum Pricing policy (The Scottish Government, 2012b). Reviews of these strategies showed a reduction in the rates of consumption of tobacco and alcohol in Scotland, although the most deprived communities continued to exhibit higher prevalence of smoking and alcohol misuse compared to the least deprived areas (NHS scotland, 2016a; Reid et al., 2017).

There is also a need for midstream community or downstream clinical setting approaches, including, for example the, development of a more "tailored" approach that prioritises those from lower socioeconomic strata groups. General dental practitioners as well as other healthcare professionals should be encouraged to educate patients, particularly those from the most deprived areas of Scotland, on the major health risks associated with tobacco and alcohol consumption and the benefits of cessation, and also provide support by referring the patients to appropriate cessation programs. The establishment of community-based support groups and help-lines for the cessation of smoking and alcohol consumption, particularly in the most deprived areas, should be promoted.

The Scottish Government (2017b), in *Scotland's Oral Health Plan*, proposed the introduction of an Oral Health Risk Assessment (OHRA), defined as "a full dental examination" accompanied by "a discussion between the dentist and patient about the associated risk factors such as smoking, alcohol intake and medication". Execution of such an assessment by general dental practitioners is recommended as it will permit identification of "high risk" individuals (i.e. males, individuals who smoke and drink, and those from lower socioeconomic strata). General dental practitioners should also be encouraged to follow-up

this subgroup of the population at the highest risk of developing oral cancer, and carry out opportunistic screening when possible, as identification of an OPMD and cessation of smoking could reverse the disease or prevent the manifestation of malignancy.

The prevalence of human papilloma virus infections, a major risk factor for oropharyngeal cancer (Herrero, 2003), can be minimised with the help of the prophylactic HPV vaccines. Rowhani-Rahbar et al. (2009), in their case-control study nested within a randomised controlled trial of a bivalent vaccine for the prevention of cervical dysplasia, reported that the prevalence of oral HPV infections was lower in the vaccine arm of their study compared to the placebo arm 4 years after vaccination. Therefore, it has been hypothesized that vaccination could prevent the incidence of oral HPV infections and, subsequently, decrease the incidence of HPV-associated oropharyngeal cancer (Gillison, 2014). However, currently only women receive the HPV vaccine under the National Health Service in the United Kingdom, and vaccination of adolescent males is not recommended as there is still limited evidence on its cost-effectiveness (The Scottish Government, 2017c). Although there is preliminary evidence of a certain level of "herd-immunity" in Scotland following the introduction of the national vaccination program in 2008 (Cameron et al., 2016), further efforts are still necessary. Moreover, there will continue to be unvaccinated cohorts (those who were too old for the relatively recently introduced school vaccination programme) for decades to come, and other primary (and secondary) prevention efforts will be required. Therefore, general dental practitioners as well as other healthcare professionals could be encouraged to provide preventive advice and promote the adoption of safer sexual practices (Massachusetts Dental Society, 2017). Additionally, development of community outreach programs that disseminate information on HPV infections, provide preventive advice, and encourage safer sex by distributing condoms, particularly among younger and disadvantaged populations, is encouraged.

#### 5.6.2.2 Recommendations for the secondary prevention of oral cancer through early detection

##### 5.6.2.2.1 Recommendations at the community level

The Scottish Government's Oral Health Improvement Plan clarified that the previously proposed Oral Health Risk Assessment would now be introduced in general dental practices and, in time, "all adult patients would receive an OHRA on a regular basis with intervening reviews between assessments" (The Scottish Government, 2018). It is recommended that, following widespread implementation, this OHRA should be utilised to undertake risk stratification of communities and identification of subgroups of the population requiring additional support, so as to better target early detection efforts in the future.

One of the key findings of this thesis was that a considerable proportion of the patients with oral cancer that were included in this study did not have regular contact with a general dental practitioner. Therefore, development of community-based programs that reach out to people, particularly those from the most deprived areas of Scotland, and encourage them to consult general dental practitioners on a regular basis could be developed. The Scottish Government recently introduced the Community Link Worker Programme, which aims to mitigate the effects of the social determinants of health among individuals living in the most deprived areas of Scotland (The Scottish Government, 2017d). A Community Link Worker (CLW) has been defined as a "generalist social practitioner based in a GP practice serving a socioeconomically deprived community", and their main role is to provide non-clinical support to patients and encourage them to take control of their health by setting and accomplishing goals and overcoming barriers (The Scottish Government, 2017d). CLWs essentially act as links between people and their communities through GP practices and, therefore, may have a potential role in the secondary prevention of oral cancer. The possibility of utilising such workers to reach out to those at the highest risk of developing cancer should be further explored. Such efforts could include home visits by the CLWs to identify high-risk individuals based on whether they exhibited key behavioural risk factors such as smoking and alcohol consumption, and

delivery of preventive advice regarding the risks associated with such habits and the benefits of cessation, and provision of motivation to attend cessation programs. Additionally, the CLWs could also reach out to the section of the population that was not registered or exhibited poor attendance patterns with a general dental practice and encourage them to contact GDPs more regularly by providing information on the benefits of doing so. The possibility of carrying out superficial examinations of the oral cavity for detection of possible OPMDs and referral could also be examined, although it is necessary to take associated governance issues and training and resources necessary into consideration when doing so.

The results of this thesis showed that the patients with oral cancer had increased their frequency of healthcare service contacts in the months immediately preceding diagnosis. This suggests that there were avoidable delays in the diagnostic process, and early detection efforts should aim to minimise them by targeting the patient, professional, and system levels. Antonovsky and Hartman (1974), in their seminal review of delays in the detection of cancer, first suggested that the most common determinant of patient delay was cancer knowledge. This was more recently reinforced by Tromp et al. (2005) in their case-series analysis conducted in the Netherlands (reviewed previously in Chapter 1) where they suggested that patients were more likely to minimise the delay in seeking professional help upon self-discovery of symptoms if they had prior knowledge of the signs and symptoms of cancer. Therefore, early detection strategies should aim to increase awareness among the general population, and particularly the disadvantaged communities, through the dissemination of information on the signs and symptoms of oral cancer among communities; promotion of community-based educational events; provision of training on self-examination for lesions by health care professionals; mass media campaigns; and distribution of educational materials including leaflets, flyers, and videos that are easily understandable by the general public, thus creating awareness, empowering patients, and discouraging them from delaying seeking help. However, these programs have also been reported to have limited benefits. Austoker et al.

(2009), in their systematic review, reported that although such cancer awareness programs, when delivered to individuals, were efficient in increasing cancer knowledge in the short term, they showed no evidence of promoting early presentation of cancer. Moreover, there was also no evidence of public education programs reducing the stage of cancer at the time of diagnosis. Therefore, although efforts to minimise patient delays and increase cancer awareness cannot be ignored entirely, it is apparent that greater emphasis should be given to efforts targeting delays at the professional and system levels.

#### 5.6.2.2.2 Recommendations for healthcare services

Although community-based measures are a key element of early detection efforts, even the most well-planned, structured appeals often fail, creating a need to adopt a wider approach. As Jackson (1985) powerfully articulated, "when the burden of 'doing all the many things one should do' falls differentially, behavioural change techniques require supplementation with environmental strategies". Such approaches should address deficiencies and gaps in the existing systems, so as to avoid "victim-blaming". This section uses the findings of this thesis to make recommendations for improvement of early detection at the healthcare service level.

The findings of this thesis repeatedly draw attention to the fact that the patients with oral cancer exhibited poor dental attendance patterns, thus automatically limiting early detection of oral cancer. Therefore, greater efforts to develop and evaluate innovative strategies for dental services to reach out to all patients, particularly those from the deprived communities, and fully engage and provide additional motivation and support to increase regular attendance rates are necessary. Furthermore, the possibility of using a policy approach to incentivising engagement with this section of the population through the development of a system that "rewards" practitioners for broadening the reach of their practices and reaching out to subgroups of the population that require additional motivation and support should be

explored (Birch, 2015). These efforts may in the long run help to improve the early detection of oral cancer.

It has also been suggested that failure on the part of health professionals in recognising malignant lesions can be attributed to several factors such as a low index of suspicion (Holland, 1975), lack of experience or unfamiliarity with the disease (Guggenheimer et al., 1989), knowledge gaps regarding risk factors and preventive measures (Gómez et al., 2010), and low prevalence of the disease and its non-specific appearance and potentially insidious nature (Güneri and Epstein, 2014). Mighell and Gallagher (2012) suggested that healthcare practitioners should be encouraged to regularly assess their levels of awareness and keep up-to-date with Continuing Professional Development topics recommended by the General Dental Council. Additionally, strategies to promote education (via hands-on training sessions, video demonstrations, or seminars) of dental practitioners on the early detection of oral cancer, including provision of information on the use of adjunctive techniques for diagnosis and proficiency in recognition of the signs and symptoms of oral cancer in a timely manner should be developed so as to minimise professional diagnostic delays.

