Risk Prediction Modelling in Head and Neck Cancer:

Development and Validation of a Model using the UK Biobank

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by Caroline Elizabeth McCarthy.

December 2018

Abstract

Risk Prediction Modelling in Head and Neck Cancer: Development and Validation of a Model using the UK Biobank.

Caroline Elizabeth McCarthy

Introduction and Aims

Head and Neck Cancer (HNC) is the sixth most common cancer worldwide and it causes significant morbidity and mortality. A risk prediction model could help to stratify patients according to risk of disease and be used in the design of clinical trials to aid selection of participants. This thesis concerns the development and validation of a risk prediction model for absolute risk of HNC, using the UK Biobank dataset. The changes in incidence of HNC in England between 2002-2011 will be explored and novel female-specific risk factors will be reviewed.

Methods

The model has been developed within the UK Biobank dataset, using logistic regression. The internal validity of the model was assessed using discrimination and calibration statistics. The model was externally validated within a cohort of the UK Biobank not used to develop the original model.

Results

The risk model developed contains variables for age, smoking, gender, alcohol, diet, household income, BMI, number of sexual partners, fruit consumption and exercise. The c-statistic was 0.67 and the model displayed good calibration. On external validation, the c-statistic was 0.64 with good calibration.

Conclusions

Methods for assessing the implementation and impact of the model are discussed.
The model has shown reasonable performance through internal and external validation methods. Risk prediction models have the potential to inform the design of future clinical trials in HNC and this could be translated to work in OED.

Acknowledgements

I have received guidance, support and teaching in abundance. I am grateful for this opportunity to acknowledge some of the individuals involved. Firstly, Dr Laura Bonnett. You have a wonderful ability to know when to teach me something and when to guide me. I have learned so much from you about risk modelling and I have really enjoyed our meetings. I hope we can work together regularly in the future. Thank you. Dr. Michael Marcus taught me everything I needed to know about statistics and statistical software, by guiding me through weekly tutorials. Your support as a teacher and a friend has been significant for me and I am thankful for your encouragement, especially when things were difficult. Professor John Field was the inspiration behind this project and I am privileged to have received his guidance and support throughout. Both Professor John Field and Professor Anne Field are passionate about the future of academic Oral Medicine and they have supported me, unwaveringly, to get to this point. My other clinical colleagues have been understanding about the challenges of splitting my time between clinical and academic work and I am grateful for this. Professor Alan McCarthy, my Father-in-Law, has been the voice of wisdom and experience when it comes to completing a PhD. I am immensely grateful for his thorough review of this thesis and helpful comments. I have enjoyed our conversations on the way to work. I hope that I can mirror the respect and value you have for your students, if I am fortunate to be in a similar role in the future.

My husband, Liam. Your love and consistency always amaze me. Thank you for giving me two incredible children, who are loved more than they know. Anna and Ned, you delight us. Anna, keep drawing flowers. Ned, keep singing. Thank you for helping me to keep things in perspective. You are far more important than this!

My Mum would have been proud of this and my Dad is proud. Thank you to my whole family, for raising me to believe that, with God, anything is possible.

Table of Contents

List of Tables

List of Figures

Abbreviations

ANOVA	Analysis of Variance
AU(RO)C	Area Under the (Receiver Operating) Curve
BAHNO	British Association of Head and Neck Oncologists
BMI	Body Mass Index
CCT	Controlled Clinical Trial (non-randomised)
CT	Computed Tomography
E/O	Expected/Observed ratio
EPV	Events per Variable
ESP	European Standard Population
HNC	Head and Neck Cancer
HPV	Human papillomavirus
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
INHANCE	International Head and Neck Cancer Epidemiology Consortium
LLP	Liverpool Lung Project
LOOCV	Leave-One-Out Cross Validation
MET	Metabolic Equivalent
MI	Multiple Imputation
MSOA	Middle Super Output Area
MT/MTT	Malignant Transformation/Mean Time to Transformation
NICE	National Institute for Health and Care Excellence
NOS	Newcastle Ottawa Scale
NS-SEC	National Statistics Socio-Economic Class
OED	Oral Epithelial Dysplasia
ONS	Office for National Statistics
OR	Odds Ratio
OSCC	Oral Squamous Cell Carcinoma
PDT	Photodynamic Therapy
PLCO	Prostate, Lung, Colorectal, Ovarian
RCT	Randomised Controlled Trial
RR	Relative Risk/Risk Ratio
SCC	Squamous Cell Carcinoma
SES	Socio-Economic Status
TNM	Tumour, Nodal Spread, Distant Metastases
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
UKACR	United Kingdom Association of Cancer Registries

