Investigations into oral health and dental care factors associated with oral cancer risk and management

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Abstract

Introduction

In Scotland in 2010, 460 new cases of cancer of the oral cavity were reported with a crude rate of 8.8 per 100,000 person/year risk (ISD Scotland). Worldwide, oral cancer (also known as lip and oral cavity cancer) is the 15th most common cancer, with more than 300,000 new cases diagnosed in 2012 (2% of the total). Oral cancer is the 15th most common cancer in Europe, with around 61,400 new cases diagnosed in 2012 (2% of the total) (GLOBOCAN 2012). In order to reduce the incidence of oral cancer, risk factors need to be identified and appropriate preventative strategies developed.

In addition to significant mortality, there is significant morbidity associated with oral cancer. Patients can suffer from disfigurement, pain, reduced function and depressive illness as a result of the disease and its treatment. Guidelines state that oral cancer patients should receive pre- and post-operative dental assessments and management as part of their cancer treatment to reduce complications and improve outcomes (British Association of Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

Aims

To carry out a systematic review and meta-analysis of the world-wide literature regarding oral health and dental care factors associated with oral cancer risk.

To examine the level and degree of clinical dental care for patients diagnosed with and treated for head and neck/ oral cancer.

Materials and Methods

A systematic review and meta-analysis of the world literature was undertaken assessing the association between oral health and dental care factors and the incidence risk of oral cancer. Studies were included if they reported odds ratios

and corresponding 95% Confidence Intervals of oral cancer with respect to oral health or a dental care factor or if the estimates could be calculated or obtained. Meta-analyses were performed to quantify the risk associated with each factor. Included studies were assessed regarding heterogeneity and meta-analysis were carried out using a random effects model where heterogeneity was significant and a fixed effects model where heterogeneity was not significant. Included studies were also assessed regarding their methodological quality and sensitivity analyses and publication bias assessments were conducted.

Case records for head and neck cancer patients diagnosed 2002-2004 were examined and assessed for evidence of dental assessments in parallel to a large multi-centre case-control study. Data were compared to audit data collected from patients diagnosed with head and neck cancer 2013-2014.

Results

The systematic search retrieved 8534 articles (after removal of duplicates, books and patents) which were screened against the inclusion criteria. This resulted in 18 studies that met the inclusion criteria. The overall estimate for general oral health associated with increased risk of oral cancer comparing the best oral health score with the worst was OR 3.91 (95% CI 2.29, 6.67) based on 3 studies. The overall estimate for gum bleeding associated with increased risk of oral cancer comparing the absence of gum bleeding with the worst score was 1.76 (95% CI 1.20, 2.58) based on 6 studies. The overall estimate for poor oral hygiene associated with increased risk of oral cancer was 3.56 (95% CI 2.52, 5.04) based on 2 studies. The overall estimate for 6 or more missing teeth associated with increased risk of oral cancer was OR 2.3 (95% CI 1.27, 4.18) based on 6 studies. The overall estimate for non-attendance at the dentist associated with increased risk of oral cancer was 1.45 (95% CI 1.12, 1.87) based on 3 studies. The overall estimate for denture-wearing associated with increased risk of oral cancer was 1.08 (95% CI 0.80, 1.46) based on 5 studies. The overall estimate for reduced frequency of toothbrushing associated with increased risk of oral cancer was reported as OR 1.75 (95% CI 1.21, 2.53) based on 6 studies.

Regarding dental assessment of head and neck cancer patients, 6 out of 43 (14%; 95% CI 4%, 24%) dentate patients from the 2002-2004 cohort had a pre-operative

dental assessment compared to 45 out of 71 (63%; 95% CI 52%, 74%) of the dentate patients in the 2013-2014 cohort, which was a significant improvement. In the 2002-2004 cohort, 14 (18%; 95% CI 9%, 27%) patients out of 76 had a post-operative dental assessment compared to 19 (26%; 95% CI 16%, 36%) out of 74 patients were identified as having had some form of post-operative assessment or management, which was not a significant improvement (p= 0.28).

Conclusions

The available evidence indicates that general oral health, gum bleeding, oral hygiene, missing teeth, dental attendance and frequency of toothbrushing are all risk factors for oral cancer. Denture use *per se* is not associated with an increased risk of oral cancer. Oral health factors and, more widely, dental care factors should be acknowledged alongside traditional smoking and alcohol behaviours as important risk factors for oral cancer.

An improvement in the frequency of pre-operative dental assessments has been seen. However, guidelines and standards that state that all oral cancer patients should receive a pre-operative dental assessment are not being met (British Association of Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006) and we don't appear to have achieved the quality performance indicator (Healthcare Improvement Scotland, 2014) stating that at least 90% of oral cancer patients should receive a pre-operative dental assessment. Post-operative dental assessments have not seen a significant improvement and compliance is difficult to assess against other research as there is little published work in this area. As standards have not been met, further efforts should be made to attempt to ensure dental assessment and management are integrated as part of the multidisciplinary team approach for patients with oral cancer.

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Preface

Oral cancer is a devastating condition. I have worked with patients with oral cancer throughout my specialist training and into my consultant position and have seen the impact that it has on sufferers and their families. It is difficult to convey the magnitude of the morbidity associated with this debilitating and disfiguring condition. Simple things that the majority of us take for granted can become a significant challenge such as talking, eating and even going out in public. Two things become apparent to anyone involved in the clinical management of oral cancer: everything should be done to try and prevent this disease, and everything that can be done to improve the quality of life of patients who have suffered from oral cancer should be done.

It is my hope that this work will aid in understanding the role of oral health and dental care factors in the risk of oral cancer so systems can be put into place to attempt to prevent this devastating disease. I also hope that this research will go some way towards identifying potential gaps in the cancer service and facilitate change with the aim of ultimately improving outcomes and quality of life for oral cancer sufferers.

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Finally, I would like to thank my family and in particular, my wife Gurpreet, who have supported me throughout this project and helped keep me motivated and focused especially through the title screening months! Thank you for putting up with me.

Author's Declaration

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

Andrew Pye

Definitions/Abbreviations

ARCAGE- Alcohol-Related Cancers and Genetic Susceptibility in Europe
BAHNO- British Association of Head & Neck Oncologists
DNA- Deoxyribonucleic acid
GDC- General Dental Council
HIS- Healthcare Improvement Scotland
HPV- Human papillomavirus
IACR- International Association of Cancer Registries
ICD– International Classification of Diseases
ISD- Information Services Division
MOOSE- Meta-analysis Of Observational Studies in Epidemiology
NICE- National Institute for Health and Care Excellence
OR- Odds Ratio
ORN- Osteoradionecrosis
SIGN- Scottish Intercollegiate Guidelines Network
UK- United Kingdom
WHO- World Health Organisation

1 Introduction

1.1 Background

1.1.1 Oral cancer

1.1.1.1 Definition

Cancer is a term for a group of related conditions where some cells within the body begin to divide uncontrollably and invade the surrounding tissues. Old or damaged cells do not die as is seen in normal tissues and new cells are formed by division without control. The extra cells that this process produces result in tissue growths termed tumours (National Cancer Institute, 2014).

There is no universally accepted definition of oral cancer (Cancer Research UK, 2015). One paper reported identifying 17 different terms being used for oral cancer in the literature (Tapia and Goldberg, 2011). Using the WHO International Classification of Diseases (ICD) codes from the 10th revision (ICD-10), the following are sites and associated ICD-10 codes commonly accepted as defined as oral cancer or as lip and oral cavity cancer: internal lip (ICD-10, C00), tongue (ICD-10, C01, C02), gum (ICD-10, C03), floor of the mouth (ICD-10, C04), palate (ICD-10, C05), other unspecified parts of the mouth (ICD-10, C06), tonsil (ICD-10, C09), oropharynx (ICD-10, C10), and other ill-defined sites (ICD-10, C14) (World Health Organisation, 2015). The usual exclusions are the external surface of the lip (ICD-10, C00.0, C00.1, C00.2), and the salivary glands (ICD-10 C07, C08).

Oral cancer can originate from many different types of cell, however the most common is squamous cell, seen in 90% of cases (Johnson et al., 2011).

1.1.1.2 Epidemiology

Oral cancer is the 15th most common cancer in the UK (2010), accounting for 2% of all new cases. In males, it is the 11th most common cancer (3% of the male total), whilst it is 15th in females (1%) (Cancer Research UK). In 2010, there were 6,539 new cases of oral cancer in the UK: 4,307 (66%) in men and 2,232 (34%) in women, giving a male: female ratio of more than 19:10 (Cancer Research UK). The crude incidence rates show that there are 14 new oral cancer

cases for every 100,000 males in the UK, and 7 for every 100,000 females (Cancer Research UK). In Scotland in 2010, 460 new cases of cancer of the oral cavity were reported with a crude rate of 8.8 per 100,000 person/year risk (ISD Scotland). Worldwide, lip and oral cavity cancer is the 15th most common cancer, with more than 300,000 new cases diagnosed in 2012 (2% of the total). Lip and oral cavity cancer is the 15th most common cancer in Europe, with around 61,400 new cases diagnosed in 2012 (2% of the total) (GLOBOCAN 2012).

Although management of oral cancer has seen a number of advances in recent years, mortality rates are still high. In 2012, there were 2,119 deaths from oral cancer in the UK: 1,426 (67%) in men and 693 (33%) in women, giving a male: female ratio of more than 2:1. The crude mortality rate shows that there are 5 oral cancer deaths for every 100,000 males in the UK, and 2 for every 100,000 females (Cancer Research UK). Survival data from Scotland indicates that the 5 year survival of oral cavity cancer is 57.4% 2007-2011 which has not substantially improved in many decades (ISD Scotland).

In addition to significant mortality, there is significant morbidity associated. Patients can suffer from disfigurement, pain, reduced function and depressive illness as a result of the disease and its treatment (Ross et al., 2010, Duke et al., 2005, Irish et al., 2009, Koster and Bergsma, 1990, Meyer et al., 2004).

1.1.1.3 Treatment

Patients diagnosed with oral cancer are primarily treated surgically, with or without radiotherapy / chemoradiotherapy (Shaw et al., 2011). Treatment and rehabilitation are conducted by a multi-disciplinary team which should include head and neck cancer surgeons, clinical oncologist, restorative dentist, pathologist, radiologist, clinical nurse specialist, speech and language therapist, dietician, and palliative care specialist (National Institute for Clinical Excellence, 2004). The post-surgical changes to the anatomy and oral / dental condition can be dramatic and patients need to be informed of this pre-operatively and steps taken to manage these changes as part of their rehabilitation following treatment (Pace-Balzan et al., 2011). In the past, oral cancer patients were treated by the oncology team and the focus was very much on survival of the patient and little or no thought was given to the patient's oral

rehabilitation. This approach can lead to a number of problems including inability to achieve satisfactory oral and dental rehabilitation and potentially serious complications. There has been a shift now from a focus on survival to improving quality of life for oral cancer survivors (Rogers et al., 2002, Chandu et al., 2006). It is now widely recommended that patients have a dental assessment prior to treatment for oral cancer and that they have access to a Consultant in Restorative Dentistry to plan and manage their rehabilitation (British Association of Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006, Healthcare Improvement Scotland, 2014).

Radiotherapy is the use of high energy radiation to cause damage to cancer cells. The radiation can cause direct damage to the DNA of a cell or, more commonly, cause indirect damage to DNA by creating reactive oxygen species within cells. Death of the cell can happen immediately or when the cell attempts to divide. Where there is a time period between the damage and the attempted replication, it is possible for the cell to repair the damage. Radiation is particularly effective against tumour cells as the cells are dividing rapidly and without control and so there is less time and scope for the cells to repair and so cell death occurs. Unfortunately, damage occurs to healthy structures as well and there are a number of changes that occur within and around the oral cavity that requires dental consideration such as the increased risk of osteoradionecrosis and caries secondary to reduced quality and quantity of saliva (Ray-Chaudhuri et al., 2013, McCaul, 2012).

1.1.1.4 Osteoradionecrosis

The risk of osetoradionecrosis is of particular concern for patients undergoing treatment for oral cancer using radiotherapy / chemoradiotherapy (Reuther et al., 2003). Osteoradionecrosis is defined as “when the irradiated bone becomes devitalised and becomes exposed through the overlying skin or mucosa without healing for three months, without recurrence of tumour” (Lyons and Ghazali, 2008). It is a particular risk in patients who receive radiotherapy to the head and neck as dental disease and oral factors can predispose to osteoradionecrosis, especially where extractions are required. The incidence of osteoradionecrosis

following extractions in patients with a history of radiotherapy was reported in a recent systematic review as 7% (Nabil and Samman, 2011).

Osteoradionecrosis is thought to occur as a result of the tissues becoming hypoxic, hypocellular and hypovascular following radiotherapy (Marx, 1983). The tissues are no longer able to repair as before and break down either spontaneously or as a result of trauma. Unable to repair as normal and exposed to oral bacteria, the bone becomes necrotic and superinfected with bacteria. There can be a high morbidity associated with this condition and may require extensive resective surgery to manage it (Buchbinder and St Hilaire, 2006, Bennett et al., 2012).

Although osteoradionecrosis can occur spontaneously, it is often as a result of an initial trauma to the tissues. Certain factors predispose to the condition such as post-operative dental extractions, periodontal disease and poorly fitting dental prostheses (Reuther et al., 2003, Niewald et al., 2013). In an attempt to manage this risk, patients should see a suitably qualified dental professional and have potential risk factors managed prior to radiotherapy / chemoradiotherapy (Scottish Intercollegiate Guidelines Network, 2006, National Institute for Clinical Excellence, 2004). Recommendations have been made as to how teeth should be managed prior to radiotherapy (Jansma et al., 1992, Schiodt and Hermund, 2002), however there is no universally accepted guidance on management.

It is of paramount importance that we understand factors which have an effect on the risk of developing the disease so that prevention strategies can be put into place. Factors which have an impact on the outcomes of treatment need to be managed appropriately so that outcomes and quality of life can be maximised and adverse events can be avoided or minimised.

1.2 Risk factors for developing oral cancer

In order to develop appropriate prevention strategies to prevent oral cancer, risk factors need to be identified and the relationship demonstrated. The focus of epidemiology research has been on smoking and alcohol and, increasingly on the

role of genetic variants and oral human papilloma virus (Parkin, 2011a, Lubin et al., 2011, Gandini et al., 2008, Parkin, 2011b, Turati et al., 2013, D'Souza et al., 2007, Radoi and Luce, 2013).

1.2.1 Smoking

Smoking is considered to be a major public health problem resulting in significant premature death and morbidity (Warren et al., 2014). An estimated 65% (70% in males and 55% in females) of oral and pharyngeal cancers in the UK are linked to tobacco smoking (Parkin, 2011a). A meta-analysis found oral cavity cancer risk is 3 times higher in current smokers compared with never-smokers and pharyngeal cancer risk is over 6 times higher in current smokers compared with never-smokers (Gandini et al., 2008). A meta-analysis showed individuals who smoke but have never consumed alcohol are still at increased risk of oral cancer OR 2.13 (95% CI 1.52, 2.98) (Hashibe et al., 2007).

The relationship between smoking and detrimental effects has been shown to have a dose-response relationship i.e. with an increased number of cigarettes smoked over a longer period of time, comes a higher risk of health problems. Oral cavity cancer risk in men is almost 3 times higher in those who have smoked the most cigarettes for the most years, compared with those who have smoked the least for the fewest years. Oral cavity cancer risk in women is more than 4 times higher in the heaviest- and longest-smokers versus the lightest- and shortest-smokers. Oropharynx cancer risk in men is almost twice as high in the heaviest- and longest-smokers versus the lightest- and shortest-smokers. Oropharynx cancer risk in women is more than 3 times higher in the heaviest- and longest-smokers versus the lightest- and shortest-smokers (Lubin et al., 2011).

The benefits of stopping smoking have been investigated and demonstrated. Oral cavity cancer risk is 35% lower in ex-smokers who quit 1-4 years previously, compared with current smokers. Oral cavity cancer risk is no higher in ex-smokers who quit 20+ years previously, compared with never-smokers. Oropharynx/hypopharynx cancer risk is 49% lower in ex-smokers who quit 5-9 years previously, compared with current smokers. Oropharynx / Hypopharynx

cancer risk is no higher in ex-smokers who quit 20+ years previously, compared with never-smokers (Marron et al., 2010).

1.2.2 Alcohol

Alcohol is considered to be a significant public health problem as well as contributing to a number of social problems such as interpersonal violence (ISD Scotland, 2015). An estimated 30% (37% in males and 17% in females) of oral and pharyngeal cancers in the UK are linked to alcohol drinking (Parkin, 2011b). A meta-analysis found that oral and pharyngeal cancer risk in men is 35% higher per 1.5 units of alcohol consumed per day; oral and pharyngeal cancer risk in women is 9% higher per 1.5 units of alcohol per day; oral and pharyngeal cancer risk is more than 3 times higher per 6 units of alcohol per day; oral and pharyngeal cancer risk is 2.5 times higher in regular drinkers compared with non- and occasional drinkers (Turati et al., 2013).

A meta-analysis showed that oral and pharyngeal cancer risk is almost tripled in alcohol drinkers who currently smoke tobacco, while it is 32% higher in alcohol drinkers who do not currently smoke, both compared with never-drinkers, (Hashibe et al., 2007). The same meta-analysis found that among never users of tobacco, alcohol consumption was associated with an increased risk of head and neck cancer only when alcohol was consumed at high frequency (for three or more drinks per day versus never drinking OR 2.04 (95% CI 1.29, 3.21). The association with high-frequency alcohol intake was limited to cancers of the oropharynx / hypopharynx and larynx (Hashibe et al., 2007).

1.2.3 Oral health and dental care factors

The World Health Organisation (WHO) defines Oral Health as “a state of being free from mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual’s capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing” (World Health Organisation, 2012).

General oral health is discussed in a number of papers (Balaram et al., 2002, Ahrens et al., 2014, Talamini et al., 2000). There is no consensus on the

definition of general oral health, instead studies will tend to use a number of factors as indicators of general oral health. Balaram et al. (2002) and Talamini et al. (2000) assessed oral health based on "the presence of tartar, decayed teeth, and mucosal irritation". Ahrens et al (2014) used denture wearing, age of starting to wear dentures, and frequency of gum bleeding from teeth.

Gum bleeding is often reported following toothbrushing although it can occur spontaneously or following eating (Lindhe et al., 2008). The presence of bleeding from the gums can be an indicator of inflammation of the gums and so can be a sign of gum disease (Corbet, 2012).

Periodontal disease is classified as gingival inflammation at sites where there has been apical migration of the epithelial attachment onto the root surfaces accompanied by loss of connective tissue and alveolar bone (Armitage, 1995).

Dental caries is the localised destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates (Selwitz et al., 2007).

The relationship of impaired oral health (periodontal disease, missing teeth, denture wearing, dental decay) and dental care factors (level of oral hygiene, frequency of toothbrushing, dental attendance) on the development of head and neck cancer is not well understood. Guidelines reporting on risk factors for oral cancer and methods of reducing those risks do not discuss oral health and dental care as risk factors. A recent review of all risk factors for oral cancer demonstrates that while there has been many analyses on a wide range of potential risk factors in head and neck cancer, thus far dental care and oral health has not been sufficiently considered (Winn et al., 2015).

Many studies have been conducted which have looked at oral health and dental care factors as risk factors for oral cancer, and in many cases these have produced contradictory results. For example, Zheng et al., 1990 found reduced frequency of toothbrushing in males was significantly associated with developing oral cancer OR of 7.8 (95% CI: 2.61, 23.35). However, Balaram et al. 2002 failed to demonstrate a significant association between reduced frequency of toothbrushing and oral cancer in males with an OR 0.96 (95% CI 0.58, 1.58).

These measures of oral health are largely limited by the study design of oral cancer risk factor studies, most commonly case-control studies. Often the data collected is based on self-reported or simple examinations (Ahrens et al., 2014, Talamini et al., 2000, Balaram et al., 2002, Guha et al., 2007) which fall short of in-depth oral health assessment (Scottish Dental Clinical Effectiveness Programme, 2011).

A recent systematic review (Radoi and Luce, 2013) examined all risk factors for all oral cavity cancer, including oral health, and qualitatively presented their results. They suggested that the association seen may be confounded by tobacco and alcohol and may not be independent risk factors, however acknowledged that the association has been seen even when potential risk factors are accounted for in the analysis. They did not attempt a quantitative meta-analysis and their conclusions appear to be based upon a subjective assessment of the literature.

1.3 Oral Cancer guidelines, standards and targets

There are a number of national guidelines, standards and targets relevant to the management of oral cancer (British Association of Head and Neck Oncologists, 2009, Scottish Intercollegiate Guidelines Network, 2006, National Institute for Clinical Excellence, 2004, Healthcare Improvement Scotland, 2014).

The Scottish Intercollegiate Guidelines Network (SIGN) produced guidelines for head and neck cancer in 2006. The guidelines gave evidence based recommendations through various stages from prevention through management and follow-up. Regarding prevention, a number of recommendations are made regarding established aetiological risk factors for head and neck cancer. However, notably, oral health factors are not considered potential risk factors. The guidelines make a number of recommendations on the management of this cohort of patients. They state: “Patients with head and neck cancer, especially those planned for resection of oral cancers or whose teeth are to be included in a radiotherapy field, should have the opportunity for a pre-treatment assessment by an appropriately experienced dental practitioner” (evidence level C*); “patients receiving chemoradiotherapy are more likely than those receiving radiotherapy alone to suffer from post-treatment dental problems and require

access to dental expertise" (recommended best practice based on the clinical experience of the guideline development group); "Patients receiving oral surgery or radiotherapy to the mouth (with or without adjuvant chemotherapy) should have post-treatment dental rehabilitation (evidence level C*)"; "patients should have access to a consultant restorative dentist" (Recommended best practice based on the clinical experience of the guideline development group) (Scottish Intercollegiate Guidelines Network, 2006). *Evidence level C: A body of evidence including studies rated as "Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results"; or extrapolated evidence from studies rated as "High quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal".

The National Institute for Clinical Excellence (NICE) also produced guidelines recommending how head and neck cancer patients should be managed and how services in England and Wales should be organised. The guidelines make a number of recommendations: "Patients whose treatment will affect the mouth or jaw should be examined by a specialist dentist and any dental problems should be identified and treated before cancer treatment begins"; "Expert dental assessment and treatment is important both before and after treatment, especially when radiotherapy is being considered" (National Institute for Clinical Excellence, 2004). These recommendations were based on the clinical expertise of the guideline group and review of the available evidence.