Scheduling or system delays can be caused by factors such as barriers in the health care system, availability of resources, healthcare economics, access to health care facilities, and the availability of appropriate treatments. Efforts could also be made to ensure that general dental practices are accessible to all individuals and are equipped with all the essential technologies and medications. Additionally, all members of the health care team, including general dental practitioners as well as dental care professionals such as dental nurses and dental hygienists, should receive adequate training on the signs and symptoms of oral cancer and should also be familiarised with the referral processes in place.

Implementation of the Scottish Government's (2017b) Oral Health Risk Assessment should be promoted as this would assist dental practitioners in identifying individuals at the highest risk of developing oral cancer (i.e.

smokers, drinkers, males, individuals above 60 years of age, and those residing in the most deprived areas). Additionally, *Scotland's Oral Health Plan* also recognised that six-monthly check-ups were unnecessary (except among children or cases where a specified need had been identified), and the use of frequency of attendance as part of the OHRA was suggested. The findings of this thesis showed that patients with oral cancer increased their frequency of contact with healthcare services in the months preceding diagnosis, and implementation of the OHRA would help in identifying such individuals. GDPs should also be encouraged to follow-up such "high-risk" individuals on a regular basis, and perform opportunistic screening for oral cancer when possible.

The development of a risk prediction tool, defined as one that aims to "predict the probability or risk of a condition or event among individuals, or occasionally groups, based on a combination of known or measured characteristics" (Usher-Smith et al., 2015), for oral cancer is recommended. Such a tool will allow stratification of the population by risk and, subsequently, identification of individuals that screening and behavioural change programmes should be tailored to target. This tool could also include a system (possibly electronic) that flags up unusual patterns of contact (multiple contacts over short periods of time) with healthcare services and monitors recall interval, as it will allow practitioners across all healthcare services to identify and focus greater diagnostic efforts on individuals exhibiting a sudden increase in their frequency of contact with healthcare services, thus minimising further delays.

The findings of this thesis showed that although there were opportunities for early detection, they did not all lie within the dental setting. Therefore, efforts to engage alternative healthcare services, particularly general practitioners and pharmacists, in early detection efforts for oral cancer by providing them with adequate training, preferably by dental practitioners, on the recognition of the signs and symptoms of oral cancer and the appropriate referral practices in place are necessary. Pharmacists have a potentially vital role in early detection efforts through regular patient contact and the

opportunity to monitor any changes in the medications prescribed and the patient's contact patterns. Therefore, policy efforts should aim to work with pharmacists and equip them with the ability to directly refer patients in case of suspected oral cancer. Additionally, the development of better networking between dental and other primary care services should be promoted.

In conclusion, opportunities for early detection exist and need to be further explored and exploited, both in dental and wider primary healthcare services, if early diagnosis and clinical stage shifts, resulting in improved outcomes and survival of patients with oral cancer, are to be achieved.

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# Appendices

## Appendix 1: List of ICD-10 codes requested from the Scottish Cancer Registry

**C00: Malignant neoplasm of lip** [*Excl:* skin of lip (C43.0, C44.0)]

C00.0: External upper lip (Upper lip: NOS, lipstick area, vermilion border)

C00.1 External lower lip (lower lip: NOS, lipstick area, vermilion border)

C00.2 External lip, unspecified (Vermilion border NOS)

C00.3 Upper lip, inner aspect (Upper lip: buccal aspect, frenulum, mucosa, oral aspect)

C00.4 Lower lip, inner aspect (Lower lip: buccal aspect, frenulum, mucosa, oral aspect)

C00.5 Lip, unspecified, inner aspect (Lip, not specified whether upper or lower: buccal aspect, frenulum, mucosa, oral aspect)

C00.6 Commissure of lip

C00.8 Overlapping lesion of lip

C00.9 Lip, unspecified

**C01: Malignant neoplasm of base of tongue** (*Incl.:* Dorsal surface of base of tongue, Fixed part of tongue NOS, Posterior third of tongue)

**C02: Malignant neoplasm of other and unspecified parts of tongue**

C02.0 Dorsal surface of tongue: Anterior two-thirds of tongue, dorsal surface

Excl.: **dorsal surface of base of tongue (C01)**

C02.1 Border of tongue: Tip of tongue

C02.2 Ventral surface of tongue: Anterior two-thirds of tongue, ventral surface, Frenulum linguae

C02.3 Anterior two-thirds of tongue, part unspecified: Middle third of tongue NOS, Mobile part of tongue NOS

C02.4 Lingual tonsil ***Excl.:*** tonsil NOS (C09.9)

C02.8 Overlapping lesion of tongue: Malignant neoplasm of tongue whose point of origin cannot be classified to any one of the categories C01-C02.4

C02.9Tongue, unspecified

**C03: Malignant neoplasm of gum** [(*Incl.:* alveolar (ridge) mucosa, gingiva; *Excl.:* malignant odontogenic neoplasms (C41.0-C41.1)]

C03.0Upper gum

C03.1Lower gum

C03.9Gum, unspecified

**C04: Malignant neoplasm of floor of mouth**

C04.0 Anterior floor of mouth: Anterior to the premolar-canine junction

C04.1 Lateral floor of mouth

C04.8 Overlapping lesion of floor of mouth

C04.9 Floor of mouth, unspecified

**C05: Malignant neoplasm of palate**

C05.0 Hard palate

C05.1 Soft palate (*Excl.:* nasopharyngeal surface of soft palate (C11.3)

C05.2 Uvula

C05.8 Overlapping lesion of palate

C05.9 Palate, unspecified: Roof of mouth

**C06: Malignant neoplasm of other and unspecified parts of mouth**

C06.0 Cheek mucosa: Buccal mucosa NOS, Internal cheek

C06.1 Vestibule of mouth: Buccal sulcus (upper)(lower), Labial sulcus (upper)(lower)

C06.2 Retromolar area

C06.8 Overlapping lesion of other and unspecified parts of mouth

C06.9 Mouth, unspecified: Minor salivary gland, unspecified site, Oral cavity NOS

**C07: Malignant neoplasm of parotid gland**

**C08: Malignant neoplasm of other and unspecified major salivary glands**
[*Excl.:*malignant neoplasms of specified minor salivary glands which are classified according to their anatomical location, malignant neoplasms of minor salivary glands NOS (C06.9), parotid gland (C07)]

C08.0 Submandibular gland: Submaxillary gland

C08.1 Sublingual gland

C08.8 Overlapping lesion of major salivary glands: Malignant neoplasm of major salivary glands whose point of origin cannot be classified to any one of the categories C07-C08.1

C08.9 Major salivary gland, unspecified: Salivary gland (major) NOS

**C09: Malignant neoplasm of tonsil** [*Excl.:* lingual tonsil (C02.4), pharyngeal tonsil (C11.1)]

C09.0 Tonsillar fossa

C09.1 Tonsillar pillar (anterior)(posterior)

C09.8 Overlapping lesion of tonsil

C09.9 Tonsil, unspecified- Tonsil:NOS, faucial, palatine

**C10 Malignant neoplasm of oropharynx [*Excl.:* tonsil (C09.-)]**

C10.0 Vallecula

C10.1 Anterior surface of epiglottis: Epiglottis, free border [margin], Glossoepiglottic fold(s) *Excl.:*epiglottis (suprahyoid portion) NOS (C32.1)

C10.2 Lateral wall of oropharynx

C10.3 Posterior wall of oropharynx

C10.4 Branchial cleft: Branchial cyst [site of neoplasm]

C10.8 Overlapping lesion of oropharynx: Junctional region of oropharynx

C10.9 Oropharynx, unspecified

**C11: Malignant neoplasm of nasopharynx**

C11.0 Superior wall of nasopharynx: Roof of nasopharynx

C11.1 Posterior wall of nasopharynx: Adenoid, Pharyngeal tonsil

C11.2 Lateral wall of nasopharynx: Fossa of Rosenmüller, Opening of auditory tube, Pharyngeal recess

C11.3 Anterior wall of nasopharynx: Floor of nasopharynx, Nasopharyngeal (anterior)(posterior) surface of soft palate, Posterior margin of nasal (choana, septum)

C11.8 Overlapping lesion of nasopharynx

C11.9 Nasopharynx, unspecified: Nasopharyngeal wall NOS

**C12: Malignant neoplasm of piriform sinus** (*Incl.:*Piriform fossa)

**C13: Malignant neoplasm of hypopharynx** [*Excl.:*piriform sinus (C12)]

C13.0 Postcricoid region

C13.1 Aryepiglottic fold, hypopharyngeal aspect- Aryepiglottic fold:NOS, marginal zone

[*Excl.:*aryepiglottic fold, laryngeal aspect (C32.1)]

C13.2 Posterior wall of hypopharynx

C13.8 Overlapping lesion of hypopharynx

C13.9 Hypopharynx, unspecified: Hypopharyngeal wall NOS

**C14: Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx** [*Excl.:*oral cavity NOS (C06.9)]

C14.0 Pharynx, unspecified

C14.2 Waldeyer ring

C14.8 Overlapping lesion of lip, oral cavity and pharynx: Malignant neoplasm of lip, oral cavity and pharynx whose point of origin cannot be classified to any one of the categories C00-C14.2

**C32: Malignant neoplasm of larynx**

C32.0 Glottis: Intrinsic larynx, Vocal cord (true) NOS

C32.1 Supraglottis: Aryepiglottic fold, laryngeal aspect, Epiglottis (suprahyoid portion) NOS, Extrinsic larynx, False vocal cord, Posterior (laryngeal) surface of epiglottis, Ventricular bands

*Excl.:* anterior surface of epiglottis (C10.1); aryepiglottic fold:NOS (C13.1); hypopharyngeal aspect (C13.1); marginal zone (C13.1)

C32.2 Subglottis

C32.3 Laryngeal cartilage

C32.8 Overlapping lesion of larynx

C32.9 Larynx, unspecified

# Appendix 2: List of MIDAS treatment codes included within each grouping

There are approximately 500 treatment fee codes (Items of Service) included in the Statement of Dental Remuneration (SDR), which is the primary dental care contract for NHS Scotland (PSD, 2017). For the purpose of this thesis, these codes were divided into three groups, namely, Exam and Diagnosis, Emergency, and Treatment. The list of individual treatment codes was too extensive to include in this Appendix, and the descriptions of the main items of service provided on the ISD website have been used to define the groups below instead (ISD Scotland 2017m). Please refer to the Statement of Dental Remuneration for the individual codes (PSD, 2017).