Chapter 1

Introduction

This chapter discusses Head and Neck Cancer (HNC) and summarises the incidence of the disease according to geographical regions, gender and age (section 1.1). It then goes on to discuss potential risk factors (section 1.2) and, briefly, cancer screening for other cancers (1.3.1). Risk prediction modelling is introduced in 1.3.2 with two examples of risk models developed for related conditions.

1.1 Head and Neck Cancer

The term 'Head and Neck Cancer' [HNC] refers to a heterogenous group of cancers affecting various sites of the head and neck, including the lip and oral cavity, salivary glands, pharynx, larynx, nasal cavity and paranasal sinuses (1), each with its own risk factor profile. Figure 1.1 shows these anatomical sub-sites.

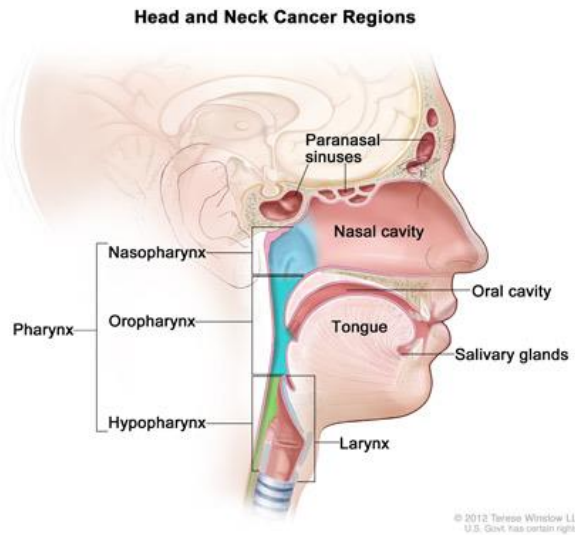


Figure 1.1. *Diagram showing sub-sites of Head and Neck Cancer.*
Image from https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet

According to the United Kingdom Association of Cancer Registries (UKACR), in their Library of recommendations on cancer coding and classification policy and practice (2), HNC includes cancers of the following sub-sites (International Classification of Diseases (ICD) codes are shown in parenthesis): oral cavity (C00-06), salivary glands (C07-08), tonsil and oropharynx (C09-10), nasopharynx (C11), piriform sinus (C12), hypopharynx (C13), base of tongue (C02.9), nasal cavity and middle ear (C30), accessory sinuses (C31) and larynx (C32). The term "oropharyngeal cancer" includes cancers of the base of tongue, tonsil, soft palate and pharyngeal walls.

There has been wide variation in the definition of HNC in the literature, with some papers including cervical oesophagus or thyroid gland (3, 4).

In the UK, there were 12,061 cases of HNC in 2015 and 4,047 deaths in 2016 (5). Over 90% of HNC are thought to be preventable. HNC is the eighth most common cancer in the UK and incidence rates have risen by 30% over the last 30 years (5).

An overall incidence for HNC of 19.9 per 100,000 persons was reported in the UK in 2015, by Cancer Research UK. Incidence varies depending on sub-site, with nasopharyngeal cancer and oral cavity cancer having incidences of 0.49 and 3.13 per 100,000 persons respectively (data from 2000-2004, South East England; Thames Cancer Registry) (1).

1.1.1 Geographical Variation

There is wide geographical variation in incidence, worldwide, with the highest incidence in South and Southeast Asia (Sri Lanka, India, Pakistan and Taiwan). Oral cancer is the most common cancer in males in Sri Lanka (incidence 10.2 per 100,000) and this is likely to be due to specific risk factors such as chewing of smokeless tobacco (6). In India, an average of 100,000 new cases of oral cancer per year are reported, in comparison to 4,564 in the UK in 2010 (5). Parts of Western Europe (e.g. France), Eastern Europe (e.g. Hungary and Slovakia), Latin America and the Caribbean (e.g. Brazil, Uruguay and Puerto Rico) and the Pacific regions (e.g. Papua New Guinea and Melanesia) also have high incidences of oral cancer (6).