Recommendations specific to radiotherapy for head and neck cancer were made by the British Association of Head and Neck Oncologists. They stated "100% of patients should be assessed by a suitably qualified dental practitioner before and after their main treatment" (British Association of Head and Neck Oncologists, 2009). These standards are based upon the clinical expertise of the authors and a review of the available literature.

Healthcare Improvement Scotland published head and neck cancer quality performance indicators setting a number of targets for the management of these patients. Included are "Patients with head and neck cancer should have oral

assessment before treatment begins to ensure that any dental work needed can be given before first treatment" and the target of 90% of patients should have a "pre-operative oral assessment before initiation of treatment" (Healthcare Improvement Scotland, 2014). These standards were based on systematic review and search, including appraisal of clinical guidelines from around the world in relation to head and neck cancer.

All the guidelines and targets make similar recommendations with regards to the management of head and neck cancer patients. The current recommendations propose that head and neck cancer patients should receive a dental assessment before and after cancer treatment and it is those recommendations that form the basis of our research into assessing the delivery of oral health assessment and management of head and neck cancer patients. Further research is required to improve the evidence base regarding the role of dental assessment and care in the management of head and neck cancer patients.

1.4 Oral Health assessment and oral cancer care

1.4.1 Oral health of patients presenting with oral cancer

Patients who present with oral cancer often have poor oral health and high levels of dental disease. A recent study in the UK examined patients diagnosed with head and neck cancer prior to treatment and found 71% of the dentate patients examined were diagnosed with periodontal disease and 61% presented with one or more carious teeth (Critchlow et al., 2014). Cancer patients often do not regularly attend dentists, as well as having high levels of dental disease. One study examined 250 sequential patients requiring radiotherapy and found that 68% of patients required immediate dental treatment, 20.8% were edentulous and had poorly fitting dentures and only 11.2% were regular dental attenders and were dentally fit (Lizi, 1992).

1.4.2 Rationale for pre-treatment oral health assessment as part of cancer care

Dental disease is often given low priority in the overall management of oral cancer patients (NHS Information Centre, 2013). Unfortunately, this can lead to a number of problems, particularly for those who require radiotherapy or

chemoradiotherapy. It is important that once radiotherapy or chemoradiotherapy is initiated, treatment is not interrupted. Interruptions in treatment are associated with poorer outcomes and quality of life, increased risk of complications, and reduced survival (Suntharalingam et al., 2001). Dental infections as a result of pre-existing dental disease can cause complications during cancer treatment such as febrile (fever) episodes (Laine et al., 1992).

In addition to oral cancer patients often presenting with higher levels of dental disease, patients who receive radiotherapy are more at risk of future dental disease. Salivary gland tissue is particularly sensitive to radiation and is often unavoidably included within the radiation field. The outcome of this is a reduction in the quality and quantity of saliva. One questionnaire study found in group of 75 head and neck cancer patients more than six months after radiotherapy, 93% suffered from a dry mouth and 65% had moderate to severe xerostomia (Dirix et al., 2008). This has a profound effect on a patient's risk of dental caries (decay). Dry mouth has also been identified as a patient priority when assessing quality of life following cancer treatment (List et al., 2000, Ramaekers et al., 2011)

Saliva protects teeth against dental decay (Kidd and Joyston-Bechal, 1997). The protective effect is a result of a number of mechanisms. Saliva acts as a buffer and neutralises acid. Plaque bacteria will produce acid as a result of the fermentation of carbohydrates in the diet. Where the acid produced outweighs the buffering capacity of saliva, demineralisation of tooth structures occur which can progress to dental decay. Saliva has a number of constituents that are able to act as a buffer and neutralise the acid, preventing dental decay such as bicarbonate. Where demineralisation has occurred, remineralisation is possible due to minerals within saliva. Saliva is supersaturated with minerals. The high concentrations of minerals such as calcium and phosphate allow remineralisation of dental hard tissues by diffusing into areas of demineralisation as a result of plaque acids (Humphrey and Williamson, 2001).

Unfortunately radiotherapy has a substantial effect on saliva. It not only effects the quantity of saliva produced but also the quality. Clinically, saliva often appears thick and frothy in radiotherapy patients. The qualitative changes in the

composition of saliva result in a reduction in the buffering capacity of the saliva and a reduction in the salivary pH resulting in conditions that favour demineralisation of dental hard tissues and caries. The dramatic effect that this has and the rapid breakdown seen has resulted in the term “radiation caries” to highlight the unique presentation in this cohort of patients (Aguiar et al., 2009).

The pre-treatment dental appointment primarily serves to examine the patient’s dentition and assess for and manage dental disease before cancer therapy. Teeth of questionable prognosis are removed to reduce the risk of dental infections during chemotherapy and to reduce the risk of extractions following radiotherapy with the associated risk of osteoradionecrosis (Joshi, 2010). However, it should be noted that there is a lack of high quality evidence to support this practice. A Cochrane systematic review found that “There are no randomised controlled trials to assess the effect of extracting teeth prior to radiotherapy compared to leaving teeth in the mouth during radiotherapy to the jaws” (Eliyas et al., 2013). Further research is required to validate this treatment.

The pre-treatment dental appointment not only aims to reduce the risk of complications but it serves other purposes too. It is recommended that patients are counselled on the expected changes to their mouths and the future treatment required. This visit also serves as an opportunity to provide targeted dental prevention advice and treatment to attempt to prevent future dental disease based on expert opinion (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

1.4.3 Post-cancer oral and dental rehabilitation

Following oral cancer treatment, patients often have complex needs for rehabilitation as a result of altered oral anatomy, increased risk of future disease and complications, and trismus (reduced mouth opening). It is for these reasons that this cohort of patients are considered a priority for specialist Restorative Dentistry rehabilitation. Guidelines state that oral cancer patients have access to a Consultant in Restorative Dentistry as part of their

rehabilitation (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

As a result, it is important that oral cancer patients receive a pre- and post-operative dental assessment and be given a preventive / rehabilitation treatment plan which may require specialist care or be delivered within primary dental care.

1.4.4 Frequency of oral health assessment as part of oral cancer care

The National Head and Neck Cancer Audit in England found that 32.6% of head and neck cancer patients in 2013 received a pre-operative dental assessment. This was an improvement on 2012 which reported 27.8%, but is still significantly short of recommended guidelines that state that all head and neck cancer patients should receive a pre-treatment oral health assessment (NHS Information Centre, 2013, British Association of Head and Neck Oncologists, 2009).

There do not appear to be published studies citing the frequency of post-treatment dental assessments as part of the care of oral cancer patients or head and neck cancer patients who may have adverse oral health symptoms associated with radiotherapy or chemotherapy as a result of poor oral health.

1.5 Gaps in the literature and rationale for research

1.5.1 Oral health and dental care as risk factors for oral cancer

As outlined in previous sections, there are a large number of studies, often with conflicting results, examining oral health and dental care factors related to oral cancer risk. The risk associated with these factors is poorly understood and is often not reported in guidelines (Scottish Intercollegiate Guidelines Network, 2006). Since conducting our systematic review and in the process of writing this thesis, there have been two systematic reviews published specifically related to oral health factors as risk factors for head and neck cancer which looked at periodontal disease and missing teeth (Zeng et al., 2013b, Zeng et al., 2013a). These reviews focused on specific oral health factors for all head and neck cancer patients and did not take a broad view of oral health and dental care

factors as related to oral cancer risk. They will be reviewed and compared in the discussion.

Another systematic review attempted to review all risk factors for oral cancer, including oral health and dental care factors and qualitatively presented their results (Radoi and Luce, 2013). There is no systematic review that we are aware of the attempts to quantitatively examine the range of oral health and dental care factors as risk factors for oral cancer.

A full literature review of the oral and dental care factors related to oral cancer risk would be best achieved with a systematic review and meta-analyses due to the large body of often conflicting evidence. The definition of the problem is as follows: it is currently not known if oral health and dental care factors are risk factors for oral cancer or the strength of the association. To date, there has been no systematic review that has attempted to quantitatively examine the range of oral health and dental care factors as risk factors for oral cancer. As such, this thesis presents the findings of a systematic review of oral health and dental care factors related to oral cancer risk.

The use of alcohol containing mouthwashes as a risk factor for oral cancer has been investigated and is a source of controversy (Warnakulasuriya, 2009). A systematic review and meta-analysis was conducted and found no statistically significant association between the use of mouthwash and oral cancer risk (Gandini et al., 2012). As the use of mouthwash has been recently systematically reviewed as a risk factor for oral cancer, it will not be considered further in this thesis.

1.5.2 The role of dental assessment and care in the management of patients with oral cancer

The National Cancer Audit in England has been collecting data related to pre-operative dental assessments for head and neck cancer patients for a number of years (NHS Information Centre, 2013). However, there does appear to be a lack of published data specifically looking at dental assessments for patients within Scotland. There also does not appear to be data reported for improvements seen over the last decade with the introduction of a number of guidelines, standards

and targets and a shift in the treatment philosophies for oral cancer patients including the Scotland specific guidelines (Scottish Intercollegiate Guidelines Network, 2006). However, the National Cancer Quality Operational Group are now collecting data regarding pre-dental assessments in Scotland to assess compliance with Quality Performance Indicators. Generally, there seems to be little data available on the frequency of post-treatment dental care and rehabilitation. Those data would add to the literature and allow for some interpretation of the impact of guidelines and could be used to influence policy with regards to the future of oral cancer services within Scotland.

2 Aims and objectives

1. To undertake a systematic review and meta-analysis of the world-wide literature regarding oral health and dental care factors associated with oral cancer risk

a) To systematically search the literature regarding oral health and dental care related risk factors for the development of oral cancer

b) To evaluate the methodological quality of the current body of evidence relating to oral health and dental care related risk factors for the development of head and neck cancer

c) To perform a meta-analysis to attempt to quantify the risk of oral health and dental care related risk factors for the development of head and neck cancer

2. To examine the level and degree of clinical dental care for patients diagnosed with and treated for head and neck / oral cancer

a) To examine the level and degree of clinical dental care for head and neck / oral cancer patients in the Glasgow area prior to and following their head and neck cancer treatment from 2002-2004 and more recently 2013-2014

b) To assess if there has been any improvement in dental care provision between 2002-2004 and 2013-2014.

3 Systematic Review Chapter

3.1 Introduction

There is a large body of often conflicting evidence available regarding the oral health / dental care factors as risk factors for oral cancer. In order to collate, summarise and quantify the risk, a systematic review and meta-analysis is warranted (Ahrens et al., 2014).

Problem definition: It is currently not known if oral health and dental care factors are risk factors for oral cancer or the strength of the association. To date, there has been no systematic review that has attempted to quantitatively examine the range of oral health and dental care factors as risk factors for oral cancer. Hypothesis statement: Oral health and dental care factors are risk factors for oral cancer. Study population: general adult population worldwide.

3.1.1 Aim

The aim of this study is to conduct a systematic review of the literature relating to oral health and dental care related risk factors for oral cancer and, where possible, perform meta-analyses of the data in order to quantify the risk of each factor and where possible to take into account the behavioural confounding factors in the analysis and conduct sensitivity analysis related to the quality of the studies. This will be reported in accordance with MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000).

3.1.2 Definition

A systematic review is a process whereby an attempt is made to identify, appraise and synthesise the literature relating to a given topic to answer a research question. This is conducted in a predetermined, systematic way in an effort to minimise bias. A meta-analysis combines the results of the included studies to produce an overall statistical estimate (Petticrew and Roberts, 2006).

3.2 Methods

As there are no definitive guidelines on systematic reviews of observational studies, the systematic review methodology was established through examination of guidelines and other systematic reviews in the field (Stroup et al., 2000, Petticrew et al., 1999, Radoi and Luce, 2013, Conway et al., 2008). The following potential risk factors for oral cancer were identified for further investigation: oral hygiene, toothbrushing frequency, bleeding gums, periodontal disease, dental caries, dental attendance, sharp teeth, denture use, and dental materials. A search strategy was designed to attempt to identify relevant case control studies examining these oral health factors as risk factors for oral cancer. A protocol for the systematic review and meta-analyses was developed and presented as part of the 1st year annual monitoring for research degrees at the University of Glasgow.

There were no additional sources of funding for conducting this systematic review and meta-analyses

3.2.1 Search strategy

A search strategy was devised with guidance from a Team Librarian at University of Glasgow. In July 2012 the following databases were searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, Embase Classic+Embase 1947 to 2012 June 29, and Web of Science. Key words and search terms were identified in order to identify relevant papers. The validity of the search was checked with 13 “sentinel” papers identified as articles that this search would be expected to find and the search was modified until all papers were included. Contact with authors were attempted particularly where it was suspected that data were available but was not presented in their papers or presented in such a way that it did not fulfil the inclusion criteria. Experts in the field were contacted to identify unpublished work. No language restriction was imposed. Titles, abstracts and full articles were entered into Google Translate software and inclusion / exclusion criteria applied as for English papers. A native Polish speaker was identified at the University of Glasgow to translate, data extract and carry out methodological assessment for a Polish study that had fulfilled the requirements for inclusion.

Bibliographies of relevant papers were hand-searched. Details of the search used for Ovid Medline and Embase can be found in Appendix A and for Web of Science Appendix B.

3.2.2 Inclusion criteria

All included studies were independently reviewed against set criteria by two reviewers (ADP and DIC). The review process was carried out based on the following inclusion criteria: (i) Study of oral and / or oropharyngeal cancer; (ii) The study included at least one oral health factor in relation to patients with head and neck cancer; (iii) the study used case-control or cohort methodology; (iv) the study presented the odds ratio of the oral health or dental care risk factor or the odds ratio could be calculated from the data provided. Studies were screened by title and abstract and then full articles were obtained for the final screening. At each stage, articles were included for screening at the next stage where they could not be clearly excluded. Disagreements between the reviewers were resolved through discussion.

3.2.3 Methodological assessment of included studies

Pre-assessment meetings were held to agree and standardise the quality appraisal and data abstraction processes. Three reviewers (ADP reviewed all papers, DIC and LJC acted as second reviewers examining half each) independently assessed the individual methodological characteristics of the selected studies according to set criteria (Sutton et al., 1998, Petticrew et al., 1999) based on the main sources of bias in case-control studies Table 3.2-1. One study (Szczesiul, 1995) was published in Polish and methodological assessment was carried out by Dr Marta Czesnikiewicz-Guzik (Clinical Senior Lecturer in Periodontology, University of Glasgow) in conjunction and with guidance from ADP. Assessment discrepancies between the reviewers were resolved through discussion.

Table 3.2-1 Methodological assessment of included studies

	Methodological aspect												
Study ID	A	B	C	D	E	F	G	H	I	J	K	L	Totals
(Ahrens et al., 2014)	1	1	0	0	1	1	1	1	0	1	1	1	9
(Balaram et al., 2002)	0	1	0	0	1	1	1	1	0	0	1	1	7
(Browne et al., 1977)	1	0	0	1	0	0	1	0	0	0	0	0	3
(Bundgaard et al., 1995)	1	1	1	1	1	1	1	1	1	0	1	1	11
(Divaris et al., 2010)	1	1	1	0	1	1	1	1	0	1	1	1	10
(Guha et al., 2007)	0	1	1	1	0	1	1	1	0	1	1	1	9
(Marshall et al., 1992)	1	0	1	0	0	1	1	0	0	0	1	1	6
(Moreno-Lopez et al., 2000)	1	1	1	1	0	1	1	1	1	1	1	1	11
(Rosenquist, 2005)	1	0	1	1	1	1	0	0	1	0	1	0	7
(Schildt et al., 1998)	1	0	0	0	1	1	1	1	1	1	0	1	8
(Subapriya et al., 2007)	0	0	0	0	0	1	0	0	0	0	0	0	1
(Szczesiul, 1995)	0	1	1	1	0	1	1	1	1	0	1	1	9
(Talamini et al., 2000)	0	1	0	0	0	1	1	1	1	1	1	1	8
(Vaccarezza et al., 2010)	1	1	0	0	0	1	1	0	0	1	1	1	7
(Velly et al., 1998)	1	1	1	0	1	1	1	1	0	1	1	1	10
(Winn et al., 1991)	1	1	1	1	1	1	1	1	1	0	1	1	11
(Wynder et al., 1957)	0	0	0	0	1	1	0	0	0	0	0	1	3
(Zheng et al., 1990)	1	1	1	0	1	1	0	1	1	1	1	1	10

A: Explicit case definition (defined by ICD codes or descriptors). B: Limited to newly diagnosed ('incident") cases only. C: Histologically confirmed cases. D: Utilised population–rather than hospital–based controls. E: sample size ≥300. F: Evidence of identical data collection methods in both cases and controls. G: Description of 'base-line characteristics of both cases and controls. H: Adjustments for potential confounders by matching or adjusting. I: Defined response rate, and >70% in both cases and controls. J: Standardised method of assessing oral health factor. K: Appropriate statistical analyses of oral health factor data. L: Robust method of assessing lifestyle history **1: Present, 0: Absent.**

3.2.4 Data extraction

Two of the three reviewers (ADP all papers, DIC and LJC secondary reviewers) independently extracted data from the included papers. Any discrepancies were resolved by discussion. One study (Szczesiul, 1995) was published in Polish and the data were extracted by Dr Marta Czesnikiewicz-Guzik (Clinical Senior Lecturer in Periodontology, University of Glasgow) in conjunction and with guidance from ADP. For all studies, the study centre was recorded, as well as the continent for those participating. Where possible the time period that the

study was conducted over was noted. The study participants' age range or mean was recorded. The sex of the participants in the study was extracted and where this included both males and females, whether the data had been presented with the data combined or separate was noted. The site of the oral cancer was recorded. Where possible, data were recorded for oral cavity cancer. However, where the data were combined with oral pharyngeal / pharyngeal cancer, this was accepted. If the data were purely pharyngeal cancer or the data were combined with cancer of other sites, then the study was excluded. The source of the control subjects was extracted i.e. population or hospital controls. Studies that included controls from other types of cancer were excluded (n = 5) due to the risk of overmatching controls with common risk factors (Wacholder et al., 1992). Where adjusted odds ratios were presented, the factors that were taken into account for the purposes of adjustment, minimum smoking and alcohol, were also recorded. In order to carry out meta-analyses of the data, the number of cases and controls, odds ratios (adjusted and unadjusted) and 95% confidence intervals were extracted for each oral health / dental care factor examined. Where the odds ratios were not presented, an attempt was made to calculate the unadjusted odds ratios from the data provided. Where different measures were made to assess an oral health / dental care factor e.g. toothbrushing frequency, the odds ratios comparing the best with the worst variable strata as defined by the authors was used or calculated.

3.2.5 Meta-analysis

All meta-analyses were carried out using Comprehensive Meta-analysis version 2. The main output data for this systematic review and meta-analyses were odds ratios adjusted for a minimum of smoking and alcohol as this was considered the most robust data of estimates of risk association available. However, meta-analyses were also carried out on combined adjusted and unadjusted data and analysed to see if this differed from the adjusted data. In order to assess the sensitivity of the findings, meta-analyses were carried out on the following key quality criteria: only including studies where the methodological quality assessment was higher than the median quality score i.e. 8.5, where oral cavity only data were provided, and where the sample size was greater than 300 (Chuang et al., 2011). Analysis with "one study removed" were carried out on

the adjusted meta-analyses to assess if the outcome was significantly affected by any one study.

Heterogeneity of the studies were examined and recorded using the Inconsistency Index (I^2). Where the data were significantly ($p<0.05$) heterogeneous, a random effects model was used for the meta-analysis. Where the data were not significantly heterogeneous, a fixed-effects model was used. The data were plotted on forrest plots and a summary odds ratio with 95% confidence intervals calculated.

3.2.6 Publication bias

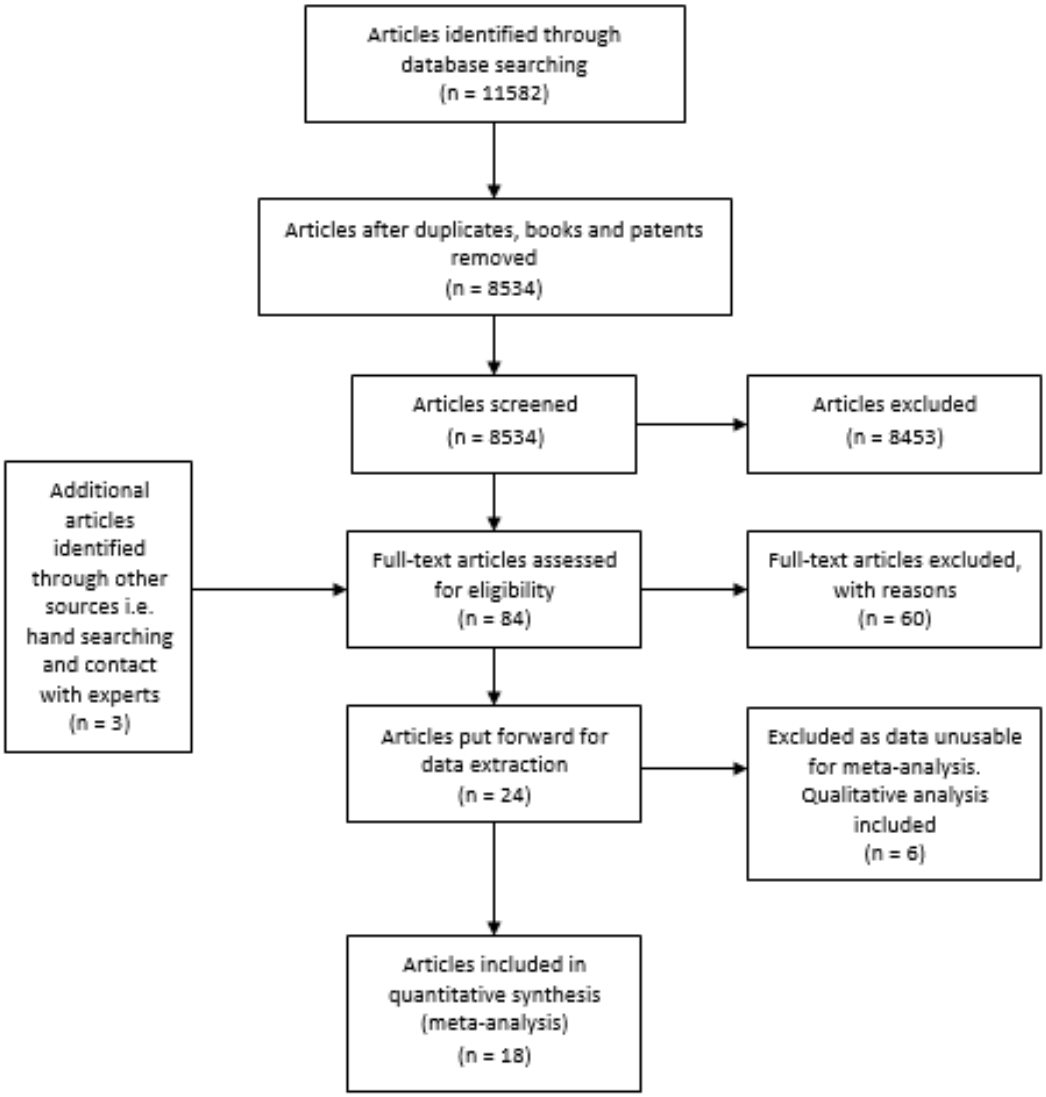
Funnel plots were generated for each meta-analysis of adjusted data and were examined for evidence of potential publication bias.