**Exam and Diagnosis**

*1) Examinations:* This includes three types of examination

(a) Simple examination: This is the most common and can be claimed every 6 months for an adult patient.

(b) Extensive examination: This can be claimed every 24 months for an adult patient.

(c) Full case assessments: This can be claimed every 24 months for an adult patient.

*2) Radiographs (x-rays)*

**Emergency**

*1) Recalled attendance:* happens when a dentist is required to return to his/her surgery out-with normal working hours to treat a patient who has a dental emergency.

*2) Treatment Urgently Required for Acute Conditions*

*3) Occasional Treatment: assessment and advice*

**Treatment**

*1) Simple periodontal*: Treatment of the gums and supporting tissues of the teeth. Simple treatment includes scaling and polishing of the teeth and oral hygiene instruction.

*2) Complex periodontal:* Complex periodontal treatment includes scaling of the teeth over a prolonged period with removal of overhanging ledges and oral hygiene instruction.

3) *Fillings:* The most common method of treating caries is to provide a filling, also known as a restoration. The table shows data on fillings made from all materials available to dentists practising under the NHS General Dental Service regulations. The most common material used is silver amalgam.

4) *Root treatments*: Root canal therapy is provided when infection reaches the pulp chamber (the nerve) within the hollow centre of the tooth. It involves removal of the inflamed or diseased tissue, shaping and sterilisation of the root canal and sealing of the canal with an inert, sterile sealant material. High incidence of claims for this item of treatment may indicate: poor dietary habits leading to decay; social deprivation; or dental treatment being sought only after pain occurs.

5) *Veneers:* A thin layer of tooth coloured material to restore the appearance of a natural tooth surface if it is damaged or discoloured.

6*) Inlays:* A gold restoration cast to fit a prepared tooth cavity when there is insufficient tooth tissue remaining to retain a filling.

7) *Crowns:* Crowns are provided where there is insufficient sound tooth tissue remaining to restore the tooth by means of a filling. A crown is an artificial cap made of porcelain, porcelain and metal, metal or plastic material. It is shaped to represent the natural tooth surface which it replaces and is fitted over the

stump of the remaining natural tooth or over a metal post inserted into the root canal of a tooth which has previously undergone root canal treatment.

*8) Bridges:* A bridge is a fixed dental appliance replacing a missing tooth or teeth. This appliance is fixed to natural teeth adjacent to the space created by the missing tooth or teeth. The pontic is the part of the bridge filling the space created by each missing tooth.

*9) Dentures:* Dentures are removable appliances containing artificial teeth which replace natural teeth. The artificial teeth are held on a plate covering a greater area of the oral tissue than the space created by the missing tooth/teeth. A full denture is a plate containing artificial teeth replacing all natural teeth in the upper and/or lower jaw. A partial denture is a plate replacing one or more but not all natural teeth in the upper or lower jaw.

10) *Orthodontic treatment:* Orthodontic appliance therapy is the treatment of crowded or misaligned teeth using removable and/or fixed appliances.

11) *Domiciliary visits:* Domiciliary visits made by a dentist to provide dental treatment for a patient confined, because of their physical or mental condition, to their current place of residence.

12*) Extractions:* Teeth are extracted when they are beyond repair, by patient treatment choice or electively for treatments such as orthodontics.

13) *Surgical treatments:* A surgical extraction is an extraction which requires the lifting of a flap of gum and possibly the removal of a portion of bone to allow access to a tooth or root before it can be extracted.

# Appendix 3: Ethical approval letter from the West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

***WoSRES***
***West of Scotland Research Ethics Service***

Dr Mitana Purkayastha

**West of Scotland Research Ethics Service**
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT

| | |
|---|---|
| Date | 5th June 2014 |
| Our Ref | WoS ASD 958 |
| Direct line | 0141 211 2126 |
| Fax | 0141 211 1847 |
| E-mail | Judith.Godden@ggc.scot.nhs.uk |


Dear Dr Purkayastha

Full title of project: **Burden of Oral Cancer in Scotland and the UK**

You have sought advice from the West of Scotland Research Ethics Service Office on the above project. This has been considered by the Scientific Officer and you are advised that based on the submitted documentation (email correspondence 2nd April 2014) it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (A Harmonised Edition). This advice is based on the following.

- The project is a surveillance study using data only obtained as part of usual care. The data will be supplied as fully anonymous data sets and will be dealt with according to the governance arrangements already in place for each of these datasets.

Note that this advice is issued on behalf of the West of Scotland Research Ethics Service and does **not** constitute a favourable opinion from a REC. It is intended to satisfy journal editors and conference organisers and others who may require evidence of consideration of the need for ethical review prior to publication or presentation of your results.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

Kind regards

Dr Judith Godden, WoSRES Scientific Officer/Manager

# Appendix 4: Ethical approval letter for Study 1 (Chapter 2) from the University of Glasgow College of Medicine, Veterinary and Life Sciences Research Ethics Committee


5th December 2014

Dear Mitana Purkayastha, Dr David Conway, Dr Alex McMahon, Dr John Gibson

**MVLS College Ethics Committee**

***Project Title:*** UK Trends in Head and Neck Cancer
***Project No:*** 200140024

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. They are happy therefore to approve the project, subject to the following conditions

- Project end date: September 2017
- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

- Data Storage: the GU Code of Good Practice in Research states: “The University requires data to be securely held for a period of ten years after the completion of a research project.”

Yours sincerely

Prof. Andrew C. Rankin
Deputy Chair, College Ethics Committee

Andrew C. Rankin
Professor of Medical Cardiology
BHF Glasgow Cardiovascular Research Centre
College of Medical, Veterinary & Life Sciences
University of Glasgow, G12 8TA
Tel: 0141 211 4833
Email: andrew.rankin@glasgow.ac.uk

# Appendix 5: Ethical approval letter for Study 2 and 3 (Chapters 3 and 4) from the University of Glasgow College of Medicine, Veterinary and Life Sciences Research Ethics Committee


17th December 2015

Dear Mitana Purkayastha, Prof David Conway, Dr Alex McMahon, Prof John Gibson

**MVLS College Ethics Committee**

***Project Title:*** Opportunities for opportunistic oral cancer screening

***Project No:*** 200150057

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. It is happy therefore to approve the project, subject to the following conditions:

- Project end date: March 2018
- The data should be held securely for a period of ten years after the completion of the research project, or for longer if specified by the research funder or sponsor, in accordance with the University's Code of Good Practice in Research: (http://www.gla.ac.uk/media/media_227599_en.pdf)
- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the

change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.

- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Prof. Andrew C. Rankin
Deputy Chair, College Ethics Committee

Andrew C. Rankin
Professor of Medical Cardiology
BHF Glasgow Cardiovascular Research Centre
College of Medical, Veterinary & Life Sciences
University of Glasgow, G12 8TA
Tel: 0141 211 4833
Email: andrew.rankin@glasgow.ac.uk

# Appendix 6: ISD data confidentiality form

## Confidential Data Release Form

**for users of NHS personal data**

NHS National Services Scotland

**1 User Details**

Name: Mitana Purkayastha
Job title: Student
Organisation: University of Glasgow Dental School
Address: 378, Sauchiehall Street,

City centre.
G2 3JZ
United Kingdom

Tel No:07586408109

Data Protection Reg No:
Z6723578.

**2 Sponsor Details**
See Rule 6 for appropriate sponsor
Name: Dr David Conway
Job title: Clinical Senior Lecturer

Organisation: University of Glasgow Dental School
Address: R1012 Level 10
Glasgow Dental Hospital & School
378 Sauchiehall Street
Glasgow G2 3JZ

Tel No: 01412119750

**3 Name(s) of all co-user(s):**
Only the user and people listed here will have access to the data. This should include only those for whom access is essential to the work. Please see rule 3

Dr Alex McMahon

Mitana Purkayastha

**4 Nature of data requested, including a list of variables required:**
Only data essential to the proposed work should be requested.