Within the UK, there are variations in incidence, with Scotland reporting a higher incidence of HNC than the rest of the UK; the incidence in Scotland increased from 12.57 to 22.04 per 100,000 between 1975 and 2012 (7). Up to 2010, the middle super output area (MSOA) of Liverpool experienced a peak incidence of HNC of 35 per 100,000, which is higher than less economically developed areas of the Indian subcontinent for example (8).

1.1.2 Gender

Gender differences in incidence of HNC are marked, with 64.3-78.6% of HNC patients being male (1, 9-12), however, an increasing incidence in females has been noted (13, 14). Males are three times more likely than females to develop HNC in the UK (incidence 12.7 per 100,000 vs 4.9 per 100,000) (1). In the USA, the percentage of women affected increased from 40% to 45% between 1990 and 2004 and this is thought to be due to changes in smoking habits between men and women (13).

1.1.3 Age

HNC has higher incidence in older age groups; most tumours develop in persons in the fifth and sixth decade (1, 10, 11, 15). 60% of HNC patients in the UK are aged between 40 and 69 years and this is similar for the rest of the world (1). Canada reports 60% of HNC patients are over the age of 60 years (11). In the Middle East, 51% are in the 50-69 years age category (10) and 50% are aged 60-79 years in Germany (15). More recently, a trend for younger individuals developing HNC has been noticed, particularly in the USA and Scotland (13, 16). In Scotland, where this trend was first reported, the incidence rate in males under 45 years of age more than doubled, from 0.6 to 1.3 per 100,000, between 1990 and 1999 (7).

1.1.4 Global changes in Incidence of HNC

Changes in incidence of HNC/oral cancer, over different time periods, have been reported (1, 10, 11, 17, 18). In the UK, between 2002 and 2006, certain sub-types of HNC demonstrated a significant increase in incidence: oropharyngeal cancer doubled in incidence and oral cancer has been rising by 2.7% per year for the last twenty years (19). There has been an increase of 12% in males and 11% in females in the UK between 1995-1999 and 2000-2004 (1). In the same period, the incidence of

laryngeal cancer decreased by 16% in males and 14% in females, possibly due to a decrease in smoking (1).

In Europe, the incidence of oral cancer has been steadily increasing over the last two decades, although reports vary in whether or not they include the sub-site of the oropharynx (5). In the Netherlands, a 0.5-2% annual increase in oral cavity cancer and 2.3-3% annual increase in oropharyngeal cancer was noted between 1989 and 2006 (17). Canada reported a decrease in incidence from 10.7 to 8.8 per 100,000 for oral cancer between 1992 and 2009 and an increase in oropharyngeal cancer from 1.6 to 2.6 per 100,000 in the same period (11). Croatia reported a 24% decrease in HNC from 1988 to 2008 (18) whilst Denmark reported an increase of 5 per 100,000 between 1982-2007 (10). In Australia, between 1982 and 2005, cancers of the base of tongue and tonsil increased in incidence by 1.39% and 3.02% respectively in males (20). Oral cavity cancers decreased by 1.69% in the same time-frame (20). The general trend is that the incidence of oropharyngeal cancer is rapidly increasing. Human papillomavirus (HPV) infection is strongly implicated as a risk factor for oropharyngeal cancer and will be discussed in section 1.2.4 (20).

1.2 Risk Factors

Smoking and alcohol are significant risk factors for HNC and will be discussed in 1.2.1. Other risk factors will be considered in sections 1.2.3 – 1.2.8, including diet, HPV, periodontal disease and socio-economic status.

1.2.1 Tobacco and Alcohol

Tobacco smoking, chewing tobacco and alcohol cause 75% of HNC (21). Tobacco and alcohol act synergistically, as well as independently (21). The relative risk for heavy smokers who consume 100-180g/ethanol per day (a heavy drinker) is 50.1 (95% CI 33.54 – 74.91), compared to 6.21 (95% CI 3.76–10.24) for heavy smokers who only drink 0 – 24g ethanol/day and 2.27 (95% 1.11–4.63) for a heavy drinker who does not smoke (22). The risk of HNC related to smoking increases with increasing frequency, duration and pack years (23). (Pack years is calculated as: number of cigarettes

smoked per day/20 × number of years smoked). Earlier age of starting smoking is also associated with increased risk (23). It is known that mortality rates from HNC are higher amongst smokers (19).