3.3 Results

3.3.1 Search Strategy

The search strategy retrieved 11582 articles. Nine books and 145 patents were removed. A total of 2894 duplicates were removed at this stage leaving 8534 articles for screening. There were 8453 articles removed following screening resulting in 81 articles that were selected for full text review. A further 2 articles were identified by hand searching and another unpublished study was identified by contact with experts. The unpublished study has subsequently been published and so is cited in this thesis by the published article (Ahrens et al., 2014). This resulted in an additional 3 studies for inclusion, and so 84 articles were screened by full article. A total of 60 articles were removed at this stage that did not meet the inclusion criteria or that included data from the same study as another article. A further 6 articles met the inclusion criteria, but the data could not be used for the purposes of the meta-analysis and were excluded from the meta-analyses. However, a qualitative analysis was included in the review to assess whether findings of the excluded studies were comparable or contradictory to the meta-anaylses. There were 18 studies included in the meta-analysis. A flow chart of the search strategy can be found in Figure 3.3-1.

Figure 3.3-1 Flowchart for the selection of articles included in the meta-analysis



3.3.1.1 Reasons for exclusion of studies selected for full article screening

There were 66 studies excluded from the meta-analysis based on the full article screening against the selection criteria. Reasons for exclusion are listed in Appendix C.

3.3.2 Study Characteristics

Eighteen case control studies were included in the meta-analysis. The characteristics of the studies are included in Table 3.3-1.

Table 3.3-1 Characteristics of included studies

Study ID	Study Years	Study base	Continent	Oral Health factor examined	Sex	Age (mean or range)	Cancer definition	Study design	Total number of cases	Total number of controls	Adjusted
(Ahrens et al., 2014)	2002-2005	13 centres, Prague, Bremen, Athens, Aviano, Padova, Turni, Dublin, Oslo, Glasgow, Manchester, Newcastle, Barcelona, Zagreb	E	Oral health, dental care behaviors, denture wear, age of first wearing a denture, bleeding gums, tooth cleaning frequency, use of a tooth brush, use of floss, use of toothpaste, dental attendence	M + F	59.8 overall for cases and controls	OC +OP	Hospital	934 (Mouth/ Oropharynx)	1993	S, A, C, T, Al, SES, E, D
(Balaram et al., 2002)	1996-1999	Bangalore, Mardras and Trivandrum; Southern India	As	tooth cleaning + instrument used, denture wear, dental check ups, gum bleeding, missing teeth, general oral condition	M & F	Males: Mean 56, Range 22-85. Females: Mean 58, Range 18-87	OC	Hospital	591	582	A, C, E, Ch; and for men only: T, Al
(Browne et al., 1977)	1957-71	Stoke on Trent, England	E	own teeth, denture wear, number of sets of dentures, denture cleaning, toothbrushing, denture cleaning habits, night wear	M & F	Males: Range 41-90, mean 70. Females: Range 28-81, mean 64.	OC	Community	75	150	0
(Bundgaard et al., 1995)	1986-90	Denmark	E	number of teeth, dental check-ups	M + F	≤45 - >75	OC	Community	161	400	A, S, Al, T
(Divaris et al., 2010)	2002-2006	N Carolina, USA	NA	tooth loss, tooth mobility, frequency of dental visits	M + F	20-80	OC	Community	692	1,361	A, S, R, E, T, Al, D, OH
(Guha et al., 2007)	1998-2003	Europe, Latin America	E + SA	oral hygiene, missing teeth, toothbrushing, denture wear, instrument used to clean teeth, material used with toothbrush, gum bleeding, dental checkups	M + F	under 39 yrs to over 70	OC	population-based and Hospital	274 central Europe, 414 Latin America	928 Central Europe, 1805 Latin America	A, S, Co, Ed, T, Al, OH

Table 3.3-1 continued

Study ID	Study Years	Study base	Continent	Oral Health factor examined	Sex	Age (mean or range)	Cancer definition	Study design	Total number of cases	Total number of controls	Adjusted
(Marshall et al., 1992)	1975-1983	New York, USA	NA	Dentures (years), Sets of dentures, Teeth lost but not replaced	M + F	<50 to 76+	OC + OP + P	population	290	290	T, Al
(Moreno-Lopez et al., 2000)	pre-2000	Madrid, Spain	E	dentist attendance, brushing frequency	M + F	<40 - >80	OC + OP	hospital	75	150	0
(Rosenquist, 2005)	2000-2004	Sweden	E	oral hygiene, dental check-up, missing teeth, marginal bone loss	M + F	33-87	OC + OP	population	132	320	T, Al
(Schildt et al., 1998)	1980-1989	Sweden	E	denture, fixed prosthesis, dental amalgam, gold restoration, plastic restoration, ever dental care, dental x-rays, caries, tooth loss, dental calculus, oral infections	M + F	m70, f72	OC + OP	population	354	354	0
(Subapriya et al., 2007)	1991-2003	Chidambaram, Tamil Nadu, India	As	Oral hygiene	M + F	30-75	OC	Friends and relatives of non-cancer patients	388	388	A, S, T, Al, Re, D, E, Oc
(Szczesiul, 1995)	1985	Bialystok, Poland	E	Toothbrushing	M + F	patients - mean age 54, controls mean age 52	OC +OP	hospital	102	49	0
(Talamini et al., 2000)	1996-1999	Friuli-Venezia Giulia, Italy	E	Toothbrushing, gum bleeding, years with dentures, dental check-ups, missing teeth, general oral condition	M + F	27-86	OC +OP	Hospital	132	148	A, S, D, T, Al

Table 3.3-1 continued

Study ID	Study Years	Study base	Continent	Oral Health factor examined	Sex	Age (mean or range)	Cancer definition	Study design	Total number of cases	Total number of controls	Adjusted
(Vaccarezza et al., 2010)	2006-2007	Sao Paulo, Brazil	SA	Use of a denture, Recurrent sores by ill fitting dentures	M + F	14% <50, 37% 50-59, 30% 60-69, 19%> 70	OC	Hospital	124 (all smokers)	124 (all smokers)	SES, In, E, T, Al, D
(Velly et al., 1998)	1987-1989	Sao Paulo, Curitiba, Goiania, Brazil	SA	Use of denture, Denture associated sores, Broken teeth, Toothbrushing	M + F	Categories <55, 55-64, 65-74, 75+	OC	Hospital	717	1434	T, Al, D, Te, R, In, E
(Winn et al., 1991)	1984-1985	Los Angeles county, Santa Clara and San Mateo counties, USA	NA	Dentures, Periodontal disease, Bleeding gums, sores in mouth,	M & F	Ranges <50, 50-59, 60-69, 70+	OC +OP	Community	966	1249	A, R, E, T, Al, D
(Wynder et al., 1957)	Unknown	New York, USA	NA	Dental irritation,	M & F	Groups 30-39, 40-49, 50-59, 60-69, >69	OC +OP	Hospital	659, Males 543, Females 116	439, Males 207, Females 246	A, R
(Zheng et al., 1990)	1989-1990	Beijing, China	As	Denture use, dental condition, loss of teeth, toothbrushing, Inadequate dentition	M & F	18-80	OC	Hospital	404	404	T, Al, E, S, A

E, Europe; As, Asian; NA, North America; SA, South America; M+F sex data combined; M+F sex data presented separately; OC, Oral cavity; OC+OP Oral cavity and Oral pharynx; OC+OP+P, Oral cavity and Oral Pharynx and Pharynx; 0, unadjusted; A, Age; S, Sex; T, Tobacco use; Al, alcohol consumption; SES, Socioeconomic status; E, Education; D, Diet; C, Centre; Ch, Chewing habit; OH, Oral health factor; R, Race; Co, Country; Re, Religion; Oc, Occupation; Te, Temperature of drinks; In, Income

3.3.3 Methodological characteristics

A summary of the methodological assessment of the included studies is included in Table 3.2-1. The overall score given to the included studies for the

methodology varied greatly between 1 and 11 out of a possible 12. No study scored a perfect 12 but three studies achieved a score of 11. There was no one characteristic that was seen in all studies. The closest, identical data collection in cases and controls, was seen in all but one study. A defined response rate which was >70% was seen in 8 out of 18 of the studies. Adjustment for confounding factors was seen in 12 out of 18 of the studies.

3.3.4 General oral health and risk associated with oral cancer

Three studies (Ahrens et al., 2014, Balaram et al., 2002, Talamini et al., 2000) examined the effect of general oral health on the risk of oral cancer. There was significant heterogeneity between the studies I^2= 67.407 and p-value=0.027. The overall estimate for general oral health associated with increased risk of oral cancer comparing the best oral health score with the worst was OR 3.91 (95% CI 2.29, 6.67) (Figure 2.3 2) using a random effects model.

No separate analysis was required for inclusion of studies with unadjusted data because no studies were identified with unadjusted data. Two studies (Ahrens et al., 2014, Balaram et al., 2002) had large sample sizes greater than 300 subjects and the effect remained significant OR 3.81 (95% CI 1.95, 7.42) when analysis was restricted to those studies. Only one study (Ahrens et al., 2014) was considered to be of higher methodological quality (greater than the median): OR 2.00 (95% CI 1.21, 3.31) so some degree of caution is required when interpreting the findings of the main meta-analysis. No one study was found to significantly change the outcome during analysis. Only one study (Balaram et al., 2002) looked at cancer of the oral cavity only: OR 5.21 (95% CI 3.55, 7.65) (Table 3.3-2)

In addition to general oral health, one study (Shanta and Krishnamurthi, 1964), not included in the meta-analysis, reported on the presence of “dental sepsis” as a risk factor for oral cancer. For females, the unadjusted estimate was OR 1.33 (95% CI 0.57, 3.1). For males, the unadjusted estimate was OR 5.43 (95% CI 2.98, 9.87). Another study (Fahmy et al., 1983) found that dental caries was not a significant risk factor.

Not included in the meta analysis was one study (Graham et al., 1977) that reported the risk associated with an inadequate dentition. Where the anterior and posterior dentition was deemed inadequate, a risk of 4.62 ($p<0.0001$) was found. Where a mix of adequate and inadequate dentition was observed, a risk of 2.26 ($p<0.0001$) was reported.

Figure 3.3-2 Meta-analysis of odds ratio estimates of worst score vs. best score for oral health associated with risk of oral cancer

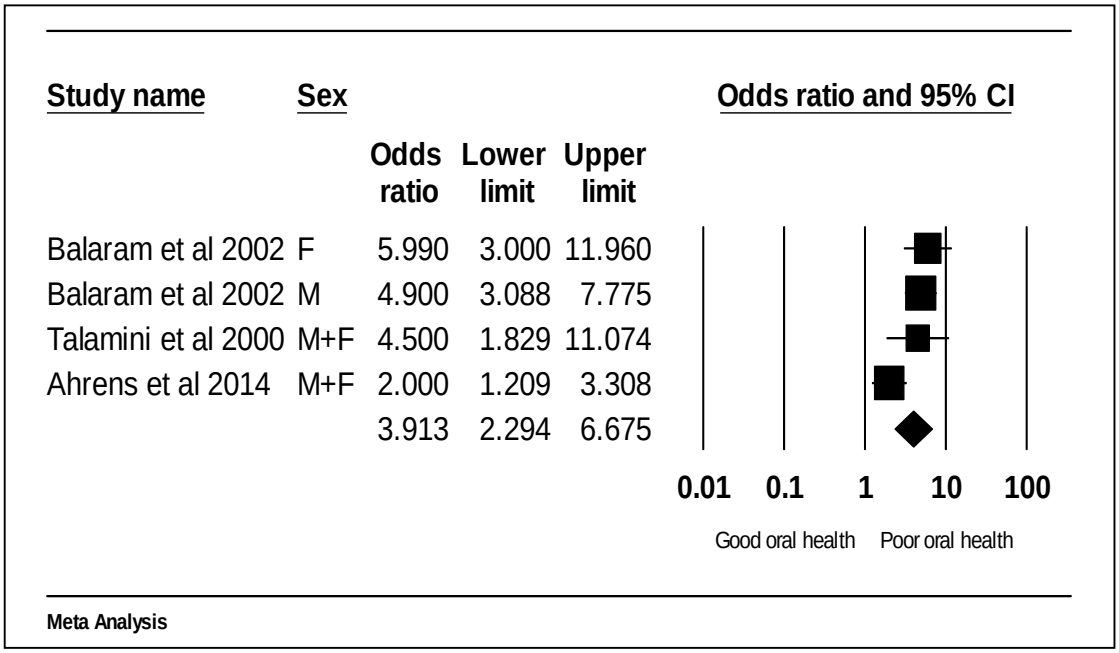


Table 3.3-2 Summary of meta-analysis and sensitivity analysis for oral health factors

Oral health factor	Adjusted only	Unadjusted included	Only sample size greater than 300	Only including studies with quality greater than median	One study removed	Only oral cancer
General oral health	3.91 (95% CI 2.29, 6.67) 3 Studies	n/a	3.81 (95% CI 1.95, 7.42) 2 Studies	2.00 (95% CI 1.21, 3.31) 1 Study	No significant difference	5.21 (95% CI 3.55, 7.65) 1 study
Gum bleeding	1.76 (95% CI 1.20, 2.58) 6 studies	1.59 (95% CI 1.12, 2.26) 6 studies	1.83 (95% CI 1.16, 2.89) 4 studies	1.28 (95% CI 0.96, 1.71) 3 studies	No significant difference	2.06 (95% CI 1.16, 3.66) 3 studies
Oral Hygiene	3.56 (95% CI 2.52, 5.04) Fixed model used 2 studies	7.01 (95% CI 1.82, 26.98) 3 studies	3.2 (95% CI 2.16, 4.73) 1 study Fixed model	3.56 (95% CI 2.52, 5.04) Fixed model 2 studies	No significant difference	3.2 (95% CI 2.16, 4.73) 1 study Fixed model
Missing teeth (6 or more)	2.3 (95% CI 1.27, 4.18) 6 studies	2.12 (95% CI 1.23, 3.63) 7 studies	2.66 (95% CI 1.26, 5.63) 4 studies	1.84 (95% CI 0.99, 3.42) 4 studies	No significant difference seen	2.52 (95% CI 1.32, 4.82) 5 studies
Never attends dentist	1.45 (95% CI 1.12, 1.87) Fixed model used 3 studies	1.49 (95% CI 1.21, 1.85) Fixed model used 5 studies	1.49 (95% CI 1.14, 1.96) Fixed model 2 studies	1.49 (95% CI 1.14, 1.96) Fixed model 2 studies	Loses significance if Ahrens 2014 study removed	1.12 (95% CI 0.68, 1.85) 1 study
Presence of a denture	1.08 (95% CI 0.80, 1.46) 5 studies	1.04 (95% CI 0.87, 1.25) 10 studies	1.06 (95% CI 0.77, 1.46) 4 studies	1.14 (95% CI 0.83, 1.58) 3 studies	No significant difference seen	0.95 (95% CI 0.76, 1.18) 4 studies
Frequency of toothbrushing	1.75 (95% CI 1.21, 2.53) 6 studies	2.41 (95% CI 1.63, 3.57) 9 studies	1.81 (95% CI 1.20, 2.73) 5 studies	1.85 (95% CI 1.18, 2.9) 4 studies	No significant difference seen	1.99 (95% CI 1.23, 3.23) 4 studies

3.3.5 Gum bleeding and periodontal disease and risk associated with oral cancer

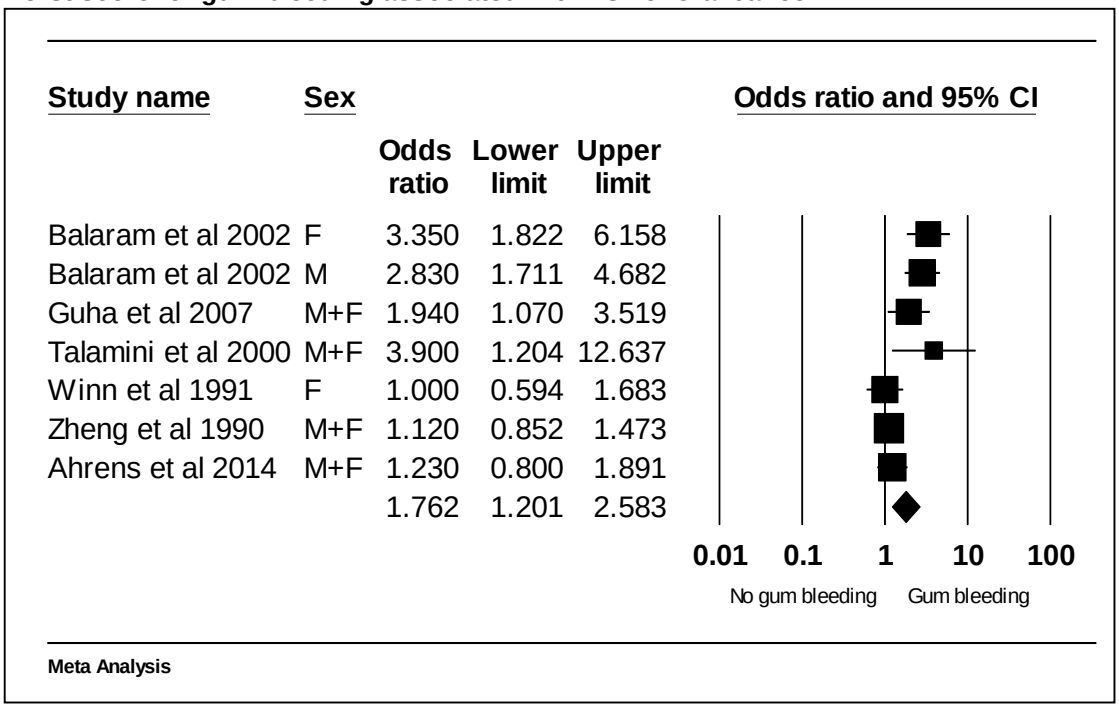
Six studies (Ahrens et al., 2014, Balaram et al., 2002, Guha et al., 2007, Talamini et al., 2000, Winn et al., 1991, Zheng et al., 1990) examined the effect of gum bleeding on the risk of oral cancer. One study (Winn et al., 1991) reported data for males only that was not compatible with the meta-analysis software and could not be included in the adjusted only data analysis. There was

significant heterogeneity between the studies I^2= 74.529 and p-value=0.001. The overall estimate for gum bleeding associated with increased risk of oral cancer comparing the absence of gum bleeding with the worst score was 1.76 (95% CI 1.20, 2.58) (Figure 3.3-3) using a random effects model.

When the unadjusted data in the analysis for one study (Winn et al., 1991) was included, the effect remained significant 1.59 (95% CI 1.12, 2.26). Four studies (Balaram et al., 2002, Ahrens et al., 2014, Winn et al., 1991, Zheng et al., 1990) had sample sizes greater than 300 and the effect remained significant 1.83 (95% CI 1.16, 2.89) when analysis was restricted to those studies. Four studies (Ahrens et al., 2014, Guha et al., 2007, Winn et al., 1991, Zheng et al., 1990) were considered to be of higher methodological quality (greater than the median) and when the analysis was restricted to those studies the estimate was found to be OR 1.12 (95% CI 0.98, 1.46) using a fixed model as the heterogeneity was no longer significant (I^2= 7.011 and the p-value= 0.358) when only these studies were included. No one study was found to significantly change the outcome during analysis. Three studies (Balaram et al., 2002, Guha et al., 2007, Zheng et al., 1990) looked at cancer of the oral cavity only and the estimated effect based on these three studies was 2.06 (95% CI 1.16, 3.66) (Table 3.3-2)

One case control study (Tezal et al., 2009), not included in a meta-analysis, reported the odds ratio associated with alveolar bone loss. For oral cavity cancer the odds ratio per millimetre lost was 4.52 (95% CI 3.03, 6.75). For oral pharyngeal cancer the odds ratio per millimetre was 3.64 (95% CI 2.54, 5.22). A cohort study (Michaud et al., 2008) not included in a meta-analysis reported on periodontal disease as a risk factor for oral cancer and found an OR 1.15 (95% CI 0.73, 1.81). Another study (Fahmy et al., 1983) found that periodontal disease was not a significant risk factor.

Figure 3.3-3 Meta-analysis of odds ratio estimates of adjusted data for no gum bleeding vs. worst score for gum bleeding associated with risk of oral cancer



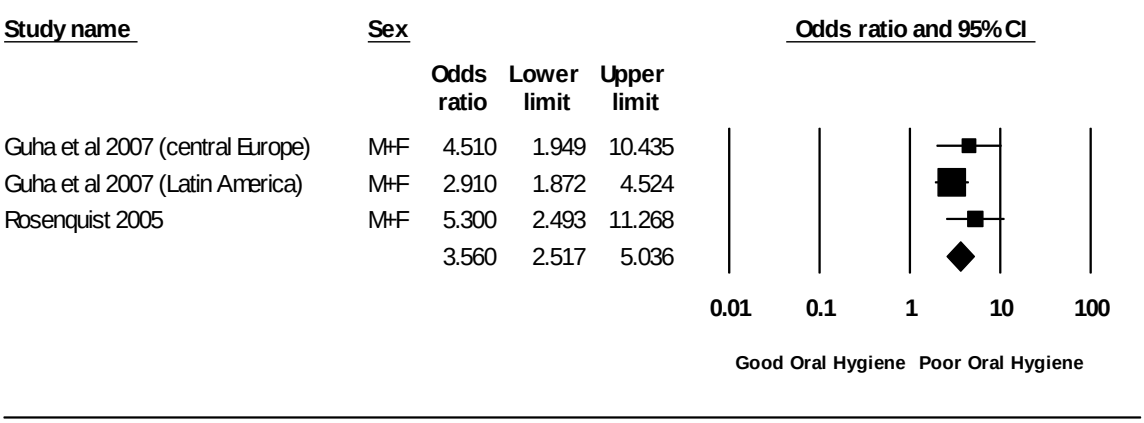
3.3.6 Oral hygiene and risk associated with oral cancer

Two studies (Guha et al., 2007, Rosenquist, 2005) were included in the final adjusted only meta-analysis which examined the effect of oral hygiene on the risk of oral cancer. The heterogeneity between the studies was not significant I^2 = 8.11 and P-value= 0.337. The overall estimate for poor oral hygiene associated with increased risk of oral cancer was 3.56 (95% CI 2.52, 5.04) using a fixed effects model (Figure 3.3-4).