See Appendix 1

**5 All purposes for which data will be used, including publications**:
No data which carries the risk of identification of an individual will be put into the public domain. Please refer to the Information Services Division's (ISD) Statistical Disclosure Control Protocol and/or discuss with the ISD Head of Statistics where disclosure is a concern. Please see Rule 5

-Research epidemiological analyses,
-PhD thesis,
-Publication in peer reviewed journal,
-Dissemination at scientific meetings/conferences

**6 Proposed method of transfer of data**:
The final decision will be taken in consultation with the NSS analyst and should comply with NSS policy

nhs.net to alexander.mcmahon@nhs.net

**7 Measures in place to protect and use the data securely and confidentially:**
Describe the physical and electronic systems for data storage and access

See Appendix 2

**8 Intended duration of use of data:**
All users and co-users must agree to destroy the data after an agreed date using a certificated electronic destruction process. Paper data must also be destroyed

10 years

**9 Date data to be destroyed:**
Staff from NSS may contact to confirm destruction

April 2024

**User's Declaration**
I declare that I understand and undertake to abide by the Rules for confidentiality, security and release of data received from NSS as specified in paragraphs 1-5 listed below.

Signature: Mitana Purkayastha Date: 16/06/2014

**Sponsor's Declaration**
I declare that _Mitana Purkayastha and Alex McMahon___ (name above as the user of the data requested), is a bona fide worker engaged in a reputable project and that the data requested 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 paragraphs 1-5 listed below. I am happy for him/her to receive these data.

Signature: ___ David Conway _____ Date: ____18/6/14_____

Professional registration no.: eg GMC/GDC 71938

**For NSS only**
Caldicott Guardian, NHS National Services Scotland, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB

Information request number _____

Release authorised by
_____Date_____ Senior manager (HOG or HOP)

_____Date_____ Caldicott Guardian or deputy

**RULES ON CONFIDENTIALITY, SECURITY AND RELEASE OF INFORMATION**
**FOR USERS OF NHS PERSONAL DATA**

1. Personal data held by NSS have been notified under the Data Protection Act 1998 for the purposes of:

| | |
|---|---|
| Staff Administration | Licensing and Registration |
| Advertising, Marketing and Public Relations | Research |
| Accounts and Records | Crime Prevention and Prosecution of Offenders |
| Consultancy and Advisory Services | Administration of Justice |
| Health Administration and Services | Trading/sharing in Personal Information |
| Information and Databank Administration | Blood Transfusion (Blood, Tissue and Stem Cells) Services |
| Legal Services | Lending and Hire Services, Library Services |
| Public and Environmental Health Surveillance and Analysis | Transfer of Primary Medical Records by Practitioner Services |
| Education | National Fraud Initiative – Data Matching |

It cannot be used for any other purposes.

2. If the data received from NSS are to be held on computer, the signatory of this request, or the organisation they represent, should have an appropriate notification with the Office of the Information Commissioner. Details of the registration number should be entered on page 1 of this document. Whether stored on computer or otherwise, the signatory should be aware that the Data Protection Act 1998 requires that all personal data is processed fairly and lawfully and in accordance with the Data Protection Principals.

3. Data received from NSS should not be divulged to any person whose name is not specified as a 'co-user of data' nor used for any purpose other than that declared on page 1 (Intended use of data) of this document. All users and co-users must understand their responsibilities in protecting data provided.

4. Proper safeguards should be applied in keeping the data secure and destroying it on completion of the work/project declared on page 1 to prevent any breach of confidentiality. Any misuse or loss of these data should be notified immediately to the NSS Data Protection Officer **nss.dataprotection@nhs.net**

5. Statistics or results of research based on data received from NSS should not be made available in a form which:
   a) directly identifies individual data subjects or creates a risk of indirect identification. The risk should be assessed using ISD's Statistical Disclosure Control Protocol and may be discussed with the ISD Head of Statistics if disclosure is a concern;
   b) is not covered by the 'intended use of data' clause specified on page 1.

6. Sponsor Details on form:
   - For release to NHS operational units of data relating to their own treated patients the sponsor should be the unit's Medical Director. For releases of data relating to patients in a specific directorate, the relevant Clinical Director may sign the statement.
   - For release to NHS Boards of data relating to their resident population the sponsor should be Director of Public Health.
   - For release to CHPs of data relating to their resident population or of people treated in their units, the sponsor should be the Clinical Director of the CHP
   - For release of data to General Practice regarding their registered patients, the sponsor should be a GP principal in that practice.
   - For releases to researchers of data which have not required PAC authorisation, the sponsor will be the registered health professional responsible for ensuring the confidentiality of the data.
   - For release of data to an organisation holding a contract with an NHS Board or with the Scottish Government: for the purpose of fulfilling that contract the sponsor will be the NHS Board Director of Public Health or a registered health professional in the Scottish Government.
   - For release of workforce data, the sponsor should be a senior manager in the organisation to which data will be released

7. The information provided to you is derived from systems used in the NHS for the administration of health services or from the registrations held by the General Register Office for Scotland. Although there are quality assurance processes in place, the data may contain undetected inaccuracies about an individual patient, member of staff or department. Therefore the data are not collected for the purpose of informing direct clinical decisions about individual patients, or judging the performance of individual staff and should be verified if to be used for either of these purposes.

8. A signed paper copy of the confidentiality statement should be sent to the analyst by mail or by fax to the following fax no. 0131 275 7606
   ***NSS would welcome copies of any publications based on data supplied.***

# Appendix 7: Information Governance training from the Medical Research Council

MRC Medical Research Council

*This is to certify that*

**MITANA PURKAYASTHA**

completed the following e-learning course assessment for Scotland with a score of
85%

***Research Data and Confidentiality e-learning course***

Covering:
- The concept of confidentiality and how to work within the law
- Principles 1, 2, 7, 8 and section 33 of the Data Protection Act
- Consent and the issues in accessing data for research without consent
- Appropriate disclosure and routes for access without consent
- Accessing data from ONS and the NHS
- Archiving and sharing research data

on Tue Sep 22 2015

# Appendix 8: University of Glasgow Data Security Protocol

**Community Oral Health Section, School of Medicine, College of Medicine, Veterinary and Life Sciences, Glasgow Dental Hospital and School.**

**CONFIDENTIAL DATA SECURITY PROTOCOL [v. 27 May 2014]**

Named responsible individual: David Conway

Data security is, however, **everyone's** responsibility.

.

- Via the consent process, we have been trusted with confidential information (defined in Appendix 1). It is our duty to ensure that the privacy and confidentiality of the data are respected.
- Data security includes recording, storage, access, transfer, uses, and retention of data records.
- Data security is relevant for both paper and electronic records and for both quantitative and qualitative data.

All new members of staff at the Community Oral Health Section will require clearance through Disclosure Scotland prior to taking up post.

Both permanent Unit staff (employed by Glasgow University or NHS Scotland) and temporary staff employed by the Community Oral Health Section through Glasgow University's approved recruitment agency (Blue Arrow) will be required to sign the Unit's research data security and confidentiality agreement.

**Recording / Entering data:**

- Data must be accurate / authenticate / credible / and verifiable.
- The data need to be accurately entered.
- Data validation and check procedures must be followed.
- Validation includes randomly checking 10% of records.
- Missing data should be logged and followed up.

**Mobile devices:**

- Data should only be collected on encrypted laptops.
- Confidential data should not be saved onto key sticks, CDs, external hard-drives or smart phones.

**Storage of data:**

- Offices must be locked when unoccupied.
- Paper records must be stored in locked cabinets.
- Computer files and databases must be password protected.

- Computers must be locked when away from desk [Ctrl, Alt, Del → Lock Workstation].
- Databases and audio recordings need to be backed up and saved in the appropriate folder on the MVLPublic (J:) drive at:
  - J:\MED\DentalSchool\DPHU
  - Access to each folder should be on a 'need to use' basis and is controlled centrally by IT Services
  - Local management of the DPHU folder is undertaken by Research Secretary – Mr John McHugh
- Duplicate copies of databases and audio recordings should be avoided.
- All audio-recordings should be deleted from recording devices once uploaded to the J Drive.

**Access to data(** J:\MED\DentalSchool\DPHU**):**

- Access to confidential Childsmile data should be accessed by authorised individuals only (please see Appendix 2).
- No unauthorised access is permitted.
- Passwords (both computer log-in and those associated with individual data files) must be changed following staff changes.
- All team members with access to data will have to sign a confidentiality form.
- Access to confidential data from individual research studies, undertaken as part of the evaluation of Childsmile, will be allocated on a strict 'need to access' policy.

**Transfer of data:**

- Data-base creation, data extraction and data transfer should be kept to a minimum.
- All transfers of confidential data, including those between named data users within the Community Oral Health Section (listed above), need to be approved by David Conway.
- Confidential data should only be transferred outwith the Community Oral Health Section following approval of David Conway.
- Electronic data containing personal identifiers must only be sent from and to nhs.net email addresses or by using a secure enhanced file sharing service such as Globalscape.
- Databases need to be password protected.
- Passwords must be sent in a separate e-mail.