The main risk factor in non-smokers is alcohol consumption and in those who do not consume alcohol, the main risk factor is smoking (23). Alcohol increases mucosal permeability and therefore allows increased uptake of carcinogens (24). As with smoking tobacco, the risk of HNC attributed to alcohol increases with daily quantity, duration of consumption and lifetime cumulative consumption (23). Research has been carried out into the effects of different types of alcohol, with varying results (25, 26); it appears that the quantity and the alcoholic content of the beverage consumed is most important (23).

1.2.1.1 Smokeless Tobacco

Smokeless tobacco is widely used in certain populations (27, 28). Betel quid (paan/areca nut) is popular amongst Bangladeshi women and this extends to ethnic groups in the UK (28). Risk increases with quantity used and duration of use (23). The betel nut is held against the oral mucosa for long periods and may or may not be mixed with tobacco. Adding tobacco increases carcinogenesis, and in Asia, the use of betel quid is a stronger risk factor for oral cancer than smoking (23). It seems to exert strongest effect on the gingivae, with a markedly increased risk of gingival carcinoma amongst users when compared to tongue cancer (23).

1.2.3 Diet

Poor diet is thought to account for 10-15% of oral/pharyngeal cancers (23). Intake of fruits and vegetables may protect against HNC (29). A large prospective study conducted by the National Institute of Health, in a cohort of 490,802 members of the American Association of Retired Persons (NIH-AARP) followed-up from 1995/1996 to 2000, showed that intake of vegetables had a more profound effect (Hazard Ratio [HR] 0.65, 95% CI 0.50-0.85) in reducing the risk of developing HNC than fruits (HR 0.87, 95%CI 0.68-1.11)(29). Cereals, butter, olive oil, grilled meat, fresh fish, pork and shellfish have all been explored with varying results regarding protective and harmful effects (23). Consuming Maté (a herbal tea from South America) is known to increase

risk of oral cancer by 2.5 to 3.7 times (23). Salted fish, consumed by Chinese populations, has also been found to increase the risk of nasopharyngeal carcinomas (28).

1.2.4 Human papillomavirus

Human papillomavirus infection [HPV] is rapidly emerging as a major cause of oropharyngeal cancer (OPC) and is thought to account for 20-25% of HNC (11, 20, 21). It is sexually transmitted and, therefore, individuals most at risk are those with early-age sexual activity and a high number of sexual partners (30). A UK multi-centre study of HPV status of oropharyngeal cancers revealed that 51.8% (95% CI:49.3 - 54.4) were HPV positive (31), whilst figures for oral cancer and laryngeal cancer were 23.5% and 24% respectively (32). Some studies report HPV detection in over 80% of oropharyngeal cancers, however it is important to remember that detection does not imply causation (10% of benign oral samples were found to be HPV positive) (23). Interestingly, the rapid increase in the incidence of OPC (section 1.1.4) is not paralleled with an increase in the proportion of HPV-positive cases of OPC (31). This demonstrates the need for further work into the underlying reasons for the increasing incidence of OPC cancers.

1.2.5 Ethnic-Specific Risk Factors

Ethnicity alone is not considered a risk factor for HNC, however ethnic-specific risk factors (such as betel quid use, discussed in 1.2.4) are very important (23). Interestingly, oropharyngeal cancer has much lower incidence in ethnic groups compared to white males and the incidence is lowest amongst black Africans (28). Incidence rates for cancer of the hypopharynx and salivary glands, which are not influenced as much by traditional risk factors, are very similar for ethnic minority groups and non-ethnic minority groups, which further supports the argument that ethnic-specific risk factors are responsible for the higher incidence of other HNC's in ethnic-minority groups, rather than ethnicity alone (28).