One additional study (Subapriya et al., 2007) was added for the analysis including studies with unadjusted data. The effect remained significant 7.01 (95% CI 1.82, 26.98). Only one of the studies (Guha et al., 2007) had a sample size greater than 300 and the effect was significant when the two arms of the study were combined 3.2 (95% CI 2.16, 4.73). This was also the only study with adjusted data that specifically looked at oral cavity. Both studies with adjusted data were considered to be of higher methodological quality (greater than the median) and so no separate analysis was required. No one study was found to significantly change the outcome during analysis (Table 3.3-2).

One study (Marshall et al., 1992) presented their data looking at the protective effect of good oral hygiene rather than the increased risk of poor oral hygiene and so could not be included in the meta-analysis. They found that better oral hygiene did not confer a statistically significant reduction in oral cancer risk. Reported odds ratio of best oral hygiene score 0.70 (95% CI 0.30, 2.10). Another study (Fahmy et al., 1983) found that poor oral hygiene was not a significant risk factor.

Figure 3.3-4 Meta-analysis of odds ratio estimates of adjusted data for best vs. worst score for oral hygiene associated with risk of oral cancer



3.3.7 Missing teeth and risk associated with oral cancer

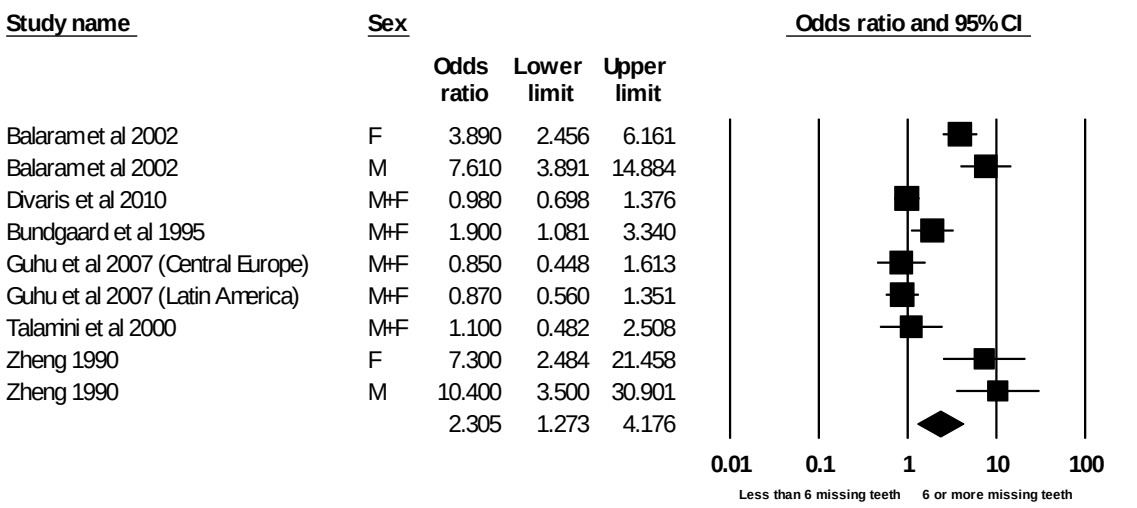
Six studies (Balaram et al., 2002, Bundgaard et al., 1995, Divaris et al., 2010, Guha et al., 2007, Talamini et al., 2000, Zheng et al., 1990) were included that contained adjusted data that examined the effect of missing teeth on the risk of oral cancer. The best scores were compared to those with 6 or more missing teeth. There was significant heterogeneity between the studies I^2 = 89.191 and P-value <0.001. The overall estimate for 6 or more missing teeth associated with increased risk of oral cancer was OR 2.3 (95% CI 1.27, 4.18), using a random effects model (Figure 3.3-5).

One additional study was added for the analysis including studies with unadjusted data (Rosenquist, 2005). The effect remained significant OR 2.12

(95% CI 1.23, 3.63). Four studies (Balaram et al., 2002, Divaris et al., 2010, Guha et al., 2007, Zheng et al., 1990) had a sample size greater than 300 and the effect was significant when only these studies were included 2.66 (95% CI 1.26, 5.63). Four studies were considered to be of higher methodological quality i.e. greater than the median, and the statistical significance was lost when the analysis was restricted to these studies OR 1.84 (95% CI 0.98, 3.69). Five studies (Balaram et al., 2002, Bundgaard et al., 1995, Divaris et al., 2010, Guha et al., 2007, Zheng et al., 1990) presented data restricted to the oral cavity and the effect remained significant when the analysis was restricted to these studies OR 2.52 (95% CI 1.32, 4.82). No one study was seen to significantly change the outcome during analysis (Table 3.3-2).

There were studies that met the inclusion criteria, but were not included in the meta-analysis due to how the data relating to missing teeth were presented. One study (Guneri et al., 2005) reported that control subjects had more natural teeth (controls mean: 19.3, cases mean: 12.04; p = 0.000). However, another study (Tezal et al., 2009) found that missing teeth were not associated with a statistically significant increased risk of cancer of the oral cavity OR per tooth= 1.03 (95% CI 0.99, 1.06) and cancer of the oropharynx OR per tooth= 1.4 (95% CI 0.5, 3.87). One cohort study (Michaud et al., 2008) also found that missing teeth was not associated with a statistically significant increase in risk of developing oral cancer. They found 17-24 teeth present had an OR 1.18 (95% CI 0.69, 2.01) and 0-16 teeth present 1.60 (95% CI 0.84, 3.04). Another case controlled study (Browne et al., 1977) reported on the risk associated with having their own teeth or not. Males who did not have their own teeth had an OR 0.67 (95% CI 0.3, 1.49) and females OR 1 (95% CI 0.33, 3.01). Another case control study (Schildt et al., 1998) reported for the presence of tooth loss OR 0.9 (95% CI 0.6, 1.5).

Figure 3.3-5 Meta-analysis of odds ratio estimates of adjusted data for missing teeth



3.3.8 Dental attendance and risk associated with oral cancer

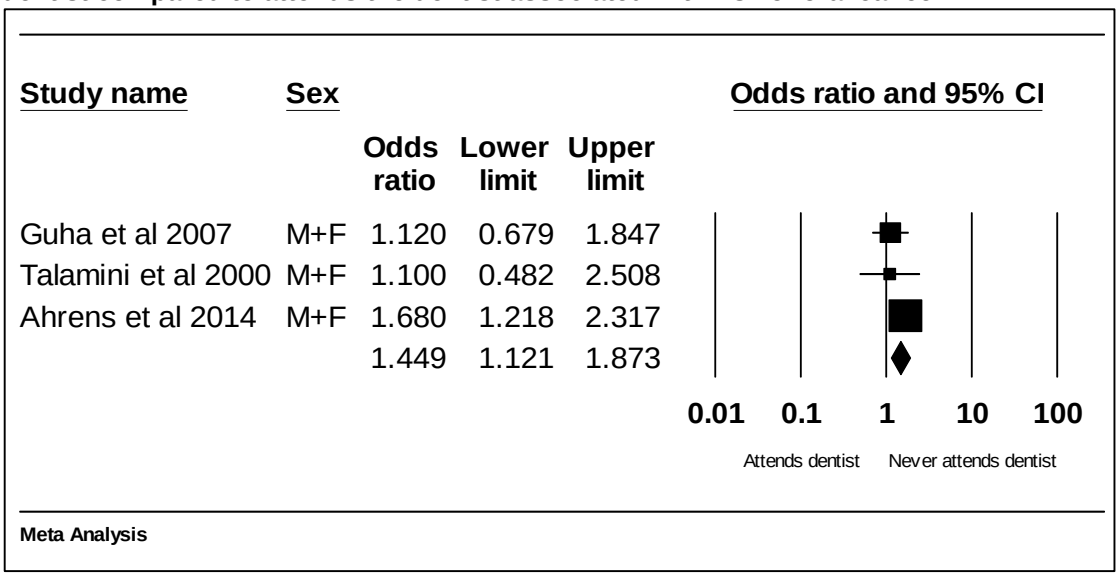
Three studies (Ahrens et al., 2014, Guha et al., 2007, Talamini et al., 2000) that reported adjusted data for the effect of non-attendance at the dentist or "never attends" on the risk of oral cancer were included. The heterogeneity between the studies was not significant I^2 = 11.53 and P-value= 0.323. The overall estimate for non-attendance at the dentist associated with increased risk of oral cancer was 1.45 (95% CI 1.12, 1.87) (Figure 3.3-6) using a fixed effects model.

Two additional studies presented data that could be used for inclusion of unadjusted data (Moreno-Lopez et al., 2000, Balaram et al., 2002). The Balaram et al 2002 study did present adjusted data for this factor, however the data analysis was carried out looking at the protective effect of regular dental attendance and so was not compatible for inclusion in the meta-analysis as all other studies examined the increased risk of non-attendance. When the unadjusted data were included in the analysis, the effect remained significant 1.70 (95% CI 1.19, 2.43) using a random effects model. Two studies (Ahrens et al., 2014, Guha et al., 2007) both had sample sizes greater than 300 subjects and were considered to be of higher methodological quality (greater than the median) and the effect remained significant 1.49 (95% CI 1.14, 1.96) using a fixed model when analysis was restricted to those studies. It was observed that

the significance was lost when Ahrens 2014 was removed from the analysis. Only one study (Guha et al., 2007) looked at cancer of the oral cavity only and reported a non-significant risk of OR 1.12 (95% CI 0.68, 1.85) (Table 3.3-2).

There were studies that met the inclusion criteria, but were not included in the meta-analysis. One study (Guneri et al., 2005) reported that infrequent dental visits were associated with oral cancer (OR 0.171). Another study examined the risk associated with not attending the dentist on a regular basis and reported a statistically significant adjusted risk of 2.1 (95% CI 1.3, 3.3) (Bundgaard et al., 1995). Finally, Rosenquist 2005 reported the protective effect of regular dental attendance compared to not regular attendance and found a statistically significant reduced adjusted risk OR 0.4 (95% CI 0.2, 0.6).

Figure 3.3-6 Meta-analysis of odds ratio estimates of adjusted data for never attends the dentist compared to attends the dentist associated with risk of oral cancer



3.3.9 Association between oral cancer and the use of a denture

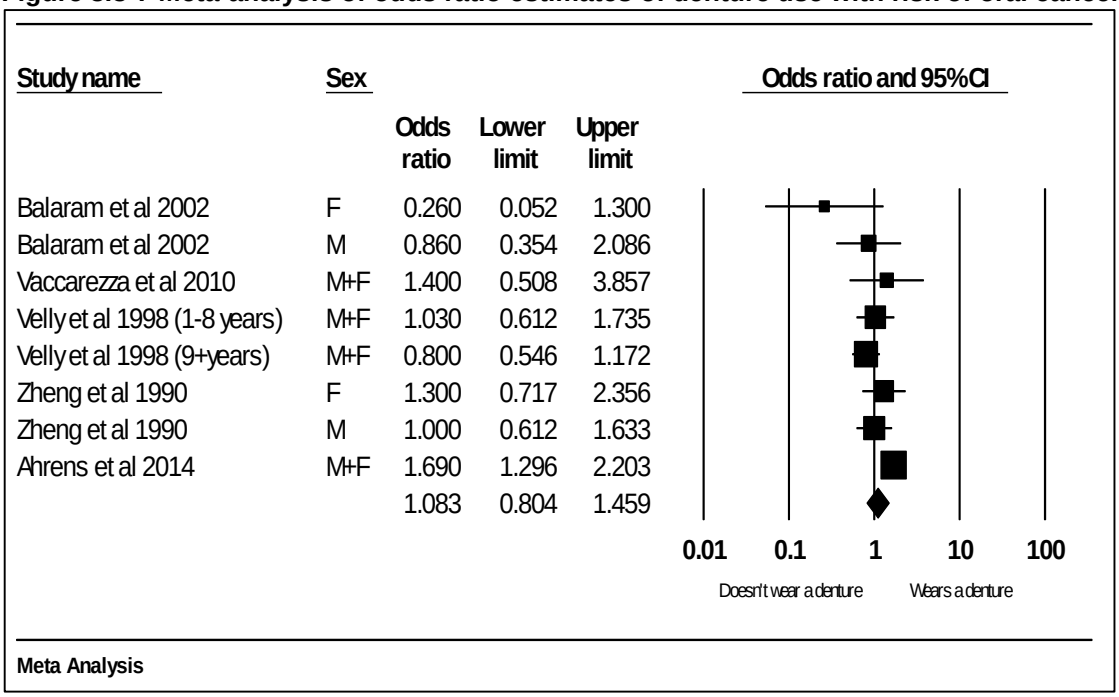
Five studies (Balaram et al., 2002, Vaccarezza et al., 2010, Velly et al., 1998, Ahrens et al., 2014, Zheng et al., 1990) were included which presented adjusted data examining the potential risk of denture use and the development of oral cancer. The overall estimate for denture-wearing associated with increased risk

of oral cancer was 1.08 (95% CI 0.80, 1.46) (Figure 3.3-7) using a random effects model.

Five additional studies (Browne et al., 1977, Guha et al., 2007, Schildt et al., 1998, Winn et al., 1991, Wynder et al., 1957) presented data that could be used for inclusion of unadjusted data. The Guha study in 2007 did present adjusted data for this factor, however the data analysis was carried out which presented the adjusted odds ratio of not wearing a denture, which was not compatible for the purposes of meta-analysis as the other studies had presented adjusted odds ratios of wearing a denture. The adjusted data for the Winn 1991 study was not accepted by the software and so unadjusted odds ratios were used. When the unadjusted data were included in the analysis, no significant effect was seen: 1.04 (95% CI 0.87, 1.25). Four studies (Ahrens et al., 2014, Balaram et al., 2002, Velly et al., 1998, Zheng et al., 1990) contained adjusted data with sample sizes greater than 300 and there was no significant change seen when the analysis was restricted to these studies 1.06 (95% CI 0.77, 1.46). There were three studies (Zheng et al., 1990, Ahrens et al., 2014, Velly et al., 1998) which were considered to be of higher methodological quality i.e. greater than the median, and the risk remained non-significant when the analysis was restricted to those studies 1.14 (95% CI 0.83, 1.58). No significant change was observed if any one study was removed from the analysis. Four studies (Velly et al., 1998, Vaccarezza et al., 2010, Balaram et al., 2002, Zheng et al., 1990) investigated cancer of the oral cavity only and the risk remained non-significant OR 0.95 (95% CI 0.76, 1.18) (Table 3.3-2)

One study (Talamini et al., 2000) examined number of years with a denture as risk factor for oral cancer and so was not included in the meta-analysis. They found that wearing a denture less than 10 years was associated with OR 0.8 (95% CI 0.4, 1.7) and greater than or equal to 10 years OR 0.5 (95% CI 0.2, 1.2).

Figure 3.3-7 Meta-analysis of odds ratio estimates of denture use with risk of oral cancer



3.3.10 Association between frequency of toothbrushing and oral cancer

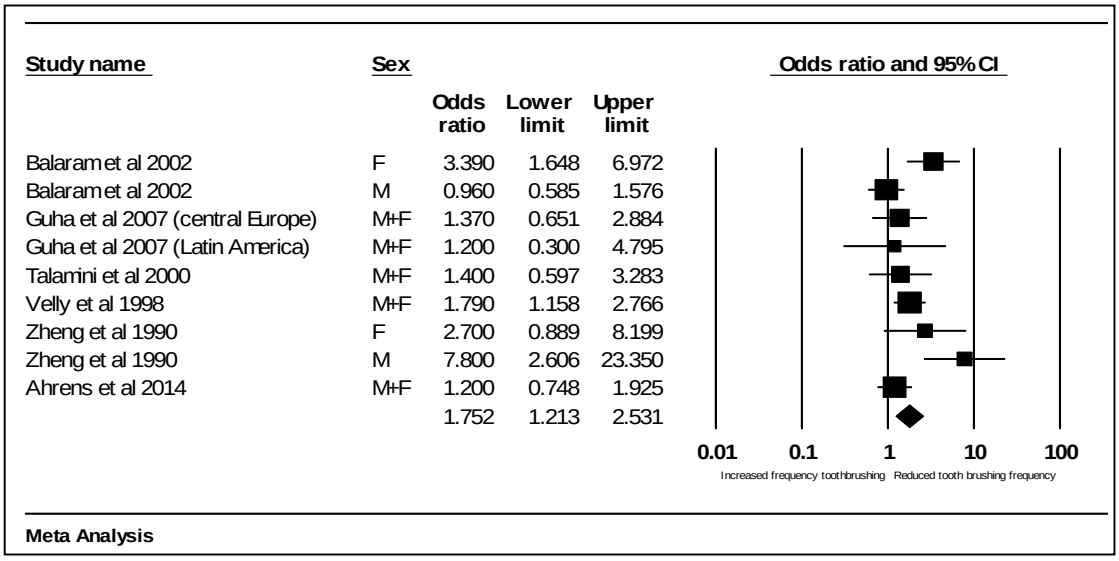
Six studies (Ahrens et al., 2014, Balaram et al., 2002, Guha et al., 2007, Talamini et al., 2000, Velly et al., 1998, Zheng et al., 1990) were included that contained adjusted data that examined the effect of frequency of toothbrushing on the risk of oral cancer. The best scores were compared with the worst scores. There was significant heterogeneity between the studies observed I^2 = 58.361 and P-value = 0.014. The overall estimate for reduced frequency of toothbrushing associated with increased risk of oral cancer was reported as OR 1.75 (95% CI 1.21, 2.53) using a random effects model (Figure 3.3-8).

An additional three studies (Browne et al., 1977, Moreno-Lopez et al., 2000, Szczesiul, 1995) were added for the analysis including studies with unadjusted data. The effect remained significant 2.41 (95% CI 1.63, 3.57). Five studies (Ahrens et al., 2014, Balaram et al., 2002, Guha et al., 2007, Velly et al., 1998, Zheng et al., 1990) had a sample size greater than 300 and the effect was significant when only these studies were included: 1.81 (95% CI 1.20, 2.73). Four studies were considered to be of higher methodological quality (greater than the median) and the effect remained significant when the analysis was restricted to

these studies: 1.85 (95% CI 1.18, 2.9). No one study was found to significantly change the outcome during analysis. (Table 3.3-2).

There were studies that met the inclusion criteria, but were not included in the meta-analysis due to how the data were presented relating to missing teeth. One study (Guneri et al., 2005) reported that toothbrushing was more common among the healthy controls (78.69%) than the cancer patients (44.30%). There was an odds ratio of 0.17 and the difference was statistically significant (p = 0.000).

Figure 3.3-8 Meta-analysis of odds ratio estimates of frequency of toothbrushing comparing the best with the worst variable with risk of oral cancer



3.3.11 Publication bias

Funnel plots were created for each oral health factor and each was examined for evidence of publication bias (Figure 3.3-9- Figure 3.3-15). The spread of the studies within the funnel (vertical line showing no effect and diagonal lines showing 95% confidence intervals) were examined and assessed for areas within the funnel for missing studies suggesting publication bias. No convincing evidence of publication bias was seen. However, for general oral health, most studies appeared on the right of the funnel, possibly indicating under-reporting of smaller negative studies. Interpretation of this is somewhat limited due to the small number of studies.