**Uses:**

- Analyses of confidential data should be done on the University J Drive only.
- For evaluation and research purposes all data will be analysed anonymously, i.e., confidential information, name, date of birth, postcode and CHI will be removed.
- Transfer procedures (above) need to be followed prior to release for analysis.
- No publication will appear in any form in which an individual may be identified unless the written permission of that individual has been obtained.

**Retention:**

- In keeping with the Data Protection Act (1998) records will not be retained for longer than necessary.

- Records required for current business: paper records should be stored in locked cabinets in the Community Oral Health Section and electronic records on the University servers.
- Following completion of a study and of all analyses, confidential data will no longer be stored at the Community Oral Health Section.
- Records no longer required for current business use will be transferred to the University Records Centre for archiving.
- In the case of Childsmile, confidential records will be transferred to NHS NSS ISD for storage in the dental data warehouse.

**Audit:**
Information stored on the University J drive will be subject to internal review on a quarterly basis and all unnecessary files (e.g.., duplicate databases or database extractions no longer required) deleted. University of Glasgow Records and Information Management Service will audit our protocols.

**SHIP Safe Haven**

Members of staff at the Community Oral Health may be authorised to access the Scottish Health Informatics Programme (SHIP) system. Access to the SHIP system is for approved only and unauthorised users must not access the system.

- Appropriate approvals (e.g.. PAC, CHIAG, Cladicott Forum) must be granted.
- Users are required to have 'SHIP-approved researcher status' which includes attendance at an appropriate training session.
- No data or tables should be removed from the SHIP system without approval from a Research Coordinator (RC). The RC will run a disclosure control on tables to be released to ensure data confidentiality.

  The Community Oral Health Section may also be asked to provide data to be used in the SHIP system.
- Data should only be provided to an approved member of the eDRIS team after appropriate data approvals have been granted.
- Data must not be provided directly to the researcher accessing the data within SHIP.
- A secure enhanced file sharing service such as Globalscape must be used to transfer data between the Community Oral Health Section and eDRIS.
- To access the file sharing service, eDRIS will supply a username by email and a the corresponding password by phone.

  For further guidelines and assistance, please contact eDRIS at nss.edris@nhs or 0131 275 7333.

**What is confidential information?**

The term "Confidential Information" applies to:

- data relating to identifiable individual patients, donors, NHS Scotland staff or practitioners:

- in hand-written, typewritten, printed or machine readable form
- on a document, microfiche, CD, magnetic medium (disk, tape, video, etc.) or computer screen

- some business data, including that relating to financial information, details of projects, trade secrets, programming code copyright.

Individuals may be identified by:

- name
- unique reference number (e.g.., CHI number, hospital case reference number/patient identifier, NHS number, GMC number, etc.)
- address
- postcode

# Appendix 9: Approval letter from the Public Benefit and Privacy Panel for Health and Social Care

**Public Benefit and Privacy Panel for Health and Social Care**
nss.PBPP@nhs.net
www.informationgovernance.scot.nhs.uk

Ms Mitana Purkayastha
University of Glasgow Dental School
Community Oral Health
378 Sauchiehall Street
City Centre
Glasgow
G2 3JZ

Date: 21st April 2016
Your Ref:
Our Ref: 1516-0378

Dear Ms Purkayastha

**Re: Application 1516-0378/Purkayastha: Opportunities for opportunistic oral cancer screening**

Thank you for your application for consideration by the Public Benefit and Privacy Panel for Health and Social Care.
Your application has undergone proportionate governance review and has been approved.

The Panel have made the following comment

- Should, following this proposal, a recommendation be made to develop an oral screening programme this phase will require completion of a Privacy Impact Assessment and should also include an appropriate public engagement exercise

This approval is given to process data as specified in the approved application form, and is limited to this. Approval is valid for the period specified in your application. You are required to notify the Panel Manager of any proposed change to any aspect of your proposal, including purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure, or any other relevant change.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection. In particular you should be aware that once personal data (irrespective of de-

identification or other controls applied) has been extracted from NHSS Board(s) and transferred to you, that you will then become the Data Controller as defined by the Data Protection Act (1998).

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (www.informationgovernance.scot.nhs.uk).

I hope that your proposal progresses well,

Yours Sincerely

Ashley Gray
Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: **nss.PBPP@nhs.net**

## Appendix 10: eDRIS User Agreement


# National Services Scotland (NSS)
# eDRIS User Agreement

NSS is the commonly known name of the Common Services Agency (CSA)

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## 1. INTRODUCTION

This document is the Agreement that Users of eDRIS enter into prior to accessing data. It also contains information on the current legal framework and the penalties that may apply should you breach this Agreement.

1.1 The Parties

Parties to this Agreement are:-

I. You being an individual User (as hereinafter defined); and

II. The Common Services Agency (more commonly known as National Services Scotland), a statutory body constituted pursuant to the National Health Service (Scotland) Act 1978 (as amended) and having its headquarters at Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB, acting through eDRIS ("NSS"); and

III. The Sponsoring or Employing Organisation[1] (as hereinafter defined)

1.2 The Context

1.2.1 The Farr Institute @ Scotland[2] is a research collaboration bringing together the Universities of Aberdeen, Dundee, Edinburgh, Glasgow, St Andrews and Strathclyde with NSS. The Farr Institute is a collaboration to harness health data for patient and public benefit and to ensure the safe and secure use of electronic patient records and other population-based datasets for research purposes. The Farr Institute follows the Guiding Principles for Data Linkage.

1.2.2 Electronic Data Research and Innovation Service (eDRIS) is a service designed to provide a single point of contact and to assist researchers in study design, approvals and data access via a secure analytical environment. eDRIS is designed to assist researchers to uphold the Guiding Principles for Data Linkage and is a NSS service.

1.3 NSS eDRIS User ('User' and also referred to herein as "you")

To be given NSS eDRIS User status and provided with appropriate access to study datasets you must comply with the following:-

1.3.1 You must demonstrate that you have satisfactorily completed a mandatory NSS approved training course which ensures you are fully aware of the policies and procedures governing individual privacy, data protection and freedom of information.

1.3.2 You must be aware of the sanctions which may apply should you breach this Agreement or compromise the security, availability or confidentiality of the data.

1.3.3 You will re-attend training within 2 weeks of the expiry of your training certificate if this occurs within the time period of your study.

1.3.4 The study you are working on must have evidence of approval from the relevant authorising bodies, for example, Privacy Advisory Committee ("PAC"),
CHI Advisory Group (CHIAG), ethics where appropriate.

1.3.5 You have read the NHS Confidentiality Code of Practice

1.3.6 You are affiliated with an Approved Organisation.

1.3.7 You sign, date and complete the declaration agreeing to be bound by the requirements of this document and return it prior to being given access to your data. The declaration must also be signed by an authorised signatory from your Authorising organisation.

1.3.8 You confirm to be bound by this Agreement at every login to eDRIS.

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[1] Hereafter referred to as Authorising Organisation.
2 The Farr Institute @ Scotland replaced the ScottisH Informatics Programme (SHIP).

## 2 RESPONSIBILITIES

### 2.1 User Responsibilities

2.1.1 As a User you are required to familiarise yourself with the contents of this Agreement and the Data Protection Principles (see Appendix A hereto). You are obliged to be guided by the Guiding Principles for Data Linkage and uphold the security and confidentiality of the data and IT resources made available to you as a User.

2.1.2 As a User you are responsible for ensuring that the data you are working on is not read, viewed or handled by anyone not named in the relevant approvals for that study. If it appears that anyone is deliberately attempting to view, read or handle data not within their authorised duties, the facts must be reported by you immediately to the Research Coordinator.

2.1.3 As a User if you are responsible for, or aware of the occurrence of an unintentional disclosure of information, you must report this without delay to the Research Coordinator.

2.1.4 As a User you must not login, or attempt to login to the national safe haven from an environment not meeting the national safe haven requirements notified to you by NSS from time to time. Some Users will be allowed remote access to the national safe haven but they must ensure that the data can not be viewed by anyone not identified in the relevant approvals for this study.

2.1.5 As a User you should not discuss information which could breach an individual's privacy in public places; in this context a public place may be taken to be anywhere where people not directly involved with the study may be present.

2.1.6 As a User you must only access the national safe haven from workstations managed by your Authorising Organisation or from a recognised safe setting (safe access point).

2.1.7 'Revolution R Enterprise' analytical tool is provided for 'Academic Use' only for bona-fide academic, non commercial purposes by academics. 'Academic Use' means any teaching and/or non-government funded research as conducted by or under the direction of a professor or other academic professional within an academic environment and excludes any and all commercial use.

2.1.7.1 Academic Users will not be allowed to use data or data outputs generated through use of the data, regardless of their origin for *any* commercial exploitation.

Examples of commercial use of data (and therefore forbidden use) include:
2.1.7.2 Using the data for "commercial" research where the research is undertaken for the private purposes of an organisation and / or where the primary objective is to generate income. This objective is distinct from non-commercial research where the primary objective is to put material in the public domain for the public benefit.