1.2.6 Periodontal Disease

Periodontal disease and poor oral health have been investigated as possible risk factors for HNC. Eliot *et al*. reported an Odds Ratio [OR] of 1.09 (95%CI 1.02-1.16) for

periodontal disease, controlling for smoking, in a case-control study of 513 cases and 567 controls (33). This supports the findings of another study which found that increasing alveolar bone loss is associated with an increased risk of HNC (34). Periodontal disease involves a shift in the bacterial flora in the gums, accompanied by a potentially pathogenic inflammatory response, which may lead to alterations in the immune system, increased cellular proliferation and the generation of DNA-damaging free radicals (33).

1.2.7 Socio-economic Status

Low socio-economic status (SES) is known to be a risk factor for many diseases and has been recognised as a significant risk factor for HNC (35). Although SES is highly correlated with other risk factors, such as smoking and alcohol consumption (16), there remains a significant proportion of risk associated with social deprivation that cannot be attributed to other risk factors (35).

HNC is more common in low socio-economic groups and those with lower educational attainment (OR 1.9, 95%CI 1.6-2.3) (23). Low educational attainment remained as a risk factor for HNC, when controlling for age, sex, smoking, alcohol and diet (OR 1.34 95% CI 1.04 – 1.73) in a meta-analysis of 16 studies with 4,395 cases of HNC (35). Low household income was also associated with an increased risk of HNC, in a meta-analysis of 8 studies with 1,048 cases of HNC (OR 1.56 95% CI 1.29 – 1.88), controlling for age, sex, smoking and alcohol (35).

A meta-analysis of 41 case-control studies (15,344 cases and 33, 852 controls) investigated the impact of SES on oral / oropharyngeal cancer risk. Low income, low occupational social class, and low educational attainment were all associated with HNC (36). Compared with individuals who were in high SES strata, the pooled ORs for the risk of developing oral cancer were 1.85 (95%CI 1.60- 2.15) in 37 studies for those with low educational attainment, 1.84 (95%CI 1.47-2.31) in 14 studies for those with low occupational social class, and 2.41 (95%CI 1.59-3.65) in 5 studies for those with low income (36).

The effect of poor education on health, lack of access to healthcare, hygiene, poor nutrition, unfavourable working environments and poor living conditions may

contribute to causation of oral cancer via complex interactions with well-established risk factors such as smoking and alcohol (35, 36). The high incidence in Liverpool (described in section 1.1.1) is likely to be linked, in part, to social deprivation; Liverpool was rated the most deprived local authority in England in 2010 (8).

1.2.8 Occupational Risk Factors

The International Agency for Research on Cancer (IARC) consider wood dust and leather dust-exposure as risk factors for sino-nasal cancers (37). A systematic review of occupational risk factors for HNCs, based on 14 eligible studies (38), concluded that there was an association between exposure to formaldehyde and nasopharyngeal (39) and hypopharyngeal cancers (40) (OR 2.7 (95% CI 1.2-6.0) and OR 3.78 (95% CI 1.50-9.49) respectively) , wood dust and nasopharyngeal cancer (41), coal particles and hypopharyngeal cancer (40), asbestos and pharyngeal cancer (42) and leather dust and HNC (42). However, each of these associations is only based on an individual study and two of these studies did not control for alcohol consumption (39, 41), which increases the risk of confounding. Seven of the included studies did not control for all relevant risk factors such as age, smoking and alcohol, therefore the results should be interpreted with caution.

1.3 The Benefit of Early Detection of HNC

It is known that early detection of HNC improves outcome, with 5 year survival rates of around 80%, compared to those diagnosed with nodal metastases, in whom this figure falls to 20% (19, 43, 44). Presently, most HNCs are TNM (Tumour size, Nodal spread, distant Metastasis; TNM Classification of Malignant Tumours) stages 3 or 4 at diagnosis; in a Danish study of nearly 10,000 HNC cases, 58% were diagnosed at late stage. Risk factors for late stage diagnosis of oral cancer included male gender (female gender was protective): OR 0.63 95% CI 0.62 – 0.65), low income (OR 1.83 95% CI 1.59 – 2.10) and shorter length of education (OR 1.80 95% CI 1.58 – 2.05)(45), which supports the role of social deprivation in HNC.

Treatment of HNC is often multi-modal, including surgery, radiotherapy and/or chemoradiotherapy in the curative setting. For recurrent or metastatic disease chemotherapy or immunotherapy may be offered. Treatment carries significant

morbidity; early detection is crucial to the survival of cancer patients and enables less invasive treatments, which are associated with less morbidity, such as speech or swallowing impairment (46).