Figure 3.3-9 Funnel plot for General Oral Health adjusted studies

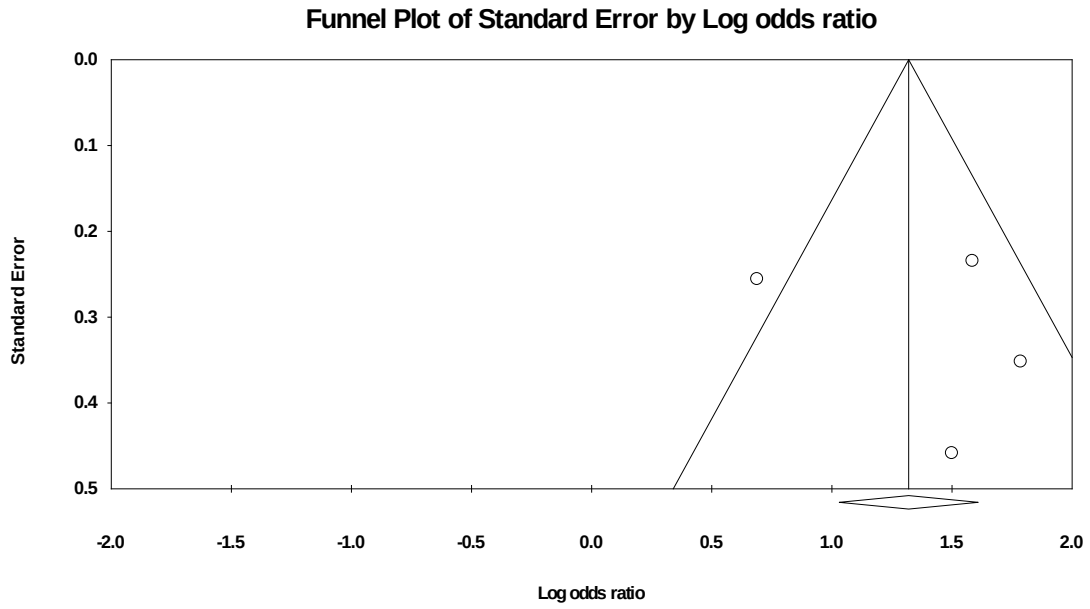


Figure 3.3-10 Funnel plot for Gum Bleeding adjusted studies

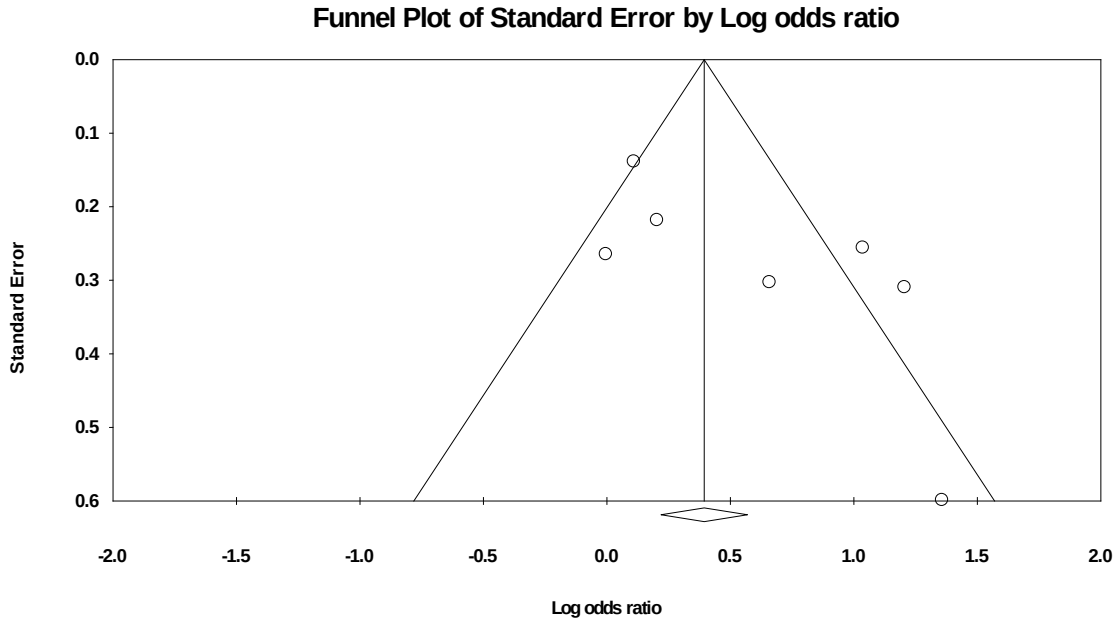


Figure 3.3-11 Funnel plot for Oral Hygiene adjusted studies

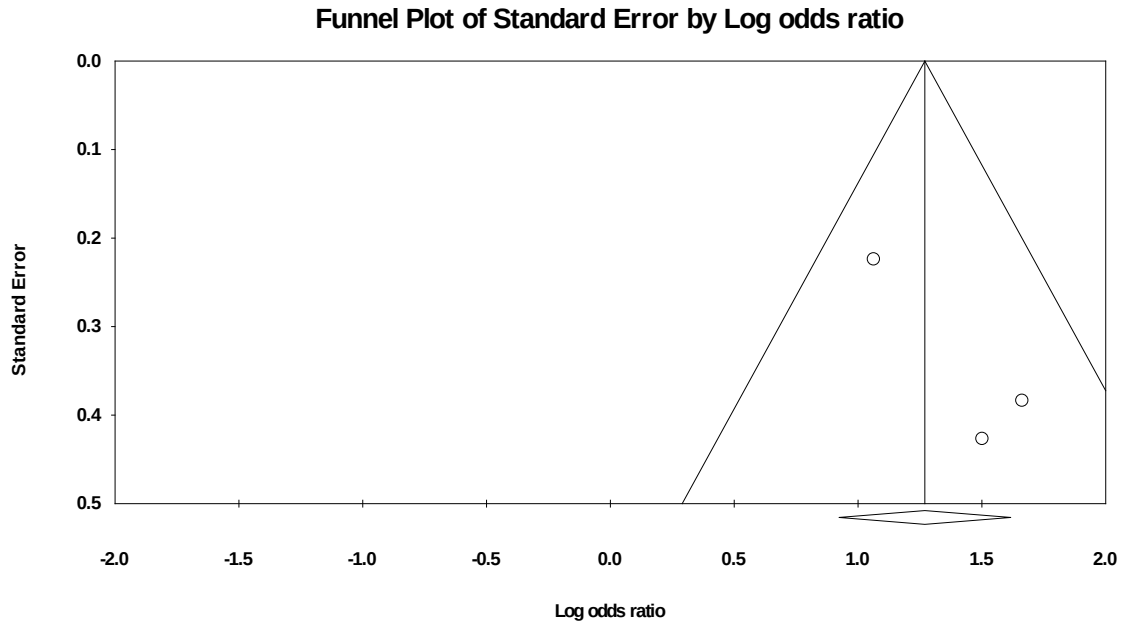


Figure 3.3-12 Funnel plot for Missing Teeth (6 or more) adjusted studies

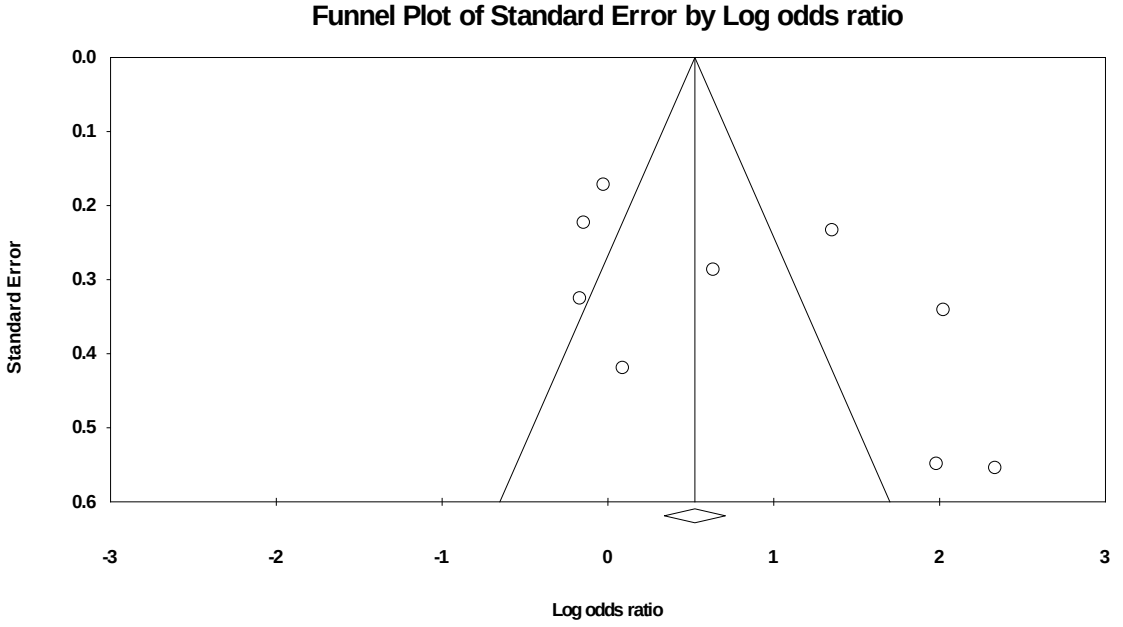


Figure 3.3-13 Funnel plot for Never Attends the Dentist adjusted studies

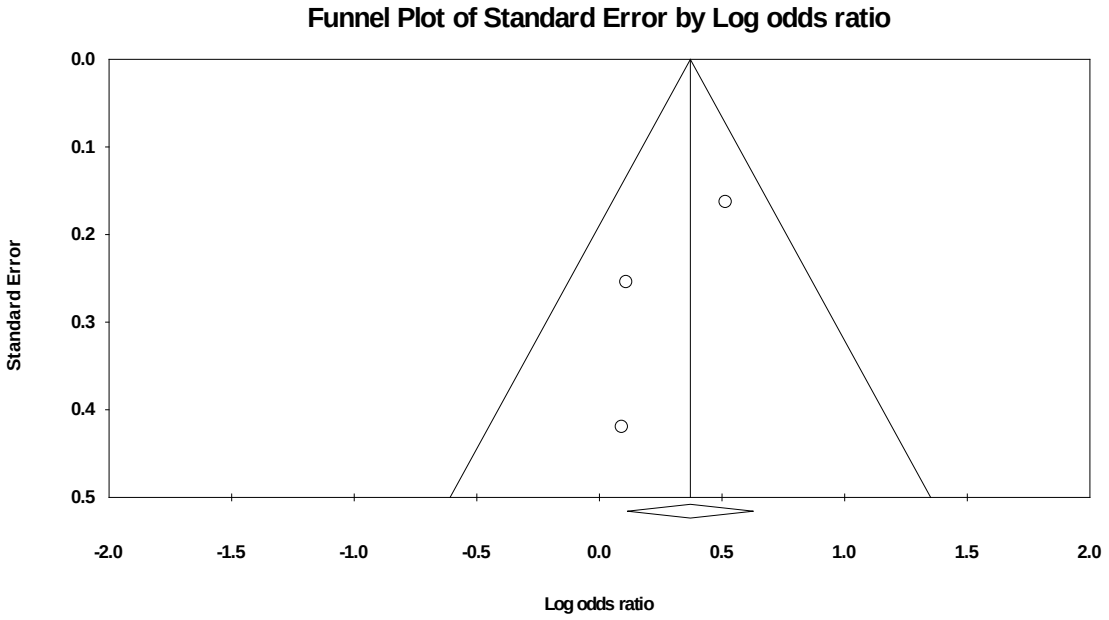


Figure 3.3-14 Funnel plot of included adjusted studies for Denture Wear

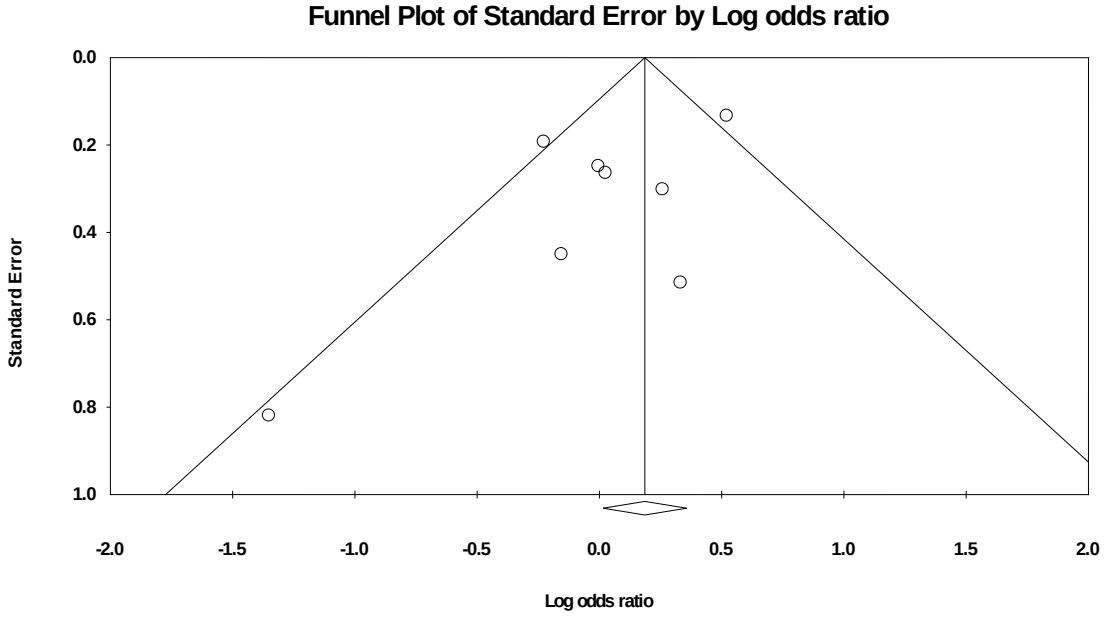
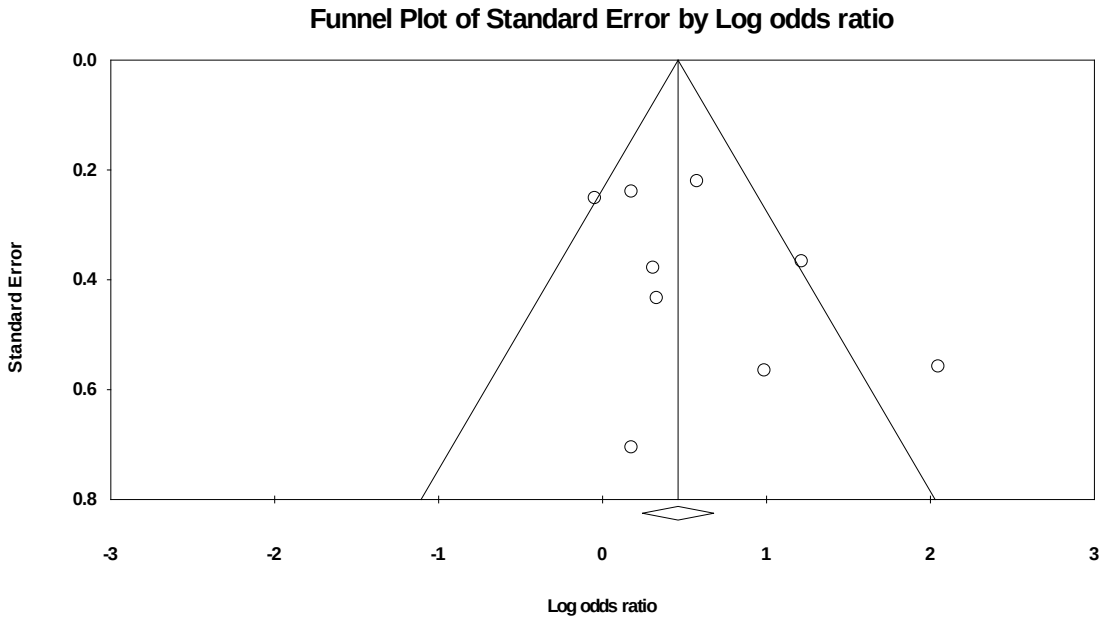


Figure 3.3-15 Funnel plot of adjusted studies for Toothbrushing Frequency



3.4 Discussion

3.4.1 Summary

To my knowledge this is the first systematic review and meta-analysis that has attempted to quantify the risk association of the range of oral health / dental care factors with oral cancer. General oral health, gum bleeding, oral hygiene, missing teeth, dental attendance and toothbrushing frequency were all associated with a statistically significant risk of oral cancer when examining adjusted studies. However, for some of the factors the robustness of these findings could be questioned due to the limited number of studies included. This was particularly relevant where sensitivity analysis was attempted resulting in only one or two studies remaining when examining for studies of a higher methodological quality or greater sample size. It was interesting to note that denture use is not a significant risk factor for oral cancer.

3.4.2 Advantages of systematic review

A systematic review is conducted in a predefined and carefully conducted manner to attempt to eliminate the risk of bias (Stroup et al., 2000, Sutton et al., 1998). Traditional reviews allowed authors to choose which papers to include and are prone to a high risk of bias. By adhering to a set methodology,

the results of a systematic review should be transparent and reproducible, and as such the risk of bias reduced or eliminated. This allows the literature on a given topic to be summarised to allow readers to gain an understanding of the relevant research.

A systematic review describes the process of conducting a search and processing the results against set inclusion and exclusion criteria to decide on the studies included within the review. Where a number of studies are included, the data can be difficult to interpret, particularly where the results conflict. By combining the data and analysing the data to produce a single statistic, a summary of the data available in the literature can be more easily assessed by readers.

3.4.3 Limitations of systematic review and meta-analysis

The validity of the systematic review relies upon good methodology and reporting (Stroup et al., 2000). Where poor methodology has been used, bias can be introduced or data can be missed reducing the validity of the findings. Not all systematic reviews can include a meta-analysis for a number of reasons, e.g. heterogeneity of the study designs meaning that the results are not comparable and so not suitable for combination.

Meta-analysis of observational studies has been criticised. Some have expressed concern that selection bias and confounding factors distort the findings from the individual studies and meta-analysis may produce very precise but spurious results (Egger et al., 1998). It has also been suggested that an individual participant data approach should used to pool the data from the participants rather than attempt to combine the outcomes of the studies. This may be a more robust way of combining the data and manage the heterogeneity of the studies, but is more expensive, time consuming and sometimes not practical (Conway et al., 2009, Riley et al., 2010).

3.4.4 Search Strategy strengths

The search strategy employed was based on established and accepted guidelines (Stroup et al., 2000) and was considered sound and wide in scope. By using three databases and an inclusive and wide search strategy, a large number of potential articles were identified. This resulted in an extensive screening process to identify relevant studies. The subsequent hand-searching of bibliographies and contact with experts in the field resulted in more studies for inclusion.

3.4.5 Search Strategy limitations

It could be argued that more databases could have been utilised for the search. It was felt that the databases used resulted in a large number of studies and this was assessed against 13 "sentinel" papers that it was expected that the search would identify. The searches were modified until all of the papers were included. This resulted in a very broad search with a large number of articles to screen, suggesting that the search strategy employed was robust.

The cut off for the search strategy, July 2012, reflects when the search was conducted. As this is over 2 and half years ago, it may be that further studies have been published in that time that would meet the requirements for inclusion. In an attempt to address this concern, contact with experts in the field was carried out which resulted in the inclusion of one unpublished study, which has subsequently been published and so is cited in this thesis by the published reference (Ahrens et al., 2014). In order to assess the potential impact that the 2012 cut-off has had, a further search was conducted to identify studies that have been published since 2012. This resulted in identification of a further 3 studies (Oji and Chukwuneke, 2012, Rotundo et al., 2013, Wen et al., 2014) that may have potentially been included in this study. Although not subject to the same scrutiny and methodological assessment as the papers included in this study, the studies were briefly reviewed to assess to see if the findings were in agreement or contradictory to the findings of our systematic review and are discussed further in the relevant sections.

3.4.6 Inclusion criteria limitations

Our inclusion criteria meant that studies that used cancer controls could not be used. This resulted in a number of studies that were excluded that could have potentially had useful data (Albuquerque et al., 2011b, Campbell et al., 1997, Whitaker et al., 1979, Elwood et al., 1984, Young et al., 1986). It could be argued that cancer controls could help to control for certain confounding factors and differences in oral health / dental care factors in the oral cancer group would highlight potential risk factors specific to oral cancer. However, studies that used cancer controls were excluded due to the risk of overmatching controls with common risk factors (Wacholder et al., 1992).

Our inclusion criteria also stipulated that the data would need to be extractable and able to be included in the meta-analysis. This meant that a number of studies that had otherwise met the inclusion criteria were not used in the final analysis (Guneri et al., 2005, Michaud et al., 2008, Tezal et al., 2009, Shanta and Krishnamurthi, 1964). In addition, two studies were identified that had potentially collected oral health / dental care data related to oral cancer risk but the authors could not be contacted and so were excluded (Lewin et al., 1998, Wahi et al., 1965). Other studies were excluded from analysis if the data presented could not be separated from general cancer of the head and neck (Tezal et al., 2005, Hiraki et al., 2008, Maier et al., 1993, Olasz and Szabo, 1989). The potential loss of data from these areas reduces the validity of the findings of this research.

Our inclusion criteria stipulated that a minimum of smoking and alcohol needed to be adjusted for to be included within the adjusted analysis. This could have been widened to include adjustment for age and sex as well given the strong association with age and gender (Cancer Research UK). Without adjustment for age and sex, there is potential to observe a stronger association than truly exists. One study (Rosenquist, 2005) was included within the adjusted meta-analyses that adjusted for smoking and alcohol but did not adjust for gender or age. However, during sensitivity analysis, the Rosenquist 2005 study did not significantly alter the findings of any of the adjusted meta-analysis.

Another study (Balaram et al., 2002) only partially fulfilled the inclusion criteria for adjusted data as they only adjusted for smoking and alcohol for male participants. The reason for this was that very few women reported smoking or consumption of alcohol, less than 3%. Following discussion, it was agreed that the data for women were included in the adjusted meta-analysis as the results are unlikely to be substantially different given the small number of women that smoked or consumed alcohol and that losing the data would be more detrimental to the validity of the meta-analyses. There was an endeavour to extract estimates for males and females separately in this study which negates the need for sex adjustment.

3.4.7 Methodological assessment

Methodological assessment of the included studies highlighted the great variation between the quality of the studies. Scores of between 1 and 11 were observed with three studies achieving a score of 11. Two of the three studies (Browne et al., 1977, Wynder et al., 1957) that scored 3 or less were greater than 35 years old. However the study with the lowest score of 1 (Subapriya et al., 2007) was a relatively new study. The great variation in methodological quality of the studies and the observation that none of the included studies achieved a perfect score of 12, highlights the need for high quality studies following accepted best practice for case-control methodology.

3.4.8 Explanations

3.4.8.1 General oral health

General oral health was found to be a significant factor for the development of oral cancer with an OR 3.91 (95% CI 2.29, 6.67). However, only three studies were included. Two of the studies (Ahrens et al., 2014, Balaram et al., 2002) had sample sizes of greater than 300 cases and only one (Ahrens et al., 2014) was considered to be of higher methodological quality. Only one study (Balaram et al., 2002) looked at the oral cavity so it is difficult to take significant findings from this. It is also worth noting that the studies included used very different definitions of oral health. Balaram et al 2002 and Talamini et al 2000 assessed oral health based on “the presence of tartar, decayed teeth, and mucosal

irritation". Ahrens et al 2014 used denture wearing, age of starting to wear dentures, and frequency of gum bleeding from teeth. The disparity between the studies in terms of this definition could be used to argue that the use of a meta-analysis to combine the studies is not appropriate. However, when conducting a one study removed analysis, no significant difference was seen.

It is difficult to suggest the reason why general poor oral health would confer such an increased risk. It may be the combination of the other factors examined in this study combine to increase the risk. Irritation of the oral soft tissues predisposing to oral cancer has been suggested and may be more likely found in those with poor oral health. It may be that other factors associated with poor oral health such as poor oral hygiene, chronic mucosal irritation, gingival or periodontal disease increases the risk of oral cancer and as such, so does poor oral health. Chronic irritation as a risk factor for oral cancer has been suggested and evidence exists within laboratory studies (Perez et al., 2005). One theory that has been proposed is that for a neoplasm to occur, there needs to be initiation (damage to the DNA) and promotion (promotes the proliferation of initiated cells) (Boutwell, 1964). Chronic mucosal irritation may act as a promoter within the context of this theory. Another theory is that chronic mucosal irritation results in breakdown of the surface of the epithelium allowing carcinogens in the mouth to have a greater effect (Dayal et al., 2000). The possibility of reverse causation (as with many of the oral health factors examined) must be considered. It may be that individuals with pain or discomfort from the oral cavity may avoid brushing and as a result, have worse scores for oral health.