2.1.7.3 Acting as paid 'agents' of businesses for whom the research study was not designed nor funded.

2.2 Authorising Organisation[3]

2.2.1 Approved Organisations for direct access to individual level data via eDRIS are restricted to public sector organisations (e.g.. Universities, NHS, Local Authorities and Scottish Government). Researchers/Users from the Scottish Government and Local Authorities will have access to data via a safe setting only.

2.2.2 The Authorising Organisation agrees to abide by the terms of this Agreement and takes responsibility for ensuring that the User(s) comply with the provisions of this Agreement.

2.2.3 The Authorising Organisation needs to be aware that any breach of this Agreement may lead to the withdrawal of access to eDRIS for the Organisation and its staff, and that NSS may report serious legal or regulatory breaches to the appropriate authorities (such as the Information Commissioner and professional regulatory bodies).

2.2.4 Licences for MS Office 2010 (e.g.. word, excel etc) must be provided entirely at its own expense by the Authorising Organisation for Users accessing eDRIS remotely.

## 3 ACCESS TO DATA

3.1 Requirements for accessing data in the national safe haven both via remote access and via a safe setting.

3.1.1 Prior to being given access to the data, you must have read and signed this Agreement. If you have any questions about the contents of this Agreement you should raise them with your Research Coordinator.

3.1.2 At the start of the study you will be allocated a user name and password which will provide you with access to the study data folder.

3.1.3 At each login to the study you will be required to re-affirm your undertaking to uphold data confidentiality and security in terms of this Agreement.

3.1.4 Telephone conversations should not be held while accessing the national safe haven. The only exception being to contact the Research Coordinator or a member of the research team for the relevant study.

3.1.5 You must not leave your workstation unattended for any reason unless you ensure that you either log out or activate the screen saver.

3.1.6 All output(s) must be cleared with the Research Coordinator to ensure that they do not breach an individual's privacy. Under no circumstances will uncleared output(s) be released (see Section 5 below).

3.2 The national safe setting is located at Nine BioQuarter, Little France Road, Edinburgh.

3.2.1 Your visit to the safe setting must be pre arranged and take place within normal working hours (08.30 - 16.30 Monday to Thursday, 08.30 – 15:30 Friday). Your visit is at NSS convenience and may be cancelled or rescheduled at any point.

3.2.2 On arrival at Nine BioQuarter you will come up to the 2nd floor. Please ask at the main building reception for the location of the lifts or stairs. Access to the Farr Institute office is via the buzzer at our main office door.

3.2.3 You will be met by the Research Coordinator or another member of the eDRIS team. They will ask to see your Photo ID and you will be asked to sign the Visitors book. You will be issued with a visitor's pass.

3.2.4 Whilst at Nine BioQuarter you will abide by all local policies pertaining to visitors to the site e.g.. car parking, smoking, health and safety, fire evacuation, etc. These will be explained to you by your eDRIS Research Coordinator or team member.

3.2.5 The use of landlines / mobile phones or any other mobile device within the national safe haven room / booth located at Nine BioQuarter is not allowed. Phones and other devices must be switched off and stored in a locker along with any bags. Only paper, pen and reference books are allowed in the room or booth.

3.2.6 If you need to make or receive a call please do so in the kitchen area. Having telephone conversations in the safe setting room / booth where data access is provided is not allowed.

3.2.7 CCTV is in operation in each safe setting room / booth recording behaviour. No audio is recorded. Images are retained for 30 days before being overwritten. CCTV is not optional.

3.2.8 At the end of your visit you will be escorted back to reception where you must sign out from the visitors' book and return your visitor's pass.

3.2.9 Procedures to be followed at other safe settings may differ.

Authorising Organisation is defined in Appendix B - Glossary.

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## 4 DATA SECURITY

4.1 Handling of data

4.1.1 All Users are required to maintain the security and confidentiality of their study datasets in accordance with this Agreement and

- will not reuse data for purposes outside the scope of each approved study
- will not share data with anyone who is not a named user on the approvals granted for that study
- will not attempt to link the study data to any other data without explicit permission
- will not attempt to identify any individual within the study data
- will not attempt to reuse the data for commercial purposes beyond those stated in the approvals granted prior to the study commencing
- will not share their login details with any other person
- will remotely access eDRIS only in suitable locations where work cannot be read by anyone not named on the approval request.
- will not discuss information which could breach an individual's privacy in a public place, in this context a public place may be taken to be anywhere where people not directly involved with this study may be present.

4.1.2 The eDRIS Service will securely archive the data, analysis syntax, and output associated with the study when the study is complete.

4.2 Storage and copying of Data

4.2.1 The storage of or copying of data outwith the eDRIS technical environment is strictly forbidden.

4.2.2 Under no circumstances should data be written from the workstation screen or attempts made to save screen shots or photograph the screen.

4.2.3 Under no circumstances should attempts be made to use removable data storage devices (e.g.. USB storage devices, memory pens/sticks, personal digital assistants (PDAs), etc). The eDRIS technical environment includes software to monitor system use.

## 5 RELEASE OF OUTPUT

5.1 Release of Statistical Output

5.1.1 All output will be reviewed by the Research Coordinator and will only be released in line with the Data Controllers' disclosure control requirements. At the end of your session you must request your outputs to be disclosure cleared by your assigned Research Coordinator. The Research Coordinator will review your outputs, and thereafter if cleared for release will send them to you via email.

5.2 Output Clearance

5.2.1 The User agrees to meet the requirements of safe, non disclosive outputs.

5.2.2 Only outputs which have been approved as non disclosive can be used as part of presentations, publications, papers and analysis. If the approval granted stipulated a requirement that you share all analysis/papers etc. with the Data Controller it is your responsibility to ensure that you comply.

5.2.3 In the event that eDRIS, taking advice from NSS, decides not to release the requested output, the User will have an opportunity to demonstrate to eDRIS and, where appropriate, the study Data Controllers, that the outputs are anonymised and

safe for publication or release. However, the final decision to release any output remains with eDRIS and not the User.

5.2.4 On request from the eDRIS Research Coordinator the User must provide a description of variables used, new variables/measures/indices created, documentation of datasets and programs used in producing analytical output(s) to ensure that the Research Coordinator has the information needed to make a decision on the request for output release.

5.2.5 The User shall ensure that all publications in any format should acknowledge NSS. Depending on the content of the data it may also be courteous to acknowledge the Data Controller(s) associated with the study. Abstracts/papers intended for journal publication may be required to be reviewed for clearance by your Research Coordinator. If it is intended to present any unpublished data at a conference/seminar an abstract may be required for clearance. These obligations are at the discretion of the Data Controller(s) and should be agreed between all parties prior to the study commencing.

## 6. GENERAL PROVISIONS

6.1 Interpretation

If you require an explanation concerning the interpretation or the relevance of this Agreement you should discuss the matter with your Research Coordinator.

6.2 Non-Compliance

Any breach of this Agreement may result in the User and his/her organisation being subjected to investigation in accordance with eDRIS Sanctions (see Section 7 below).

6.3 Amendments

This Agreement will be amended as required to reflect the development of policy and procedures, and the changing needs in security and confidentiality.

## 7. OFFENCES AND PENALTIES

7.1 Offences

7.1.1 Signing this Agreement demonstrates that the prospective User understands the seriousness of the undertaking and that they and their authorising organisation understand the penalties that may be imposed hereunder for breaches of security or confidentiality.

7.1.2 It is essential that Users understand the nature of, and reason for, penalties for breaches which either constitutes non-compliance with this Agreement and other standards, or more serious incidents which could lead to the disclosure of personal information. Therefore, Users are only able to access study datasets if they have signed this Agreement and successfully completed mandatory training approved by NSS from time to time and also fulfilled the criteria stated in Section 1.3 above.

7.1.3 NSS reserves the right to suspend access to the national safe haven if they believe that any User is perpetrating or attempting to perpetrate any of the breaches listed in Table 1.

7.1.4 NSS has discretionary powers over the application of penalties for self-reported breaches.

7.1.5 Application of the penalties for intentional breaches of this Agreement is non-discretionary. The penalties for such breaches (set out in Table 1 below) are fixed tariffs.

7.1.6 Self-reported unintentional breaches will be penalised with discretion; if a penalty is to be applied the relevant tariff (set out in Table 1 below) will be considered a maximum only. Users who take full and prompt action to report an unintentional breach will not normally be penalised but may be asked to repeat training. Penalties for repeated self-reported but unintentional breaches will increase at NSS's discretion with each breach committed.

7.1.7 All breaches and the penalties and tariffs applied will be reported in full by the Research Coordinator to the NSS Executive Team and other interested parties.

7.2 Legal / Statutory Penalties

7.2.1 NSS believe that penalties will only be an effective deterrent if they are fully understood, and it should also be clear that we are much more concerned about prevention than punishment.

7.2.2 The Statistics and Registration Services Act (SRSA) 2007 Act states, in section 39(9) that a person who contravenes subsection (1) "is guilty of an offence and liable —
(a) on conviction on indictment, to imprisonment for a term not exceeding two years, or to a fine, or both; (b) on summary conviction, to imprisonment for a term not exceeding twelve months, or to a fine not exceeding the statutory maximum, or both."