1.3.1 Cancer Screening

The aim of cancer screening is to detect patients with a high risk of having the disease in question. These individuals would then be offered a diagnostic test to confirm if they have the disease. The hope is that screening would identify cases at an earlier stage, which maximises survival. Cancer screening can also reduce the incidence of disease through the accurate detection and treatment of pre-malignant conditions, before a cancer develops. For example, the cervical cancer screening programme in the UK has resulted in a large decrease in incidence (OR 0.18 95% CI 0.16 – 0.20; females aged 35-64 years regularly screened) (47).

Despite increased incidence of some cancer types, there has been a decreased incidence in age standardised mortality rate from all cancers (US data) (48). This has been attributed to the combined effect of early detection due to screening and the availability and provision of improved treatment (48). In the UK there are screening programmes in place for breast cancer, bowel cancer and cervical cancer. Breast cancer mortality is 35% lower amongst those who attend for breast screening compared to those who do not (OR 0.65 95% CI 0.53 – 0.80) (49) and cervical cancer screening prevents 70% (95% CI: 66–73%) of deaths from cervical cancer (47). Regular bowel cancer screening reduces the risk of dying from bowel cancer by 15% (50, 51).

There is no current lung cancer screening programme in the UK, although results from randomised controlled trials are favourable (52-54). The European position statement on lung cancer screening was published in 2017 and recommends European countries should begin planning their respective lung cancer screening programmes (55); this statement suggests only high- risk individuals are selected for screening and the use of risk prediction modelling to identify such patients.

No screening programme is currently in place for HNC in the UK and this is partly due to the low detection rates demonstrated in studies (56). Most screening studies for

oral cancer have been completed in India, with varying results (57). It has been suggested that more research into targeted screening of high risk individuals is needed (58). The U.S Preventive Task Force published recommendations regarding oral cancer and recommended that future research should aim to clearly define high risk individuals that will allow the efficacy of screening programmes to be accurately assessed. They also stated that screening high-risk individuals may be cost-effective (59). Screening for oral cancer is usually non-invasive, involving a clinical oral examination, whereas screening for other smoking-related cancers, such as lung cancer, involves exposure to radiation using a computerised tomographic (CT) scan. With any screening programme, there is a risk of false positive diagnosis, unnecessary surgery for benign lesions and associated psychological harm, and these effects must be carefully balanced against the benefits of screening (55).

Often, individuals are selected for screening for cancers based on age or gender, e.g. the UK bowel cancer screening programme offers flexible sigmoidoscopy at age 55 years, with two-yearly faecal occult blood test (FOBT) from age 60-74 years (60). However, cancers for which an invasive test is required may be targeted though screening of high-risk individuals, to balance the risk of harm and benefit (55). High-risk individuals can be identified using risk prediction models (section 1.3.2).

1.3.2 Risk Prediction Models

In recent years, epidemiological research has played a prominent role in predicting individual risk of developing chronic diseases. The potential public health benefits of individualised estimates of the probability of developing a disease cannot be overemphasised. Because of the public health significance, the National Cancer Institute has recognised risk prediction as an area of extraordinary opportunity (58).

Risk prediction models for cancer are statistical models that estimate the probability of developing cancer over a defined period. Risk prediction for HNC would involve identifying the risk factors (so-called predictive or prognostic factors) of HNC and combining them into probability estimates of predicting HNC, either over a discrete time period or over a lifetime. The risk factors included in the model can be environmental, behavioural, genetic or psychological attributes of individuals, or any

combination of these. The development of a simple-to-use, validated, statistical model that estimates the probability of developing HNC over a defined period will help clinicians identify individuals at higher risk; this could allow more frequent screening in general dental practice and counselling of behavioural changes to decrease risk. These types of models will also be useful for designing future chemoprevention and screening intervention trials in individuals at high risk of HNC in the general population. Although risk models have been developed for cardio-vascular disease (61), lung (62), breast (58, 63, 64) and colorectal cancer (65), a model incorporating oral cancer does not exist.