3.4.8.2 Gum bleeding

Gum bleeding was observed to carry a significantly increased risk of oral cancer OR 1.76 (95% CI 1.20, 2.85). This risk remained significant when only studies with a sample size of greater than 300 were included. However, when only studies of high methodological quality were used, significance was lost. This could potentially call into question this finding if the significance of the risk was inflated by studies of poorer quality. It is also worth considering reverse causality here, where oral cancer could cause lesions of the gingival tissues

which could increase the propensity for gum bleeding. There is also the possibility as previously mentioned that pain or swelling of the oral tissues could lead to reduced oral hygiene and as such an increased risk of gum bleeding.

A recent systematic review carried out a meta-analysis on the potential for periodontal disease as a risk factor for oral cancer and found a statistically significant risk OR 2.63 (95% CI 1.68, 4.14; $p < 0.001$) (Zeng et al., 2013a). Although gum bleeding and periodontal disease are not the same, they may represent a similar aetiological basis for increased risk. The systematic review and meta-analysis was examined using MOOSE guidelines (Stroup et al., 2000). The study satisfied the guidelines for most points, however there are a number of potential criticisms. No mention is made in the paper regarding contact with authors or attempt to identify unpublished work. They did not report on the quality of the studies included. They also included a study in the meta-analysis that had not been adjusted for any factors (De Rezende et al., 2008). However, perhaps the greatest criticism is with the inclusion and meta-analysis of studies that used significantly varied criteria for periodontal disease. Indicators of periodontal disease used included alveolar bone loss, Community Periodontal Index of Treatment Need (CPITN), clinical attachment loss, tooth mobility and poor condition of mouth. Poor condition of mouth (Guha et al., 2007) was defined as the presence of tartar, gingival bleeding, mucosal irritation and decaying teeth. The use of oral health as defined above as a measure of periodontal disease is, in the opinion of this author, inappropriate. The quality of the methodology, inclusion of unadjusted data, and the suitability of the measures of periodontal disease calls into question the validity of their findings.

3.4.8.3 Oral hygiene

The overall estimate for poor oral hygiene associated with increased risk of oral cancer was 3.56 (95% CI 2.52, 5.04). However, there were only two studies included with adjusted data and so sensitivity analysis was somewhat restricted. Only one study had a sample size greater than 300 or looked at the oral cavity (Guha et al., 2007). No separate analysis was required for the methodological quality as both studies included were of higher methodological quality.

Based on the available evidence, poor oral hygiene would appear to be a risk factor for oral cancer, although this conclusion needs to be interpreted with caution given the limited number of studies available for inclusion. If we are to accept that oral hygiene is indeed a risk factor, why such a relationship exists should be explored. It has been suggested that there may be biological plausibility to the link between poor oral hygiene and cancer. The suggestion is that poor oral hygiene results in periodontal inflammation which results in the release of inflammatory cytokines which has been linked to systemic disease (Scannapieco, 2004). It has been proposed that a key aspect of the pathogenesis of cancer is an aberrant epithelial barrier that can be instigated by microbial toxins with resultant loss of epithelial integrity. This results in activation of resident inflammatory cells by microbial invaders which can result in a number of disorders including cancer (Karin et al., 2006). If this biological process explains the possible link between oral cancer and oral hygiene, then it may also explain why other oral health / dental care factors also demonstrate a statistically significant risk such as toothbrushing, gum bleeding and general oral health.

3.4.8.4 Toothbrushing

The overall estimate for reduced frequency of toothbrushing, comparing the best and worst scores, associated with an increased risk of oral cancer was reported as OR 1.75 (95% CI 1.21, 2.53). Of all the oral health / dental care factors examined, frequency of toothbrushing showed the least variation when subjected to sensitivity analysis. The findings remained statistically significant when analysis was restricted to studies of greater than 300 cases or studies of higher methodological quality assessment. Again, the findings remained similar and statistically significant, with a slight increase, when the analysis was restricted to studies examining the oral cavity.

Although not subjected to the same screening process or assessment of the methodological process as the included studies, one study was identified that had been published subsequent to the search (Oji and Chukwuneke, 2012) that looked at oral hygiene habits as a risk for oral cancer. They reported that the inadequate and infrequent use of chewing sticks in a Nigerian sample was associated with an increased risk of oral cancer.

The rationale or biological basis for toothbrushing frequency to act as a risk factor for oral cancer may be similar to those outlined in general oral health and oral hygiene. Those with reduced frequency of toothbrushing are likely to have more plaque and gingival inflammation and as such, a similar aetiology can be suggested. Another possible explanation is that individuals with reduced toothbrushing may demonstrate other health behaviours predisposing them to an increased risk of oral cancer such as poorer diet (although in many cases diet has been adjusted for). Again, the risk of reverse causation has to be considered and patients with a painful mouth as a result of the oral cancer may be less likely to brush their teeth.

3.4.8.5 Missing teeth

The overall estimate for 6 or more missing teeth associated with increased risk of oral cancer was OR 2.3 (95% CI 1.27, 4.18). There were only slight differences seen in the odds ratios and the findings remained statistically significant when the analysis was restricted to studies with greater than 300 cases and studies examining the oral cavity. However, when the analysis was restricted to studies of higher methodological quality i.e. greater than the median, the odds ratio reduced and was no longer statistically significant OR 1.84 (95% CI 0.99, 3.42). The loss of statistical significance when the analysis was restricted to studies of greater methodological quality questions the validity of this finding and the results should be interpreted with caution.

Missing teeth as a risk factor for oral cancer may be due to the association between missing teeth and other oral health / dental care risk factors such as poor oral hygiene and gingival / periodontal diseases. This may be supported by the findings of Guha et al 2007 that found an increased risk of oral cancer with between 6-15 missing teeth, but not when there were more than 15 missing teeth. They suggest that if the underlying causative factor is the presence of periodontal disease, then when more than 15 teeth are missing, the periodontal / periodontal pathogen burden is reduced due to less remaining teeth and so is the risk of oral cancer. The biological basis for increased risk of oral cancer associated with missing teeth due to factors such as poor oral hygiene or gingival disease is outlined in the above sections.

Other factors that may be related to missing teeth include diet. Diet has been shown to be a significant factor in oral cancer risk (Chuang et al., 2012). Patients with missing teeth may have poorer masticatory efficiency and so reduced nutritional uptake as a direct result of the missing teeth (Sierpinska et al., 2006, Nowjack-Raymer and Sheiham, 2007). Although diet is adjusted for in some studies, this may not account for differences in nutritional uptake as a result of reduced masticatory efficiency.

Another suggestion is that the microbial flora in individuals with missing teeth is altered and may predispose individuals to an increased risk of oral cancer. This is thought to be due to the microbial flora in individuals with missing teeth being more likely to metabolise alcohol to produce acetaldehyde which has been shown to be carcinogenic (Homann et al., 2001) although this may only be seen in heavy drinkers.

A systematic review and meta-analysis published during the write up period of this dissertation reported on missing teeth as a risk factor for head and neck cancer and found that 6 or more missing teeth to be a significant risk factor [6 to 15 teeth loss (OR1.58; 95% CI1.08, 2.32; p=0.02), 11+ teeth loss (OR1.63; 95% CI1.23, 2.14; p<0.001), 15+ teeth loss (OR1.72; 95% CI 1.26, 2.36; p<0.001), and 20+ teeth loss (OR1.89; 95% CI1.27, 2.80; p<0.001)] (Zeng et al., 2013b). They found a stronger association than that found in our own study, however, both studies demonstrated an increased risk of cancer with missing teeth. The systematic review was examined using the MOOSE guidelines. The study satisfied the guidelines for most points, however there are a number of potential criticisms. No mention is made in the paper regarding contact with authors or attempt to identify unpublished work. They did not report on the quality of the studies included. However, on close inspection a potentially serious error was identified. They included two case-control studies (Lissowska et al., 2003, Fernandez Garrote et al., 2001) as well as large multicentric case-control studies (Guha et al., 2007). In the systematic review presented here, the studies by Lissowska et al 2003 and Garrote et al 2001 were excluded as the data were duplicated in the article by Guha et al 2007 which contained data from a number of other centres. The meta-analysis by Zeng et al 2013 would appear to be invalid by the duplication of data. In order to confirm that the data were the

same, contact was made with the corresponding authors for the Lissowska et al 2003 and Guha et al 2007 papers who confirmed the duplication of data. The flaws highlighted invalidate the findings of their paper.

3.4.8.6 Presence of a denture

The overall estimate for denture-wearing associated with increased risk of oral cancer was 1.08 (95% CI 0.80, 1.46). No statistically significant risk was found which was during the sensitivity analysis when analysis was restricted to studies with more than 300 cases, studies of greater methodological quality, studies of only the oral cavity and when one study removed test was conducted.

No significantly increased risk associated with the presence of a denture may seem contradictory as missing teeth was found to be a significant risk. The two factors would seem to be linked and so it is surprising that one was found to be a significant risk factor while the other was not. A possible explanation for this is that some of the studies that have been included may have patients that have missing teeth but have not been replaced with a denture, particularly where patients may be included that come from more deprived areas (Balaram et al., 2002, Guha et al., 2007, Zheng et al., 1990). There has also been the suggestion that missing teeth is a risk factor until more than 15 teeth are missing and the risk is no longer seen (Guha et al., 2007). If this is true, then this may explain why denture use is not a significant risk factor as dentures are more likely to be used by those individuals with many missing teeth.

This systematic review and meta-analysis only examined denture use as a risk factor for oral cancer. Another systematic review and meta-analysis was published during the write up for this thesis (Manoharan et al., 2014). Ill-fitting dentures was examined as a specific risk factor for oral cancer and they found OR 3.90 (95% CI: 2.48, 6.13). They also examined the presence of a denture as a risk factor and found a slightly increased risk associated OR 1.42 (95% CI 1.01, 1.99). The significantly increased risk seen with ill-fitting dentures would suggest that the associated risk may be related to chronic irritation. Examination of their study showed that they had generally complied with MOOSE guidelines (Stroup et al., 2000). There are some potential criticisms and differences in methodology with our own study which may explain the differing outcomes.

They made no attempt to identify unpublished data and so the study by Ahrens et al 2014 was not included. They also included unadjusted data in the main analysis where adjusted data were not available. Perhaps the biggest difference was their inclusion of studies which had used cancer controls.

The finding that the presence of a denture in our systematic review and meta-analysis is not a significant risk for oral cancer is a positive finding for patients and dentists. In many cases, dentures are the most appropriate and often the only means of restoring missing teeth and if it was found that denture use was a risk for oral cancer and should be avoided, this would be contradictory to current dental practices.

3.4.8.7 Dental attendance

The overall estimate for non-attendance at the dentist associated with increased risk of oral cancer was 1.45 (95% CI 1.12, 1.87). Only three studies were included in this analysis. However, a statistically significant risk was seen when analysis was restricted to studies with more than 300 cases and studies of a greater methodological quality. It is worth noting that significance was lost when Ahrens 2014 was removed from the analysis. As such, the results should be interpreted with caution and further studies are required in this area to either confirm or deny the association.

As a dentist, it would be heartening to find that dental attendance reduced the risk of oral cancer, however it is likely the biological explanation is due to factors associated with dental attendance rather than the attendance itself. As has been discussed above, there are a number of dental factors that have been shown to be a statistically significant risk for oral cancer such as oral hygiene, gum bleeding, missing teeth and general oral condition. All these factors are likely to be improved in a patient who attends the dentist compared to those that do not.

3.5 Conclusion

The findings of this study would suggest that there are a number of oral health and dental care risk factors that are significantly associated with oral cancer risk. However, this conclusion comes with the caveat that there are limited studies which are of high methodological quality and adequately controlled to base this statement on. It would be of benefit if further well designed studies could be conducted which would further strengthen or disprove the associations observed here. Nevertheless, it can be concluded that from the current evidence available that general oral health, poor oral hygiene, infrequent toothbrushing, gum bleeding, missing 6 or more missing teeth, and never attending a dentist are risk factors for the development of oral cancer. Denture use per se does not appear to be a risk factor for oral cancer.

4 Dental Assessment and Dental Care of Oral Cancer Patients

4.1 Introduction

The study on alcohol-related cancers and genetic susceptibility in Europe (ARCAGE) was established in 2002. It is a multicentre case-control study, including 15 centres from 10 countries across Europe. Glasgow was one of the centres in the study and is participating in a follow-up of head and neck cancer patients from around Europe with around 100 patients from the Glasgow area. Currently there is a Europe wide ARCAGE follow-up study underway which aims to assess tumour site, stage, treatment and patient factors including lifestyle, behavioural and HPV-related factors and co-morbidities in relation to outcomes (IARC, 2015). In addition to participating in the multicentre follow-up study, we have also examined the Glasgow patients' medical notes to assess if a pre-operative dental assessment was performed and the results are presented in this thesis and compared to similar data collected more recently.

4.2 Aims

This research aims to assess pre- and post-operative dental assessments from patients treated 10 years ago in the Glasgow area and compare this to patients treated more recently. In order to collect this information, patients included for follow-up as part of the ARCAGE follow-up study were also assessed for the above factors.

4.3 Methods

The ARCAGE multicentre case-control study was conducted in 14 centres from 10 European countries (including Czech Republic, Germany, Greece, Italy, Ireland, Norway, Spain, Croatia, France and UK). Following a common protocol, cases were defined as those newly diagnosed with primary squamous cell tumours of the upper aerodigestive tract (UADT) between 2002 and 2004. Diagnoses included malignant cancers of the oral cavity, oropharynx, hypo-pharynx, larynx, or oesophagus.

4.3.1 Interviews 2004

Data were collected from cases and controls by trained interviewers conducting face-to-face interviews using a standardised questionnaire. A number of factors were included such as socio-demographic characteristics, anthropometric measures, smoking and alcohol consumption, frequency of intake of selected foods, a detailed occupational history and a brief medical and dental history including oral health habits (Lagiou et al., 2009). Within the dental and oral health section, the patients were asked if they wore a denture, the nature of the prosthesis, which jaw it was worn on, and when they first started wearing dentures; how often they cleaned their teeth and what did they use; gum bleeding; how often they used mouthwashes; how often they attended the dentist.

4.3.2 ARCAGE Follow-up study 2002-2004

A follow-up study is being carried out which includes the hundred patients who had been previously interviewed and consented ARCAGE study patients from the Glasgow area. The study aims to examine survival outcomes and how they relate to patient, treatment and tumour factors. Outcomes are being assessed primarily through the use of a data collection form and examination of case medical records, however, data linkage to the Scottish Cancer Registries, death certificates and mortality registry were also undertaken. The results will be pooled into the multicentre study and the results will be presented with the data from the other centres. The findings of the ARCAGE follow-up study is beyond the scope of this thesis however the data extraction form can be found in Appendix D. Ethical approval was granted for the ARCAGE follow-up study and the approval form can be found in Appendix E.

4.3.3 Dental assessment of ARCAGE 2002-2004 cohort

In addition, and for the purposes of this thesis, a series of questions have been included in the data collection form for the Glasgow centre regarding dental assessment to determine if dental assessments were carried out both pre- and

post-operative. The proposed questions were developed using guidelines and expert opinion and have been examined by three Restorative Dentistry Consultants with an interest in the management of head and neck cancer patients (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006, British Association of Head and Neck Oncologists, 2009, Ray-Chaudhuri et al., 2013). The data extraction form can be found in Appendix D.

4.3.3.1 Pre-treatment dental assessment

Ideally this should involve a full dental examination, charting, appropriate radiographs and periodontal screening by a suitably qualified practitioner (Pace-Balzan et al., 2011). For the purposes of this research, any record of an examination of the dental tissues or dental radiograph was accepted as a pre-dental assessment.

4.3.3.2 Post-treatment dental assessment

Those patients included as receiving a post-treatment assessment were those who included one of the following as part of their: referred to their dental practitioner for care, where a referral to a Consultant in Restorative Dentistry was sent, and where the patient had been seen by a hygienist within the hospital.

4.3.3.3 Radiotherapy

Data were recorded specifically for dentate patients in the 2002-2004 cohort to assess if radiotherapy had been used as part of their care and if they had received a dental assessment.

4.3.3.1 Exclusion Criteria

The following exclusion criteria were used for pre-operative assessment: edentulous patients or if it was unknown if the patient was dentate or edentulous.

4.3.4 Dental assessment of 2013-2014 Cohort

For the purposes of comparison and to assess if any improvement has been achieved in the last 10 years, similar data were utilised for dental assessment only from a clinical audit supervised by the author of this thesis. No data were recorded regarding radiotherapy or interview data and so no comparison was possible within these sections. Records from the Regional Oral and Maxillofacial Surgery Department at the Southern General Hospital were examined. One hundred consecutively diagnosed oncology patient records from January 2013-January 2014 were assessed by a single assessor Fiona McDowall (Senior House Officer).

Similar data were recorded: diagnosis / staging; site; date of first multi-disciplinary team (MDT) meeting; whether an orthopantomogram (OPT) was available on the picture archiving and communications system (PACS); whether the patient was dentate or edentulous on presentation; whether there was evidence of a dental appointment pending or past; and any other evidence of a dental assessment in the records.

4.3.4.1 Pre-treatment dental assessment

Ideally this should involve a full dental examination, charting, appropriate radiographs and periodontal screening by a suitably qualified practitioner. The definition of pre-operative assessment was broadened to match the data extraction of the historical data. A pre-treatment assessment was widened to include: an assessment for a full clearance or dental extractions at the time of surgery, assessment by a Consultant in Restorative Dentistry present at the MDT meeting, evidence of a dental hygienist appointment, and evidence of an OPT taken pre-treatment.

4.3.4.2 Post-treatment dental assessment

Those patients included as receiving a post-treatment assessment were those who: had a pending referral or ongoing appointments in the Restorative unit at Glasgow Dental Hospital, had been referred for ongoing hygiene care, had been referred back to their General Dental Practitioner for ongoing care, had been

referred to the Glasgow Dental Hospital Restorative Unit between surgery and chemo-radiotherapy.

4.3.4.3 Exclusion Criteria

The following exclusion criteria were used for pre-operative assessment: edentulous patients or if it was unknown if the patient was dentate or edentulous.

The following exclusion criteria were uses for the post-operative: patients planned for palliative care, where there was insufficient time since diagnosis to assess for post-operative dental assessment / management.

4.3.5 Statistical analysis

The data were analysed and presented as basic descriptive statistics such as percentages of the samples that had undergone the various assessments. An online calculator was used to calculate 95% confidence intervals of the proportions in the various categories using https://www.mccallum-layton.co.uk/tools/statistic-calculators/confidence-interval-for-proportions-calculator/. In order to compare the two samples, Chi-squared tests were conducted by a statistician using SPSS software and p-values were calculated. The pre-and post- operative oral health assessment of dentate patients had too small a number in the 2002-2004 yes category and so a chi-square test was not a suitable test so a Fisher's exact t-test was used to compare the samples.

4.4 Results

4.4.1 Data collection

4.4.1.1 Data collection 2002-2004 cohort

Of the 100 patients identified for follow-up, 76 case records were reviewed. Interview data from 10 years ago was available for 99 patients. For 11 patients, data were collected with no interview data available. For 34 patients, interview data were available but no data from case records. For 65 patients, data were available for both interview and case records (Table 4.4-1).

Table 4.4-1 Data retrieved from oral cancer patients and source 2002-2004 cohort

		Case record data	
		-ve	+ve
Interview data	-ve	0	11
	+ve	34	65

4.4.2 Summary of dental assessment

A summary of the findings from the study can be found in Table 4.4-2

Table 4.4-2 Oral Health assessment in 1st (2002-2004) and 2nd (2013-2014) cohorts

Cohort		**2002-2004 Cohort** n=76	**2013-2014 Cohort** n=100	**Chi-square statistic**	**p value**
Dental Status	**Dentate**	43 (56.6%; 95% CI 45.5%, 67.7%)	71/100 (71%; 95% CI 62.1%, 79.9%)	6.008	0.0496
	Edentulous	25 (32.9%; 95% CI 22.3%, 43.5%)	26/100 (26%; 95% CI 17.4%, 34.6%)		
	Unknown	8 (10.5%; 95% CI 3.6%, 17.4%)	3/100 (3%; 95% CI 0%, 6.3%)		
Evidence of oral health assessment	**Yes**	19/76 (25%; 95% CI 15.3%, 34.7%)	56/90 (62.2%; 95% CI 52.2%, 72.2%)	23.05	<0.001
	No	57/76 (75%; 95% CI 65.3%, 84.7%)	34/90 (37.8%; 95% CI 27.8%, 47.8%)		
Pre-operative dentate oral health assessment	**Yes**	6/43 (14%; 95% CI 3.6%, 24.4%)	45/71 (63.4%; 95% CI 52.2%, 74.6%)	26.463	<0.001
	No	37/43 (86%; 95% CI 75.6%, 96.4%)	26/71 (36.6%; 95% CI 25.4%, 47.8%)		

Table 4.4-3 continued

Cohort		2002-2004 Cohort n=76	2013-2014 Cohort n=100	Chi-square statistic	p value
Post-op oral health assessment	Yes	14/76 (18.4%; 95% CI 9.7%, 27.1%)	19/74 (25.7%; 95% CI 15.7%, 35.7%)	1.499	0.284
	No	62/76 (81.6%; 95% CI 72.9%, 90.3%)	55/74 (74.3%; 95% CI 64.3%, 84.3%)		
Pre- and post-operative oral health assessment dentate patients	Yes	1/43 (2.3%; 95% CI 0%, 6.8%)	8/58 (13.8%; 95% CI 4.9%, 22.7%)	4.001 (not a valid test)	0.045 (not a valid test) Fisher's exact t test= 0.074
	No	42/43 (97.7%; 95% CI 93.2%, 100%)	50/58 (86.2%; 95% CI 77.3%, 95.1%)		
Dentate patients and radiotherapy	Yes	28/43 (65.1%; 95% CI 50.9%, 79.3%)			
	No	10/43 (23.3%; 95% CI 10.7%, 35.9%)			
	Unknown	5/43 (11.6%; 95% CI 2%, 21.2%)			
Dentate patient who received radiotherapy pre-operative assessment	Yes	5/28 (17.9%; 95% CI 3.7%, 32.1%)			
	No	23/28 (82.1%; 95% CI 67.9%, 96.3%)			
Interview "Did your gums bleed when you cleaned your teeth?"	No	34/63 (54%; 95% CI 41.7%, 66.3%)			
	Sometimes	25/63 (39.7%; 95% CI 27.6%, 51.8%)			
	Always or almost always	4/63 (6.3%; 95% CI 0.3% 12.3%)			
Patients with gum bleeding and a pre-operative dental assessment	Yes	3/22 (13.6%; 95% CI 0%, 27.9%)			
	No	19/22 (86.4%; 95% CI 72.1%, 100%)			
Interview "During the last 20 years, how often did you go to see a dentist?"	At least every year	25/99 (25.3%; 95% CI 16.7%, 33.9%)			
	Every 2-5 years	27/99 (27.3%; 95% CI 18.5%, 36.1%)			
	Less than every 5 years	21/99 (21.2%; 95% CI 13.2%, 29.2%)			
	Never	26/99 (26.3%; 95% CI 17.6, 35%)			
Dental attendance <5 years or never and pre-operative dental assessment	Yes	5/30 (16.7%; 95% CI 3.4%, 30%)			
	No	25/30 (83.3%; 95% CI 70%, 96.6%)			

4.4.3 Dental status

4.4.3.1 Dental Status 2002-2004 cohort

Of the case records examined, 25 out of 76 (33%; 95% CI 22%, 43%) were identified as edentulous, 43 out of 76 (57%; 95% CI 46%, 68%) were identified as dentate, and 8 out of 76 (10%; 95% CI 4%, 17%) their dental status were unknown Table 4.4-2.