7.2.3 However, this subsection of the Act does not apply when the person making the disclosure "reasonably believes" that either Personal Information is not specified in the information which is disclosed, or that that a person's identity can not be deduced from the information, or that a person's identity can not be deduced from the information taken together with any other published information.

7.2.4 Nevertheless, the removal of Personal Information from the secure confines of a Safe Haven remains a breach of this Agreement, regardless of whether a User had 'reasonable belief'. Users are advised through this Agreement that they should regard only the statistical outputs which they have received from the Research Coordinator or NSS member of staff, to be non-disclosive, and that receiving such an output from the Research Coordinator or NSS member of staff is the basis for their 'reasonable belief'.

7.2.5 Users are made aware through this Agreement that NSS will always seek prosecution for any breach of the SRSA 2007. Under the SRSA 2007 legislation, the only exceptions are where the disclosure was unintentional and self-reported, or the 'reasonable belief' defence is unambiguously relevant. However, the reasonable belief defence is effectively removed through notification in this Agreement (see Section 7.3 below).

7.2.6 Section 55 of the Data Protection Act 1998 states that the knowing or reckless obtaining or disclosure of personal data without the consent of the data controller is a criminal offence. NSS will inform the appropriate authorities if they believe a section 55 offence has been committed by a User.

7.3. Non-compliance

7.3.1 A series of penalties for breaches will come into force when this Agreement and Declaration are signed. The majority of these breaches can be dealt with by NSS with no additional input from the relevant Data Controller(s) for the specific study. The result of any *public* breaches as per sections 10 through 13 inclusive in Table 1 below would be a very high loss of trust in eDRIS, and cause considerable political damage to Farr Institute @ Scotland and NSS.

7.3.2 NSS is capable of carrying out any individual User or institutional ban.

7.4 Use of data for personal or commercial gain

7.4.1 Unless stated in the approvals granted prior to the study commencing the selling on, and any other commercial exploitation, of data or outputs created through the use of the national safe haven for any personal financial or commercial exploitation or gain, and such use of eDRIS by Users acting as paid ‘agents' of businesses, are strictly forbidden.

7.5. Right of appeal

7.5.1 The right to an internal appeal is allowed. Thus all appeals should be to the stakeholder with the highest level of involvement with the offence.

7.5.2 If a User considers a penalty following a self-reported unintentional breach is unfair, the right of appeal is to the organisation(s) with the primary responsibility for enforcement (as detailed in the Table 1 below).

7.6. Offences and Penalties

7.6.1 The penalties listed in Table 1 below, *for intentional discovered breaches,* are non-discretionary. The penalties for such breaches are fixed tariffs.

7.6.2 Penalties may be imposed at the discretion of NSS for other offences not listed in Table 1 below that are considered by NSS to breach the terms and conditions of the use of eDRIS.

7.6.3 Under this Agreement, and if an obligation agreed by all parties hereto prior to the study commencing (see section 5.2.5 above) the User agrees to inform the Research Coordinator of any publications (external conferences, journal articles, reports) using outputs from eDRIS and also of any errors found in the data, outputs or publications. Whilst there is no formal penalty hereunder for not informing NSS, the User may be contacted by the Research Coordinator to provide such information. If the User does not provide such information, NSS reserves the right to take appropriate action.

7.6.4 It should be noted that whilst data subjects are not the owners of the data for the purposes of this document, they have the right to take independent civil action against any offender who damages them by release of their Personal Information.

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**Table 1**

| Offence | Expected Penalty | Notes/Example | Type |
|---|---|---|---|
| 1. Using the service and/or data for commercial purposes beyond those stated in the relevant approvals prior to the study commencing | First offence 6 months access suspension<br>Second offence 1 year access suspension<br>Third offence permanent suspension | See Sections 2.1, 4.1.1 and 7.4 of this Agreement | NSS eDRIS User Agreement |
| 2. Infringing safe haven requirements | First offence 6 months access suspension<br>Second offence 1 year suspension<br>Third offence permanent suspension | | NSS eDRIS User Agreement |
| 3. Attempting to infringe data security requirements | First offence 2 years access suspension<br>Second offence permanent suspension | See 10 below 'infringing data security requirements' | NSS eDRIS User Agreement |
| 4. Transferring log in details to any other user | First offence 1 year access suspension<br>Second offence permanent suspension | This includes sharing login details (whether user name, password or both) with someone else, even someone working on the same project or a supervisor. | NSS eDRIS User Agreement |
| 5. Providing false information on the NSS eDRIS User Agreement or Declaration | Permanent suspension | | NSS eDRIS User Agreement |

**Table 1**

| Offence | Expected Penalty | Notes/Example | Type |
|---|---|---|---|
| 6. Attempt to access datasets to which not authorised | Permanent suspension | | NSS eDRIS User Agreement |
| 7. Attempt to use data for purpose not specified in the Application | Permanent suspension | An example includes using data obtained under a study for a new research study that has not been approved. | NSS eDRIS User Agreement |
| 8. Attempt to use data or Output other than for statistical research | Permanent suspension | An example includes selling eDRIS data or eDRIS Outputs for personal or corporate financial gain. | NSS eDRIS User Agreement |
| 9. Sharing any data which have not been disclosure cleared. | Permanent suspension<br>NB sharing data outputs which prove to be disclosive will be subject to more severe penalties. | This includes, for example, data transcribed, written or photographed from the screen | NSS eDRIS User Agreement |
| 10. Infringing data security requirements | a) Permanent suspension (individual);<br>AND<br>b) 1 year suspension (authorising organisation) | See Section 4 (Data Security). | NSS eDRIS User Agreement<br>Violation of Statutory Law (Criminal Offence) |
| 11. Failure to report a Disclosure | First offence 1 year access suspension (individual)<br>Second offence permanent suspension (individual);<br>AND<br>b) First offence 6 months suspension (authorising organisation)<br>Second offence 1 years suspension (authorising organisation) | An example includes where there has been an unintentional disclosure and the User has become aware and has chosen not to inform the Research Coordinator | NSS eDRIS User Agreement |

| | Expected Penalty | Notes/Example | Type |
|---|---|---|---|
| | a) Permanent suspension from all eDRIS data services<br>(individual);<br>AND<br>b) 1 year suspension from all eDRIS data services (authorising organisation/institution)<br>Section 55 of the Data Protection Act 1998 states that the<br>knowing or reckless obtaining or disclosure of personal<br>data without the consent of the data controller is a criminal<br>offence. | This is where a User attempts to identify an individual, household or<br>business in the data. | NSS eDRIS User Agreement<br>Violation of Statutory Law (Criminal Offence) |
| | a) Permanent suspension from (individual);<br>AND<br>b) 1 year suspension from eDRIS (authorising organisation/institution) AND<br>Making disclosive data available to others is a criminal<br>offence and breaches may be subject to prosecution.<br>Identifying a relevant individual and providing that information to another party for personal gain is a serious<br>criminal offence in terms of the Statistics and Registration<br>Service Act, with potentially a 2 year jail term, a £2000fine, and a criminal record. Section 55 of the Data Protection Act 1998 states that the knowing or reckless obtaining or disclosure of personal data without consent of the data controller is a criminal offence | | NSS eDRIS User Agreement<br>Violation of Statutory Law (Criminal Offence) |

**8. REVIEW**

This Agreement will be reviewed by NSS every two years or more frequently if appropriate, to take into account changes to legislation that may occur, and/or guidance from the Scottish Government, NSS and Farr Institute @ Scotland.

**9. DECLARATIONS AND AGREEMENT**

The parties hereto hereby declare and agree to comply with all the provisions of this Agreement as follows:-

9.1 Study Number

eDRIS – 1516 – 0378

*Please ensure that sections 9.2 and 9.3 are completed before returning this form to eDRIS.*
*Where relevant section 9.4 should also be completed.*

9.2 NSS eDRIS User (You)

By signing and dating below you confirm that you have read, understood and agree to comply with all the provisions of this Agreement. Any breach by you of this Agreement will result in your access being restricted and may be subject to eDRIS sanctions. NSS has a duty, and is entitled hereunder, to report legal or regulatory breaches to the appropriate authorities (such as the Information Commissioner and professional regulatory bodies).

Name: MITANA PURKAYASTHA

Position: PHD STUDENT

Organisation: UNIVERSITY OF GLASGOW DENTAL SCHOOL

Signature: Mitana Purkayastha

Date signed: 27/06/2016

Study Number: eDRIS – 1516 – 0378

9.3 Your Authorising Organisation
(Note: Must be signed by a Head of Department, Information Custodian, or equivalent.)

"We declare that the above named User is a bona fide researcher engaged in a reputable study for which all relevant required permissions have been granted, and that the data requested can be entrusted to this person in the knowledge that they will conscientiously discharge their obligations in regard to the confidentiality of the data. This Organisation agrees to abide by all the terms of this Agreement and shall ensure that the above named User complies with all the provisions of this Agreement.