Once a risk prediction model has been developed in a sample population, it must be validated in independent samples from the same population (internal validation) and ideally, within samples from different populations (external validation), to ensure its reliability and transportability to different populations. Results of these internal and external validation studies may stimulate the modification of the original model, leading to new or modified models being gradually developed over time (66).

There are a variety of ways of assessing the performance of a model, such as sensitivity, specificity and the AUC (area under the receiver operating curve [ROC]) (66). The E/O statistic and c statistic are the most commonly reported statistics in relation to risk model performance (67, 68). The E/O statistic measures the calibration performance of the model. It compares the expected (E) numbers to observed (O) numbers of events, so a well-fitting model should have a value close to 1 (67). The c-statistic is equivalent to the AUC and it measures the discrimination performance of the model. A value of 0.5 indicates no discrimination between those who develop the disease and those who do not, whereas a value of 1 indicates perfect discrimination (68).

1.3.2.1 A risk model for Barrett's oesophagus

Barrett's oesophagus is a pre-malignant oesophageal disease. A risk model for predicting an individual's risk of Barrett's oesophagus, as detected by endoscopic screening, has been developed (69). This study included 393 cases and 313 controls with non-Barrett inflammation of the oesophagus. 64% of cases were male and >95%

of cases and controls were Caucasian. Variables included in the model were selected by a review of the literature and participants were required to complete a standardised health and lifestyle questionnaire, to collect information on these variables. Variables included in the final model were selected by 2 phases of stepwise backward logistic regression. The accuracy of the model was then assessed by using AUC (*c*-statistic) and calibration was assessed by using the Hosmer–Lemeshow goodness-of-fit test. An AUC of 0.70 (95% CI, 0.66–0.74) was reported from the development dataset. This was reduced to 0.61 (95% CI 0.56–0.66) in the external validation dataset. Performance of the model was good as shown by the goodness-of-fit test (Hosmer–Lemeshow test, p=0.75). This model compares favourably with the Gail model for breast cancer risk and other cancer risk models (43).

1.3.2.2 A risk model for oesophageal cancer

Kunzmann *et al* published a risk model for oesophageal adenocarcinoma, developed using the UK Biobank dataset (70), a cohort of over 500,000 adults over the age of 40 years, recruited and followed up in the United Kingdom (described in detail in Section 4.3.2). They used a group of 355,034 adults over the age of 50 years with no cancer history at baseline, and identified 220 cases of oesophageal cancer during the 5-year follow-up period. They developed a risk prediction model using Cox regression modelling and included variables for age, sex, smoking, body mass index and history of oesophageal conditions or treatments. The discrimination performance was excellent with an AUC of 0.80. They defined a cut off point for high-risk individuals and demonstrated that the model had a sensitivity of 77.4% and specificity of 70.4% for identifying those with disease.

1.4 Aims: A Risk Model for Head and Neck Cancer using The UK Biobank Dataset

Head and Neck cancer is a disease that is increasing in incidence and carries significant morbidity and mortality. Efforts must be made to accurately identify high risk individuals to inform the design of future trials and to investigate the possibility

of screening of high-risk individuals. Therefore, this thesis centres around building a risk model for head and neck cancer using a large, UK based dataset, containing extensive information on over 500,000 participants.

The model was developed using logistic regression modelling (Chapter 6), using data from a section of the database containing participants from all areas of the UK excluding the North West; the model was validated in the North West cohort (Chapter 7). Further details of the dataset can be found in Chapter 4, along with details of the methodology used to develop the model. Chapter 7 presents the external validation of the model in the North West Cohort.

Prior to development and validation of the model, the trends in incidence of the disease in the UK will be investigated using data from the Office for National Statistics (Chapter 2). Novel risk factors for head and neck cancer will be explored via a systematic review in Chapter 3. The penultimate chapter will discuss Oral Dysplasia (a potentially malignant oral disease) and the potential for the use of risk modelling to guide management of this condition (Chapter 8). The thesis will conclude by considering various applications of risk modelling to the field of HNC (Chapter 9).

Chapter 2

Trends in the Incidence of Head and Neck Cancer in England: 2002 to 2011

The work within this Chapter was published in the *International Journal of Oncology* (Appendix 8).

Trends and Regional Variation in the Incidence of head and neck cancers in England: 2002-2011.