4.4.3.2 Dental Status 2nd cohort (2013-2014)

Of the case records examined, 26 out of 100 (26%; 95% CI 17%, 35%) were identified as edentulous, 71 out of 100 (71%; 95% CI 62%, 80%) were identified as dentate, and the dental status was unknown for 3 out of 100 (3%; 95% CI 0, 6.3) Table 4.4-2.

4.4.3.3 Comparison between the dental status 2002-2004 and 2013-2014 cohorts

A chi-square test was conducted across the three variables and a chi-square value of 6.008 and a p-value 0.0496 was calculated. This indicated that there was a statistically significant difference in the dental status between the groups. However, when the comparison was restricted to dentate and edentulous, the chi-square value was found to be 1.857 and a p-value of 0.1729, indicating that the difference between these two groups only, was not statistically significant.

4.4.4 Oral Health Assessment

4.4.4.1 Oral Health Assessment 1st cohort (2002-2004)

19 out of 76 (25%; 95% CI 15%, 35%) case records examined had evidence of an oral health assessment at some point in their care Table 4.4-2

4.4.4.2 Oral Health assessment 2nd cohort 2013-2014

Ten patients were assessed as not fulfilling our inclusion criteria for having a dental assessment at any stage of their care i.e. edentulous and so not requiring a pre-operative dental assessment and not requiring a post-operative assessment as they were either for palliative care or had not had sufficient time to have a post-operative assessment. Of the patients that were evaluated as having had an opportunity for a dental assessment, 56 out of 90 patients (62%; 95% CI 52%, 72%) had a form of oral health assessment / management Table 4.4-2.

4.4.4.3 Comparison between the oral health assessment frequency of 2002-2004 and 2013-2014 cohorts

A chi-square test was carried out between the two groups with regards to oral health assessment and a chi-square value of 23.05 and a p-value of <0.001 was calculated Table 4.4-2. This indicated there was a statistically significant improvement in the frequency of oral health assessments between the 2002-2004 and 2013-2014 cohorts.

4.4.5 Pre-operative dental assessment

4.4.5.1 Pre-operative dental assessment of dentate patients 2002-2004 cohort

Six out of 43 (14%; 95% CI 3.6%, 24%) dentate patients had a pre-operative dental assessment Table 4.4-2.

No dentate patients that had a pre-operative assessment had the gold standard of a dental charting, periodontal screening, dental radiographs and a dental / prevention plan.

4.4.5.2 Pre-operative dental assessment of dentate patients 2013-2014 cohort

Forty-five out of 71 (63%; 95% CI 52%, 75%) of the dentate patients received a pre-operative dental assessment Table 4.4-2.

No dentate patients that had a pre-operative assessment had the gold standard of a dental charting, periodontal screening, dental radiographs and a dental / prevention plan.

4.4.5.3 Comparison between the pre-treatment dental assessment frequency of 2002-2004 and 2013-2014 cohorts

A chi-square test was carried out between the two groups with regards to pre-treatment dental assessment and a chi-square value of 26.463 and a p-value of <0.001 was calculated Table 4.4-2. This indicated there was a statistically significant improvement in the frequency of pre-operative dental assessments between the 2002-2004 and 2013-2014 cohorts.

4.4.6 Post-operative Dental Assessment

4.4.6.1 Post-operative dental assessment of dentate patients 2002-2004 cohort

Fourteen patients out of 76 (18%; 95% CI 10%, 27%) had a post-operative dental assessment Table 4.4-2.

4.4.6.2 Post-operative dental assessment of dentate patients 2013-2014 cohort

Records were assessed regarding post-operative dental assessment. Of the 100 case records examined, 17 were excluded as they were receiving best supportive care and treatment was not expected to be curative. A further 9 were excluded as insufficient time had passed to allow for a post-operative assessment.

Nineteen out of 74 patients (26%; 95% CI 16%, 36%) were identified as having had some form of post-operative assessment / management Table 3.4 2.

4.4.6.3 Comparison between the post-treatment dental assessment frequency of 2002-2004 and 2013-2014 cohorts

A chi-square test was carried out between the two groups with regards to post-operative dental assessment and a chi-square value of 1.499 and a p-value of 0.284 was calculated Table 4.4-2. This indicated that the difference in

frequency of post-operative dental assessments between the two cohorts was not statistically significant.

4.4.7 Pre-treatment and post-treatment dental assessment

4.4.7.1 Pre-operative and post-operative dental assessment of dentate patients 2002-2004 cohort

One dentate patient out of 43 (2%; 95% CI 0%, 6.8%) received a pre- and post-operative dental assessment Table 4.4-2.

4.4.7.2 Pre-operative and post-operative dental assessment of dentate patients 2013-2014 cohort

Eight out of the possible 58 eligible patients (14%; 95% CI 4.9%, 22.7%) were assessed as having had both a pre-op and post-op dental assessment Table 4.4-2.

4.4.7.1 Comparison between the pre-treatment and post-operative dental assessment frequency of 2002-2004 and 2013-2014 cohorts

A chi-square test was carried out between the two groups with regards to post-operative dental assessment and a chi-square value of 4.001 and a p-value of 0.045 was calculated Table 4.4-2. However, due to the small numbers in the sample, a Fisher's exact t-test was carried out which gave a p-value of 0.074. This indicated that the differences between the two groups was not statistically significant.

4.4.8 Radiotherapy

4.4.8.1 Radiotherapy 2002-2004 cohort

Of the 43 dentate patients, 28 (65%; 95% CI 51%, 79%) treatment included radiotherapy, 10 (23%; 95% CI 11%, 36%) treatment did not include radiotherapy, and 5 (12%; 95% CI 2%, 21%) unknown if radiotherapy was used Table 4.4-2.

Of the 28 dentate patients that were known to have had radiotherapy, 5 (18% 95% CI 3.7%, 32%) had a pre-operative dental assessment or pre-operative and post-operative dental assessment Table 4.4-2.

4.4.9 Interviews

Data were extracted relevant to the oral health of the included patients from the interviews.

4.4.9.1 Gum bleeding 2002-2004 cohort

Of the 63 dentate patients who answered the question “Did your gums bleed when you cleaned your teeth?” 34 (54%; 95% CI 42%, 66%) answered “No”, 25 (40%; 95% CI 28%, 52%) answered “Sometimes” and 4 (6%; 95% CI 0%, 12%) answered “Always or almost always” Table 4.4-2.

Of the 63 dentate patients who answered the question “Did your gums bleed when you cleaned your teeth?” 43 had data available from case records. Of those 43, 22 answered “Sometimes” or “Always or almost always”. These records were examined for evidence of a pre-operative dental assessment and 3 patients (14%; 95% CI 0%, 28%) received a pre-operative dental assessment and 19 (86%; 95% CI 72%, 100%) had no record of an assessment Table 4.4-2.

4.4.9.2 Dental attendance 2002-2004 cohort

There were 99 patients who answered the question “During the last 20 years, how often did you go to see a dentist?” 25 (25%; 95% CI 17%, 34%) answered “at least every year”, 27 (27%; 95% CI 18%, 36%) answered “every 2 to 5 years”, 21 (21% 95% CI 13%, 29%) answered “less than every 5 years”, 26 (26%; 95% CI 18%, 35%) answered “never” Table 4.4-2.

Of the 76 patients with case record data available, 30 answered “less than every 5 years” or “never”. Of those 30, 5 patients (17%; 95% CI 3%, 30%) received a pre-operative dental assessment and 19 (83%; 95% CI 70%, 97%) had no record of an assessment Table 4.4-2.

4.5 Discussion

4.5.1 Summary of findings

By examining the records of patients from the first cohort (2002- 2004), it was possible to evaluate if pre-operative and post-operative dental assessments were included in the management of oral cancer. By comparing these data with the management of patients treated more recently, we can assess if there has been an improvement.

Examining the records of the 2002-2004 cohort revealed that only 25% (95% CI 15%, 35%) of patients had evidence of some form of oral health assessment as part of their oral cancer management. This falls below subsequent guidelines (Healthcare Improvement Scotland, 2014, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006, British Association of Head and Neck Oncologists, 2009). Possible explanations for this are either that no oral health assessment was carried out for the majority of patients or that some form of assessment was carried out but was not documented. It is also possible that communications took place e.g. over the telephone, that were not documented in the notes. Even if this has taken place, medico-legally, if there is no documentation in the patient's records, then it is regarded as not having taken place and does not fulfil the General Dental Council's Standards for record keeping (General Dental Council, 2013). It would seem likely considering the historical attitude towards dental assessment and treatment for oral cancer patients, that these assessments simply did not take place (NHS Information Centre, 2013). When examining the most recent data, 62% (95% CI 52%, 72%) of records showed some evidence of oral health assessment. The improvement seen was statistically significant ($p<0.001$). Although this is a dramatic improvement, it still falls short of the recommendations that all patients should have been assessed (British Association of Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

Recently published quality performance indicators set a target of 90% of patients diagnosed with head and neck cancer should receive a pre-operative oral assessment (Healthcare Improvement Scotland, 2014). Now that this area is a

quality performance indicator, it is hoped that this will continue to improve and be prioritised. From the dentate patients treated in the 2002-2004 cohort, 14% (95% CI 4%, 24%) had evidence of a pre-operative assessment prior to cancer treatment. This is of particular concern where radiotherapy has been used as part of their oral cancer care. 65% (95% CI 51%, 79%) of the dentate patients received radiotherapy. Only 18% (95% CI 4%, 32%) of dentate patients who received radiotherapy had a pre-operative dental assessment. It is of concern that 82% (95% CI 68%, 96%) of patients who had radiotherapy did not have a pre-operative dental assessment. It is possible that many of these patients had dental disease that was not managed prior to the radiotherapy increasing the risk of post-operative extractions and of osteoradionecrosis with the associated morbidity of this condition. Data regarding the need for extractions following radiotherapy and how many experienced osteoradionecrosis as a result was not collected, but this may be of interest in further research. From the patients treated in the 2013-2014 cohort, 63% (95% CI 52%, 75%) of dentate patients received a pre-operative dental assessment. This was a statistically significant improvement from the 2002-2004 cohort ($p<0.001$). It may be that guidelines may have influenced practice and increased compliance. Although, an improvement has been seen, this still falls short of the recommendations. It should be noted that for the historical and more recent patients, no patient received a full pre-operative assessment which included a dental charting, periodontal screening and dental radiographs.

Regarding post-operative assessment, 18% (95% CI 10%, 27%) of patients from the historical group received some form of post-operative assessment. Again, this is of concern. The dental needs and complexity of rehabilitation in this cohort of patients is often high and can require specialist input. Guidelines suggest that these patients should have access to specialist dental services as part of their rehabilitation. The risk of complications in these patients, particularly those that have had radiotherapy as part of their care is high and requires careful monitoring and preventive management. From the patients treated more recently, 26% (95% CI 16%, 36%) had evidence of post-operative assessment. This would suggest that there has been little change in the last 10 years and the difference was not statistically significant. However, this finding should be

interpreted with caution. From the historical data, post-operative assessment or care often occurred years after the initial cancer treatment. As the patient records from the most recent cohort were all treated within the previous year, it may be that with time this number will significantly improve. However, even with this in mind, no evidence could be seen in the case records for the majority of patients for a plan for post-operative management, falling below the standard suggested by guidelines (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

The ideal treatment model is that patients receive an oral health assessment prior to and following treatment for oral cancer (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006). From the data extracted from 10 years ago, only one patient or 2% (95% CI 0%, 7%) received this. From the 2013-2014 cohort, 8 patients or 14% (95% CI 5%, 23%) had a pre- and post-operative assessment. This was not seen to be a statistically significant improvement. There is clearly room for improvement with regards to this standard.

Patients who present with oral cancer often have poor oral health and high levels of dental disease. A recent study in the UK examined patients diagnosed with Head and Neck Cancer prior to treatment and found 71% of the dentate patients examined were diagnosed with periodontal disease and 61% presented with one or more carious teeth (Critchlow et al., 2014). The original ARCAGE study interview data from the patients treated 10 years ago would suggest that there were also high levels of disease present. Of the 63 dentate patients who answered the question “Did your gums bleed when you cleaned your teeth?” 34 (54%; 95% CI 42%, 66%) answered “No”, 25 (40%; 95% CI 28%, 52%) answered “Sometimes” and 4 (6%; 95% CI 0%, 12%) answered “Always or almost always”. Gum bleeding may indicate gingival or periodontal disease and is a sign of inflammation. Gum bleeding may also be an indicator of inadequate oral hygiene. On further analysis, 22 patients of the 43 dentate patients with case record data available indicated that their gums bled “Sometimes” or “Always or almost always”. Of these 22 patients, only 3 (14%; 95% CI 0%, 28%) received a pre-operative dental assessment.

To the question “During the last 20 years, how often did you go to see a dentist?” 99 patients responded, 25 (25%; 95% CI 17%, 34%) answered “at least every year”, 27 (27%; 95% CI 18%, 36%) answered “every 2 to 5 years”, 21 (21%; 95% CI 13%, 29%) answered “less than every 5 years”, 26 (26%; 95% CI 18%, 35%) answered “never”. On further analysis, 30 patients of the 76 patients with case record data available answered “less than every 5 years” or “never”. Of these 30 patients, only 5 patients (17%; 95% CI 3%, 30%) received a pre-operative dental assessment.

From these two questions, we see an indicator of dental disease and poor oral care, and poor dental attendance. These findings suggest a level of concern that very few of these patients received a pre-operative dental assessment.

4.5.2 Explanation of findings

The findings of this study show that oral cancer patients have not consistently had pre- and post-operative dental assessments. When patients present with oral cancer, there are a number of considerations which are needed regarding their care and with the focus being on treating the primary tumour and survival; dental assessment and rehabilitation can be overlooked by other healthcare workers and be given low priority by patients (Toljanic et al., 2002). However, over the last decade, there has been a recognition of the importance of these assessments in attempting to reduce co-morbidities and improving outcomes and quality of life following treatment with the publication of a number of guidelines (British Association of Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006).

Results from this study indicate that dental assessments are being carried out more often now than 10 years ago. This may be a reflection of guidelines being adopted and in particular for this cohort of patients in Scotland, guidelines specific to the Scottish population (Scottish Intercollegiate Guidelines Network, 2006). Although dental assessments are being carried out more often than before, it still falls short of recognised standards. It is likely and hoped that this is an area that will continue to improve particularly now that dental assessment is included as a Quality Performance Indicator for head and neck cancer patients

in Scotland and that there will be systems in place to monitor compliance and to continually improve (Healthcare Improvement Scotland, 2014).

Another area for discussion is what these assessments should involve. The guidelines are not specific in what should be assessed and as such, assessments can be carried out which may satisfy requirements for areas such as quality performance indicators, but which may not be ideal for the purposes of reducing morbidity and improving quality of life. For the purposes of this project, three consultants in restorative dentistry were asked for the minimum requirements for a pre-dental assessment and it was suggested that this would include a dental charting, periodontal screening and dental radiographs. It is worth noting that no patient in either the 2002-2004 or 2013-2014 cohorts satisfied these requirements. As such, in addition to the emphasis on carrying out dental assessments, clarification of the detail of what such assessments should comprise would be advantageous and is a potential area for development.

4.5.3 Comparison with literature

The National Head and Neck Cancer Audit in England found that 32.6% of head and neck cancer patients in 2013 received a pre-operative dental assessment. This was an improvement on 2012 which reported 27.8%, but is still significantly short of recommended guidelines (NHS Information Centre, 2013, British Association of Head and Neck Oncologists, 2009).

The results of data collected from the 2013-2014 cohort may indicate that patients treated in Glasgow for oral cancer are above those found in The National Head and Neck Cancer Audit in England with 63% (95% CI 52%, 75%) of patients receiving a pre-operative dental assessment. This finding should be interpreted with caution as there was limited evidence of comprehensive dental assessment in all the case records examined.

A comparison of the frequency of post-operative dental assessment with the literature was not possible as data for this could not be found. This may be a more difficult area to assess as post-operative assessment may not occur for years after treatment and is not considered time-dependant like pre-operative dental assessment. The examination of medical records for the 2002-2004 cohort

is likely to capture the number of patients that had been assessed post-operatively as records were examined up to the point of data extraction, which in many cases was 10+ years and will give a useful picture of the clinical pathway of these patients many years after treatment. The results of this research may serve as a point of comparison for future research in this area and the development of a patient pathway in Scotland.

4.5.4 Strengths

Strengths of this study include the unique opportunity to access historically collected information including data from interviews conducted on the 2002-2004 cohort and relate this to evidence of pre- and post-operative dental and oral assessments. This included access to detailed dental health and lifestyle interview data.

4.5.5 Limitations

However, there were some limitations of the study. Snapshots at two different time periods are presented with very small clinical series cohorts. This should be treated as preliminary pilot data as a basis for further research and conclusions based on the present study should be interpreted with caution.

The validity of the results from the historical data is reduced due to the relatively large number of case records (n=24) that could not be retrieved. Exhaustive efforts were made to attempt to retrieve the records. Possible reasons for the missing records are the records have been destroyed, misplaced, or they are currently in use and could not be tracked by records staff. Although the missing records may represent a random sample of patients, it may be that these patients may differ from the rest of the sample e.g. the patients may be currently undergoing treatment and / or may be undergoing post-operative dental rehabilitation as part of their care. As a result, the results here should be interpreted with some caution. Another limitation of the study is that the sample size (100) from the two cohorts is small and as such, limits our ability to extrapolate the findings to the wider population.

4.5.6 Intervention

The data used for comparison in this project formed part of a clinical audit and has been presented to the relevant practitioners at a clinical governance meeting. Since the data were collected, there has been a formalised inclusion of a Consultant in Restorative Dentistry at the multi-disciplinary meetings (MDTs) within the West of Scotland which take place on a weekly basis and includes discussion of patients recently diagnosed with cancer of the head and neck. There is recognition of the requirement to adhere to guidelines in order to achieve quality performance indicator targets. It is hoped that improvements will continue to be made and that guidelines can be met.

4.6 Conclusions

The findings indicate that there has been an improvement seen in the frequency of pre-operative assessment and joint pre- and post-operative assessment. Little change has been observed in post-operative assessment, although this may be as a result of the relatively short time since treatment. Based on these preliminary data from 2013-2014, the current expected standard of 90% has not been achieved for preoperative dental assessments.

The introduction of quality performance indicators regarding dental assessment and the formalised collection of these data is a positive step and it is hoped that this will continue to improve. The multidisciplinary approach to cancer treatment and the recognition of a Consultant in Restorative Dentistry as a core member of the Head and Neck Cancer MDT are positive moves in the right direction. Further work regarding the nature of the pre-operative dental assessment and the frequency of post-operative dental assessment and management are areas for future research.

5 Discussion

5.1 Oral health and dental care risk association with oral cancer

5.1.1 Published literature

As discussed in the introduction, there are a large number of studies that have examined oral health and dental care factors as risk factors for oral cancer. The volume and often conflicting literature suggested that the most appropriate method of summarising the available evidence was through a systematic review and meta-analysis.

Systematic reviews have been conducted which examine oral health and dental care factors as risk factors for oral cancer and cancer of the head and neck. One systematic review (Radoi and Luce, 2013) examined all risk factors for all oral cavity cancer, including oral health, and qualitatively presented their results. They suggested that the association seen may be confounded by tobacco and alcohol, and that oral health and dental care may not be independent risk factors. However, they acknowledged that the association has been seen even when confounding factors are accounted for in the analysis. They did not attempt a quantitative meta-analysis and their conclusions appear to be based upon a subjective assessment of the literature. The findings of this systematic review are contradictory to this conclusion. It was found in our meta-analyses that when limiting the analysis to studies which had adjusted for smoking and alcohol, the majority of the factors examined were found to be independent risk factors for oral cancer.

Another systematic review (Zeng et al., 2013a) examined periodontal disease as a risk factor for head and neck cancer. They found a statistically significant risk OR 2.63 (95% CI 1.68, 4.14; $p < 0.001$). Although not directly comparable to the findings of this systematic review as they examined head and neck cancer and this study looked at oral cancer, their findings seem to be in general agreement with our own. However, there are a number of potential criticisms of this paper and so their findings should be interpreted with caution. No mention is made regarding contact with authors or an attempt to identify unpublished work. They

did not report on the quality of the studies included. They also included a study in the meta-analysis that had not adjusted for any factors (De Rezende et al., 2008). However, perhaps the greatest criticism is with the inclusion and meta-analysis of studies that used significantly varied criteria for periodontal disease. Indicators of periodontal disease included alveolar bone loss, Community Periodontal Index of Treatment Need (CPITN), clinical attachment loss, tooth mobility and poor condition of mouth. Poor condition of mouth (Guha et al., 2007) was defined as the presence of tartar, gingival bleeding, mucosal irritation and decaying teeth. The use of this factor as a measure of periodontal disease is, in the opinion of this author, inappropriate. The variation between the measures calls into question the appropriateness of combining the studies for the purpose of a meta-analysis and so the validity of their findings.