We declare that we understand that any breach of this Agreement by us or by the above-named User may lead to the withdrawal of access for this Organisation and its staff, and that NSS has a duty, and is entitled hereunder, to report legal or regulatory breaches to the appropriate authorities (such as the Information Commissioner and professional regulatory bodies)."

Name: DAVID CONWAY

Position: PROFESSOR / HONORARY CONSULTANT

Signature: Dnl Conway

Date signed: 27/6/16

For and On behalf of UNIVERSITY OF GLASGOW
(Name of Authorising Organisation)

9.4 Student Supervisor
(Note: Where the User is a student, the following Declaration must be signed by the student's supervisor.)

By signing and dating below you confirm that you will ensure that the above named User has read, understood and will comply with all the provisions of this Agreement.

Name: ALEX Mc MAHON

Position: READER / HON CONSULTANT

Signature: Alex Mc Mahon

Date signed: 27/6/16

For and On behalf of UNIV. GLASGOW
(Name of Authorising Organisation)

9.5 The Common Services Agency (commonly known as National Services Scotland)
(Note: This section must be completed by the eDRIS Team for all User Agreements.)

Name:_____

Position: _____

Signature: _____

Date signed: _____

For and On behalf of
_____ The Common Services Agency

**Appendix A – The Data Protection Principles**

**1** "Personal data shall be processed fairly and lawfully and, in particular, shall not be processed unless-(a) at least one of the conditions in Schedule 2 is met, and (b) in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met".

**2** "Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes".

**3** "Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed".

**4** "Personal data shall be accurate and, where necessary, kept up to date".

**5** "Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes".

**6** "Personal data shall be processed in accordance with the rights of data subjects under this Act".

**7** "Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data".

**8** "Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data".

**Appendix B – Glossary**

**Academic Use -** any teaching and/or non-government funded research as conducted by or under the direction of a professor or other academic professional within an academic environment and excludes any and all commercial use.

**Appropriate access** - the access a User will be given to appropriate areas of eDRIS.
This access may be across network links that are fixed or virtual.

**Approved Organisations -** for direct access to individual level data held on eDRIS are restricted to public sector organisations (e.g.. Universities, NHS, Local Authorities and Scottish Government). Researchers/Users from the Scottish Government and Local Authorities will have direct access to data via the physical national safe haven only.

**Approved Researcher** - is a researcher who has demonstrated they have satisfactorily completed the mandatory NSS approved training which ensures that they are fully aware of the policies and procedures governing individual privacy, data protection and freedom of information. In addition to ensure awareness and understanding of obligations specific to health data, Approved Researchers must also read the NHS Confidentiality Code of Practice. See further criteria for 'eDRIS User'

**Anonymised information** – information from which no individual can be identified.

**Authorising Organisation** - is the employing or sponsoring organisation signing the NSS eDRIS User Agreement in support of the User. The Authorising Organisation shall ensure that the User complies with the provisions of this Agreement.

**Commercial use of information** – sharing Information (data or outputs) for corporate gain.

**Data Controller** – a person who (either alone or jointly or in common with other persons) determines the purposes for which and the manner in which any personal data are, or are to be, processed.

**Data custodian** – is responsible for the security of the database and may need to set up both physical and network security systems. If the data custodian finds evidence of unauthorized access, the data custodian is responsible for reporting the security breach to the Data Controllers, as well as fixing existing security weaknesses so future breaches do not occur.

**Data processor** – any person (other than an employee of the Data Controller) who processes the data on behalf of the Data Controller.

**Data Protection Act 1998 (DPA)** – the main UK legislation which governs the handling and protection of information relating to living people.

**Data sharing** – the disclosure of data from one or more organisations to a third party organisation or organisations, or the sharing of data between different parts of an organisation. Data Sharing can take the form of systematic, routine data sharing where the same data sets are shared between the same organisations for an established purpose; and exceptional, one off decisions to share data for any of a range of purposes.
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**Disclosure controlled/cleared outputs** - is used to describe an output which is considered not to contain information which could be used, in conjunction with other data, to identify a person.

**eDRIS User or User** – is a researcher, employed by a eDRIS Approved Organisation to whom the National Services Scotland (NSS), under the Statistics and Registration Services Act (SRSA) 2007 and Data Protection Act 1998, has granted access to study datasets for the purposes of statistical

research. The User will have approvals from the relevant authorising bodies and will have completed NSS approved training, read the NHS Confidentiality Code of Practice ensuring awareness of policy and procedures governing individual privacy, data protection and freedom of information and has signed this Agreement (see 1.3). Note an Approved Researcher refers to an individual who has satisfactorily completed the NSS Approved Training and read the NHS Confidentiality Code of Practice only.

**Information -** includes both data and outputs where data are the raw details used to create outputs resulting from an analytical operation producing analysis; graphs; tables etc. The output can be in any format e.g.. paper, electronic etc.

**NSS Approved Training** – Courses approved by NSS as suitable for researcher training in preparation for access to study datasets are listed in the frequently asked questions section of the eDRIS website.

**Outputs** – the results of an analytical operation producing analysis; graphs; tables etc. The output can be in any format e.g.. paper, electronic etc.

**Personal data (or Personal information)** – data which relate to a living individual who can be identified—

**a** from those data, or
**b** from those data and other information which is in the possession of, or is likely to come into the possession of, the Data Controller, and includes any expression of opinion about the individual and any indication of the intentions of the Data Controller or any other person in respect of the individual.

**Processing of data** – in relation to information or data, means obtaining, recording or holding the information or data or carrying out any operation or set of operations on the information or data, including—

**a** organisation, adaptation or alteration of the information or data,

**b** retrieval, consultation or use of the information or data,

**c** disclosure of the information or data by transmission, dissemination or otherwise making available, or

**d** alignment, combination, blocking, erasure or destruction of the information or data.

**Research Coordinator** – in the context of this Agreement is the eDRIS Research Coordinator employed by NSS who ensures that Users have completed the approved mandatory training, the Agreement is signed by the User, the declaration is signed by the User and the authorising organisation, and are aware of the penalties if they breach this Agreement. The Research Coordinator is also responsible for ensuring the User complies with the terms of this Agreement and approves outputs before release to the User.

**Safe Haven** – is a national or local environment operating to procedures designed to uphold the Guiding Principles for Data Linkage and providing secure access to data whilst maintaining the utmost confidentiality. Local safe havens may have virtual or fixed lines to access eDRIS. NSS operates the Safe Haven for Scotland.

**Safe Haven Requirements** – the following list the criteria for remote Safe Haven workstations accessing eDRIS.

- the safe haven should be located in a secure location e.g.. segregated area, windows and doors can be locked
- the physical safe haven setting must ensure that data can not be viewed or read by anyone not identified in the relevant approvals for this study.
- workstations must have screen savers installed and activated while left unattended
- telephone conversations should not be held while accessing the data
- data should not be written from the screen, or attempts made to photograph the screen
- no attempt should be made to save screen shots
- no attempt should be made to store or copy data
- no attempt should be made to use removable data storage devises
- MS Office 2010 Licence (e.g.. word, excel etc) must be provided by the Authorising Organisation.

**Stakeholder -** in the context of this Agreement could be NSS, NSS & Other(s) or Other(s).

Statistics and Registration Services Act - **The Statistics and Registration Services Act (SRSA) 2007 Act states that a person who discloses Personal Information "is guilty of an offence and liable — (a) on conviction on indictment, to imprisonment for a term not exceeding two years, or to a fine, or both; (b) on summary conviction, to imprisonment for a term not exceeding twelve months, or to a fine not exceeding the statutory maximum, or both."**

# Appendix 11: Search Strategy

**Databases searched:** Pubmed, EmBase, Medline, Google Scholar. Additionally, the reference lists of key papers were scanned for relevant literature, and the publication lists of notable authors in the field were checked for any recent publications.

**Search terms used (adapted to individual databases):**

1. "head and neck neoplasms"/ or facial neoplasms/ or mouth neoplasms/ or otorhinolaryngologic neoplasms/

2. (head or neck) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).ti.

3. exp Mouth Neoplasms/

4. ((oral or intra-oral or intraoral or mouth or lip* or tongue or cheek* or cheek lin* or gingiv* or gum* or palat* or "roof of mouth" or odontogenic or teeth or tooth or buccal or buccal mucosa or face or facial or maxilla*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or

squamous)).ti.

5. exp Lip Neoplasms/

6. exp Gingival Neoplasms/

7. exp Palatal Neoplasms/

8. exp Tongue Neoplasms/

9. exp Tonsillar Neoplasms/

10. exp Mandibular Neoplasms/

11. exp Maxillary Neoplasms/

12. exp Odontogenic Tumors/

13. exp Oropharyngeal Neoplasms/

14. ((oropharyn* or tonsil* or retromolar*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan* or lymphoma* or melanoma* or squamous)).tw.

15. exp Pharyngeal Neoplasms/

16. ((pharyn* or throat) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenocarcinoma* or oncolog* or malignan*

17. Incidence or burden

18. early detection or early diagnosis or screening or opportunistic screening

19. “missed opportunities” or “ delays in diagnosis” or (diagnostic delays*) or (system delay*) or (patient delay*) or (professional delay*)