Another systematic review by the same authors examined tooth loss as a risk factor for head and neck cancer and found that 6 or more missing teeth to be a significant risk factor [6 to 15 teeth loss (OR1.58; 95% CI1.08, 2.32; p=0.02), 11+ teeth loss (OR1.63; 95% CI1.23, 2.14; p<0.001), 15+ teeth loss (OR1.72; 95% CI 1.26, 2.36; p<0.001), and 20+ teeth loss (OR1.89; 95% CI1.27, 2.80; p<0.001)] (Zeng et al., 2013b). Again, although the study is not directly comparable with this systematic review and meta-analysis, as they examined risk for head and neck cancer, their findings would seem to be in general agreement with our own. However, there are a number of criticisms of this study. No mention is made in the paper regarding contact with authors or an attempt to identify unpublished work. They did not report on the quality of the studies included. However, on close inspection a potentially serious error was identified. They included two case-control studies (Lissowska et al., 2003, Fernandez Garrote et al., 2001) as well as large multicentric case-control studies (Guha et al., 2007). In the systematic review presented here, the studies by Lissowska et al 2003 and Garrote et al 2001 were excluded as the data were duplicated in the article by Guha et al 2007 which contained data from a number of other centres. The meta-analysis by Zeng et al 2013 would appear to be invalid by the duplication of data. In order to confirm that the data were the same, contact was made with the corresponding authors for the Lissowska et al 2003 and Garrote et al 2007 papers who confirmed that the same cases and controls were included in the Guha et al 2007 paper. The invalid method as shown by duplication of data

would suggest that no conclusions can be reliably taken from this study and so is not suitable to advise patients and healthcare workers or for influencing policy. In our systematic review we choose to look at the risk for 6 or more missing teeth. Zeng et al 2013 examined a number of ranges of missing teeth and this approach may have certain advantages. A large multicentric study (Guha et al., 2007) found an increased risk of oral cancer with 6-15 missing teeth, but not when there were more than 15 missing teeth. The suggestion that rather than simply missing 6 or more teeth, the number of missing teeth may carry specific risks and so further meta-analysis may be advantageous examining different categories of numbers of missing teeth to clarify this.

Another systematic review and meta-analysis was published during the write up for this thesis which examined ill-fitting dentures and denture use as a risk factor for oral cancer (Manoharan et al., 2014). Ill-fitting dentures was examined as a specific risk factor and they found OR 3.90 (95% CI: 2.48, 6.13). They also examined the presence of a denture as a risk factor and found an increased risk associated OR 1.42 (95% CI 1.01, 1.99). The significantly increased risk seen with ill-fitting dentures would suggest that the associated risk may be related to chronic irritation. Examination of their study showed that they had generally complied with MOOSE guidelines (Stroup et al., 2000). There are some potential criticisms and differences in methodology with our own study which may explain the differing outcomes. They made no attempt to identify unpublished data and so the study by Ahrens et al 2014 was not included. They also included unadjusted data in the main analysis where adjusted data were not available. They included a study (Piemonte et al., 2010) which they cite as a cohort study but we had excluded from our analysis as the study appeared to be a clinical case series. Repeat analysis of this paper confirmed that it was not a cohort study and so did not fulfil our acceptance criteria. Perhaps the biggest difference was their inclusion of studies which had used cancer controls which we had removed due to the risk of overmatching controls. I believe that the systematic review and meta-analysis presented in this thesis represents a closer approximation of the true oral cancer risk associated with denture use due to the strict inclusion criteria of adjusted data from appropriate studies without cancer controls.

5.1.2 Contribution to current evidence

The findings of this systematic review and meta-analysis summarises and clarifies the current evidence for oral health and dental care factors as risk factors. There is no other systematic review and meta-analysis which attempts to examine the full range of oral health and dental care risk factors for oral cancer.

The evidence presented here suggests that oral health factors / dental care factors are significant risk factors for the development of oral cancer with the exception of denture use. The exact aetiology for this is currently unknown, but may be multi-factorial and include chronic irritation of the oral tissues, microbial factors, and relate to proliferation of tissues due to dental disease.

With the finding that oral health / dental care factors are risk factors for oral cancer based on the current evidence, public health policy should be directed towards opportunities to reduce this risk. By making health professionals and patients aware of the risks of poor oral health and dental care, patients should be encouraged to achieve a better standard of oral health and of the importance of good dental care and dental attendance.

5.1.3 What could have been done differently?

I believe that the methods used in this systematic review and meta-analysis are robust. We have complied with good practice regarding systematic reviews and meta-analysis (Stroup et al., 2000). However, due to the broad approach to an examination of oral health and dental care risk factors, further analysis of sub-categories of the factors was not carried out. Examination of factors such as categories of numbers of missing teeth, ill-fitting dentures, duration of denture use and frequency of dental attendance may have provided further understanding of the nature of the risk associated.

5.2 Dental Care Treatment Pathway

5.2.1 Previous literature

The National Head and Neck Cancer Audit in England found that 32.6% of head and neck cancer patients in 2013 received a pre-operative dental assessment. This was an improvement on 2012 which reported 27.8%, but is still significantly short of recommended guidelines that state that all head and neck cancer patients should receive a pre-treatment oral health assessment (NHS Information Centre, 2013, British Association of Head and Neck Oncologists, 2009) and the Quality Performance Indicator for head and neck cancer patients within Scotland (Healthcare Improvement Scotland, 2014).

There does not appear to be published studies citing the frequency of post-treatment dental assessments as part of the care of oral cancer patients or head and neck cancer patients who may have adverse oral health symptoms associated with radiotherapy or chemotherapy as a result of poor oral health.

5.2.2 Contribution to current evidence

There is a lack of evidence regarding dental assessments as part of the care of patients with head and neck cancer within Scotland. The evidence presented here shows the frequency and nature of these assessments over two time periods 2002-2004 and 2013-2014. The collection of these data allowing for a comparison over time may give some indication of the changes in treatment philosophies over time and with the introduction of guidelines (Scottish Intercollegiate Guidelines Network, 2006)

The evidence presented would suggest that an improvement has been seen in the frequency of pre-operative dental assessments, however there is still room for significant improvement. This evidence may highlight the need for further improvements in the services provided and serve as a point of reference for future research. The introduction of a quality performance indicator in Scotland for oral cancer requiring that patients have a pre-operative dental assessment is welcome and it would seem likely that this will see an improvement over time. Careful monitoring of compliance is encouraged and universal adoption of a restorative dentist at head and neck oncology as part of the multi-disciplinary

team and formalised pathways to ensure that assessments are carried out is recommended.

A search of the grey literature identified an example of a pre-radiotherapy pathway for head and neck cancer patients that aims to ensure that patients receive dental assessments and by the appropriate individuals (Appendix F). Development and adoption of similar tailored pathways within heath boards in Scotland may help to formalise processes already in place and aid with achieving quality performance indicators and ultimately, reduce morbidity and improve quality of life for oral cancer patients.

Much of the published data focuses on pre-operative dental assessments and there is little known about the frequency of post-operative dental assessments despite guidelines highlighting their importance (National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006). The findings of this study highlights the need for improvement and for consideration of post-operative dental assessments to be examined and monitored as well as pre-operative dental assessments. This research can serve as a point of comparison for future research.

5.2.3 What could have been done differently?

This research has highlighted the potential limitations of the current service and services as useful pilot data for future research. However, the retrospective collection of the data for the 2002-2004 cohort, the number of missing records and the small sample size from both cohorts do limit the conclusions that can be made. In order to monitor compliance and assess current practice, this should be done prospectively, with set criteria and a larger sample. This will be undertaken by the use of quality performance indicators and monitoring. It does not however, allow for monitoring of the nature of these assessments or collect data regarding post-operative dental care.

5.3 Conclusions

Oral health and dental care are important in both the risk of oral cancer and the management of oral cancer. The available evidence indicates that general oral

health, gum bleeding, oral hygiene, missing teeth, dental attendance and frequency of toothbrushing are all risk factors for oral cancer. Denture use is not associated with an increased risk of oral cancer. There are only limited numbers of large, high quality studies examining oral health and dental care as risk factors to base these conclusions on, and caution is advised in interpreting these results, especially where the findings do not hold up to sensitivity analysis where only higher quality studies or larger studies are included. Current risk profiling for oral cancer risk considers smoking, alcohol and socioeconomic status (Conway et al., 2015). This research makes the case for oral health and dental care factors to be considered in the risk assessment process.

Dental assessment is an important part of the management of oral cancer patients. An improvement in the frequency of pre-operative dental assessments have been seen, however, compliance has not been achieved. Post-operative dental assessments have not seen a significant improvement and compliance is difficult to assess against other research as there is little published work in this area. As compliance has not been achieved, further efforts should be made to attempt to ensure patients are assessed as appropriate. In addition to ensuring a dental assessment is carried out, clarification and guidance on what constitutes an adequate dental assessment for oncology patients is required.

5.4 Recommendations for research

Further research is required to either confirm or refute the association between oral health and dental care factors as risk factors for oral cancer. This should be ideally done with large, high quality studies. Agreed standards for methodology should be agreed on and adhered to. Of particular relevance, is the need to standardise the measures used for assessing oral health and dental care factors to aid future meta-analysis and comparison of studies.

The use of an individual participant data approach to future meta-analyses may improve the estimate of risk and better manage the heterogeneity of the studies (Conway et al., 2009, Riley et al., 2010).

The need for dental assessments as part of the care of patients with head and neck cancer is recommended by a number of guidelines (British Association of

Head and Neck Oncologists, 2009, National Institute for Clinical Excellence, 2004, Scottish Intercollegiate Guidelines Network, 2006). However, little is known regarding the impact that this has on patients in terms of reduced complications and improved quality of life and there are a lack of high quality studies in this area (Eliyas et al., 2013). Further research is required to establish a stronger evidence base for current recommendations. A systematic review of the pre- and post-operative dental assessment evidence base, timings, inclusion and level of expertise required for head and neck cancer patients may help clarify the current evidence and highlight specific areas that require further research and facilitate the development of guidelines.

With the introduction of quality performance indicators, compliance should be monitored and influence policy to improve outcomes for patients. In addition, there is little available evidence on the frequency of post-operative dental assessments following oral cancer treatment. Further research in this area is recommended.

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Appendices

Appendix A

Search strategy used Ovid Medline and Embase

1. oral cancer.mp. or exp Mouth Neoplasms
2. pharyngeal cancer.mp. or exp Pharyngeal Neoplasms
3. laryngeal cancer.mp. or exp Laryngeal Neoplasms
4. esophageal cancer.mp. or exp Esophageal Neoplasms
5. 1 or 2 or 3 or 4
6. oral health.mp. or exp Oral Health
7. oral hygiene.mp. or exp Oral Hygiene
8. toothbrushing.mp. or exp Toothbrushing
9. Dental caries.mp. or exp Dental Caries
10. dental care.mp. or exp Dental Care
11. dental attendance.mp.
12. dental prosthesis.mp. or exp Dental Prosthesis
13. partial denture.mp. or exp Denture, Partial
14. complete denture.mp. or exp Denture, Complete
15. Periodontitis.mp. or exp Chronic Periodontitis/ or exp Aggressive Periodontitis/ or exp Periodontitis/ or exp Periapical Periodontitis
16. exp Gingivitis/ or Gingivitis.mp.
17. exp Jaw, Edentulous, Partially/ or missing teeth.mp. or exp Tooth Loss
18. mouthwash.mp. or exp Mouthwashes
19. exp Dentures
20. denture*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol

supplementary concept, rare disease supplementary concept, unique identifier]

21. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 5 and 21

23. remove duplicates from 22

Appendix B

Search Strategy used for Web of Science

24 #23 AND #11
Timespan=All Years
Search language=English Lemmatization=On

23 #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12
Timespan=All Years
Search language=English Lemmatization=On

22 Topic=(gingivitis)
Timespan=All Years
Search language=English Lemmatization=On

21 Topic=(mouthwash)
Timespan=All Years
Search language=English Lemmatization=On

20 Topic=(edentulous)
Timespan=All Years
Search language=English Lemmatization=On

19 Topic=(missing teeth)
Timespan=All Years
Search language=English Lemmatization=On

18 Topic=(periodontitis*)
Timespan=All Years
Search language=English Lemmatization=On

17 Topic=(denture*)
Timespan=All Years
Search language=English Lemmatization=On

16 Topic=(dental prosthesis)
Timespan=All Years
Search language=English Lemmatization=On

15 Topic=(dental attendance)
Timespan=All Years
Search language=English Lemmatization=On

14 Topic=(dental caries)
Timespan=All Years
Search language=English Lemmatization=On

13 Topic=(toothbrushing)
Timespan=All Years
Search language=English Lemmatization=On

12 Topic=(oral hygiene)
Timespan=All Years
Search language=English Lemmatization=On

11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
Timespan=All Years
Search language=English Lemmatization=On

10 Topic=(laryngeal cancer)
Timespan=All Years
Search language=English Lemmatization=On

9 Topic=(esophageal cancer)
Timespan=All Years
Search language=English Lemmatization=On

8 Topic=(esophageal neoplasm*)
Timespan=All Years
Search language=English Lemmatization=On

7 Topic=(laryngeal neoplasm*)
Timespan=All Years
Search language=English Lemmatization=On

6 Topic=(mouth neoplasm*)
Timespan=All Years
Search language=English Lemmatization=On

5 Topic=(Oral neoplasm*)
Timespan=All Years
Search language=English Lemmatization=On

4 Topic=(pharyngeal neoplasm*)
Timespan=All Years
Search language=English Lemmatization=On

3 Topic=(pharyngeal cancer)
Timespan=All Years
Search language=English Lemmatization=On

2 Topic=(mouth cancer)
Timespan=All Years
Search language=English Lemmatization=On

1 Topic=(Oral cancer)
Timespan=All Years
Search language=English Lemmatization=On

Appendix C

Excluded studies with reasons

	Study ID	Reason for exclusion
1	(Abnet et al., 2005a)	Gastric cancer only. No oral cancer data
2	(Abnet et al., 2008)	Esophageal cancer only
3	(Abnet et al., 2001)	Esophageal and gastric cancers only
4	(Abnet et al., 2005b)	Gastric cancer only
5	(Adewole, 2002)	No oral health data/ case series
6	(Ahn et al., 2012)	Mortality data only
7	(Aida et al., 2011)	Mortality data only
8	(Albuquerque et al., 2011a)	No control group
9	(Albuquerque et al., 2011b)	Cancer controls / case series
10	(Alsos, 1960)	No control / case series
11	(Andreasson et al., 1984)	Unable to calculate risk
12	(Audi, 1975)	No control / case series
13	(Baric et al., 1982)	No cancer data
14	(Behnoud et al., 2011)	No control / case series
15	(Bratoicheva and Kondeva, 2008)	Case series

16	(Bruzzi et al., 1983)	No oral health data
17	(Bundgaard et al., 1988)	No oral health data
18	(Bundgaard et al., 1994)	No control
19	(Campbell et al., 1997)	Cancer control group
20	(Datta et al., 1997)	No separate oral health data
21	(David Piemonte et al., 2010)	Case series
22	(Elwood et al., 1984)	Cancer controls
23	(Escribano Uzcudun et al., 2002)	Pharyngeal cancer only
24	(Fernandez Garrote et al., 2001)	Duplication of data
25	(Groome et al., 2011)	Early versus late endpoint
26	(Hiraki et al., 2008)	Unable to separate out oral cancer data
27	(Holmes Jr et al., 2009)	Cross sectional study
28	(Jahn et al., 2007)	Survey / no control
29	(Kabat et al., 1989)	Cancer controls
30	(Lewin et al., 1998)	No oral health data presented. Attempt at contracting authors unsuccessful

31	(Lissowska et al., 2003)	Duplication of data
32	(Llewellyn et al., 2003)	Case series
33	(Ma et al., 1995)	Self control / case series
34	(Macfarlane et al., 2010)	Duplication of data
35	(Maier et al., 1991)	No separate oral cancer data
36	(Maier et al., 1993)	No separate oral cancer data
37	(Marques et al., 2008)	Duplication of data
38	(Morris et al., 2000)	No control
39	(Nemes et al., 2006)	No control, case series
40	(Nemes et al., 2008)	No control, case series
41	(Olasz and Szabo, 1989)	Unable to separate out oral cancer data from head and neck cancer data
42	(Paymaster, 1962)	No control, oral health data not presented
43	(Shashi et al., 2009)	Cancer controls and no OH data
44	(Tezal et al., 2005)	Unable to separate out oral cancer data
45	(Tezal et al., 2007)	Duplicate
46	(Tripathy et al., 2010)	Case series
47	(Tuli et al., 2003)	Case series

48	(Wahi et al., 1965)	No control
49	(Wang et al., 1992)	Esophageal cancer only
50	(Whitaker et al., 1979)	Cancer controls
51	(Wunsch, 2002)	Review article
52	(Young et al., 1986)	Cancer controls
53	(Gorsky and Silverman, 1984)	No control / case series
54	(Davies, 2001)	General oral health survey / incorrect methodology
55	(Fahmy et al., 1983)	Data not extractable for meta-analysis. Qualitative discussion of results presented
56	(Franco et al., 1989)	Duplication
57	(Perriman, 1973)	Case series
58	(Vogler et al., 1962)	Case series
59	(Wynder and Bross, 1961)	No oral health data
60	(Lockhart et al., 1998)	Case series
61	(Guneri et al., 2005)	Unable to merge data in meta-analysis. Qualitative analysis included in review
62	(Tezal et al., 2009)	Unable to merge data in meta-analysis. Qualitative analysis included in review
63	(Shanta and Krishnamurthi, 1964)	Unable to merge data in meta-analysis. Qualitative analysis included in review

64	(Graham et al., 1977)	Unable to merge data in meta-analysis. Qualitative analysis included in review
65	(Michaud et al., 2008)	Unable to merge data in meta-analysis. Qualitative analysis included in review
66	(Rosenquist et al., 2005)	Duplication

Appendix D

ARCAGE data extraction form with oral health assessment questions

Country: _____ **Center:** _____ **Hospital id number** |__| |__| |__|__|__|__|

ARCAGE id number |__| |__| |__|__|__|__| **Form completed on (dd/mm/yyyy):**_____

Source of information for vital status & disease status (check all that apply):

☐ Cancer registry ☐ Mortality registry/vital statistics

☐ Death certificates ☐ Contact with patient or patient's family

☐ Contact with the physician ☐ Medical charts

☐ Other, specify:_____ ☐ Unknown

1) Vital status at last contact: ☐ Alive ☐ Dead ☐ No follow-up after diagnosis

Date last known to be alive or dead (dd/mm/yyyy): _____

If dead, primary cause of death:

ICD-10 code: |__|__|__|__| if available, ***only if not available*** select one of the following:

☐ UADT cancer ☐Other cancer ☐ Toxicity from treatment of primary cancer

☐ Infection ☐Cardiovascular disease ☐ Other causes, specify:_____ ☐ Unknown

2) For all cases, disease status in the course of recovery:

a) **Complete regression** ☐ Yes ☐ No ☐ Not known

b) **Relapse:** ☐ Yes ☐ No ☐ Not known

If yes: Date of diagnosis: _____

☐local recurrence ☐ systemic relapse (Metastasis) ☐ Not known

c) **2nd Primary:** ☐ Yes ☐ No ☐ Not known If yes: Date of diagnosis: _____

Site (ICD O3) **|C|** |__||__| . |__| Histology (ICD O3) : |__||__||__||__| / |__|

3) Treatment of primary tumour

Source of information: ☐ Medical records ☐ Others, specify:_____

Radiotherapy: ☐Yes ☐No ☐Not known

If yes: Type of radiotherapy: ☐External ☐Internal ☐Not known

Surgery: ☐Yes ☐No ☐Not known

If yes: Type of surgery: ☐Resection of primary ☐Node/ neck dissection ☐Not known

Chemotherapy: ☐Yes, drug(s) name …….. ☐No ☐Not known

If yes: Type of chemotherapy: ☐Induction ☐Concurrent ☐Adjuvant ☐Alone ☐Not known

Treatment completed: ☐Yes ☐No ☐Not known

4) Co-morbities:

Source of information: ☐ Medical records ☐Cancer Registry ☐Others, specify:_____

List, in English, the conditions that were present in the medical history at the time of initial diagnosis/treatment:

_____

_____

And code each to ICD-10

_____

5) Oral Health assessment

Source of original referral: ☐GMP ☐GDP ☐Other

If other, please give details

_____

Is the patient registered with a dentist? ☐Yes ☐No ☐Not known

Has the patient had an oral health/ dental assessment: ☐Yes ☐No ☐Not known

If yes, was this carried out: ☐ Pre-cancer treatment ☐ Post cancer treatment

If post-cancer, please give details (time from start of cancer treatment)

_____

If oral health assessment carried out, is the patient: ☐ Dentate (has natural teeth) ☐ Edentulous (no teeth)

If dentate, is there a record of

Dental charting ☐Yes ☐No ☐Not known

Periodontal screening e.g. BPE ☐Yes ☐No ☐Not known

Dental Radiographs ☐Yes ☐No ☐Not known

Evidence of a dental treatment/ prevention plan ☐Yes ☐No ☐Not known

If yes, please give details

Additional information/comments:

Appendix E

ARCAGE Ethics Approval Form

Greater Glasgow and Clyde

Coordinator/Administrator: Dr Erica Packard/Mrs Elaine O'Neill
Telephone Number: 0141 211 6208
E-Mail: erica.packard@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

R&D Management Office
Western Infirmary
Tennent Institute
1st Floor 38 Church Street
Glasgow, G11 6NT,

4 September 2012

Dr David Conway
Clinical Sr Lecturer in Dental Public Health
Glasgow University
Glasgow Dental Hospital
378 Sauchiehall Street
Glasgow G2 3JZ

NHS GG&C Board Approval

Dear Dr Conway,

Study Title:	**Investigation into the role of HPV in the aetiology of head and neck cancer – an analysis of the Alcohol-Related Cancers And Genetic-susceptibility in Europe (ARCAGE) study – within the International Head and Neck Cancers Epidemiology (INHANCE) consortium.**
Principal Investigator:	**Dr David Conway**
GG&C HB site	**Glasgow Dental Hospital**
Sponsor	**University of Glasgow**
R&D reference:	**GN12DN168**
REC reference:	**10/S0703/44**
Protocol no: (including version and date)	**V3; June 2012**

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

NHS
Greater Glasgow and Clyde

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a monthly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures
   e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

EPackard

Dr Erica Packard
Research Co-ordinator

Cc: Dr Debra Stuart

Appendix F

Yorkshire Pre-Radiotherapy Pathway for Head and Neck Cancer Patients