McCarthy CE, Field JK, Rajlawat BP, Field EA, Marcus MW.

Int J Oncol. 2015 Jul;47(1):204-10. doi: 10.3892/ijo.2015.2990. Epub 2015 May 7

2.1 Introduction

Chapter 1 introduced Head and Neck Cancer (HNC) as a disease and described, briefly, the problems of increasing incidence and the known risk factors. Risk prediction modelling was also introduced as a method to identify individuals at high risk of the disease. This chapter investigates the incidence of HNC in England between 2002 and 2011 using data from the Office for National Statistics (ONS), looking specifically at trends for age groups, regions of England and gender.

2.2 Background

Head and Neck Cancer (HNC) is the fifth most common cancer worldwide, with over 550,000 cases reported in 2012, and 12,061 cases in the UK in 2015 (71, 72). Incidence of laryngeal cancers has remained stable in recent years, whilst dramatic increases in incidence of oropharyngeal cancers have been reported (73). For a definition of HNC sub-sites see Section 1.1. and Fig. 1.1.

Cancer statistics form part of the evidence base to inform decisions regarding public health measures and resource planning. They can also help to define the need for further research in particular areas. In England, cancer registrations are validated by the Office for National Statistics (ONS) following submission of data by the Regional cancer registries. The validated data are freely available from the ONS for analysis. Regional differences in cancer incidence in England have been reported, with the North of England having higher incidence in both males and females, which may be linked to increased levels of deprivation (8, 74).

By 2041, it is estimated that there will be 3.2 million people, in the UK, over the age of 85, which is double the amount of 2016 (75). This ageing population will develop more cancers and the analysis of trends in incidence will form an important part of health-care planning.

The aim of this study was to assess overall incidence of HNC in England in 2002-2011. The distribution and trends in incidence of HNC's at specific anatomical subsites have

been analysed and trends have been identified in the different Regions of England. Trends in incidence between gender and age-categories were also considered.

2.3 Methods

Cases of HNC were identified from the Office for National Statistics (ONS) database. The ONS collects and publishes data related to the economy, population and society in the United Kingdom (UK). Cancer registration has been conducted in parts of the UK since 1929 but national coverage was not achieved until 1962. Cancer registries are now responsible for collecting data on cancer incidence, mortality and survival. In England, there are nine cancer registries and each uploads their regional data to a repository for validation by the ONS. The validation process is based on process recommended by the International Agency for Research on Cancer. Following internal validation by the ONS, detailed results of annual incidence of all cancers are published, categorised by age, gender and region of residence.

Head and Neck Cancer cases were identified using ICD codes C00-C14 and C30-C32 (see section 1.1). The data available included raw numbers and age-standardised/age-specific rates for males and females in 19 five-year age categories, from <1 to 85 years+. Raw numbers and age-standardised rate ratios were available for the Regions (former "Government Offices for the Regions") of England (Table 2.1). Incidence was calculated using cancer registration data and sex- and age-specific population data for each region of England, which was available from ONS. A ten-year period (2002-2011) was chosen in order to have sufficient data to allow examination of recent trends in the incidence of HNC.

***Table 2.1**. Regions used to Categorise Cancer Statistics, by the Office for National Statistics. Data on incidence of HNC and the sub-groups were analysed according to these Regions.*

Regions used to categorise Cancer Statistics
North East
North West
Yorkshire and Humber
East Midlands
West Midlands
East
London
South East
South West

Data were analysed to look for trends between age categories, gender, region and HNC subtypes within this period. Combinations of these variables were also analysed. There has been a reported increase in the incidence of Human papillomavirus-related HNC in recent years, therefore oropharyngeal (C09), base of tongue (C01) and tonsillar cancers (C10) were analysed as a subgroup, as these sites have most frequently been associated with HPV-infection (31, 32). This group will be referred to as oropharyngeal squamous cell carcinomas (OPSCC). The HPV status of these cancers is not known, however it has been reported that 36-80% of cancers at these sites are HPV-associated (31, 32). This is discussed in more detail in section 2.5.1.1.

Oral Cancer included ICD codes C00, C02-06 and C12-14. Laryngeal cancers were also analysed separately (C32) as they account for a significant proportion of HNC (72). Salivary gland cancers (C07-08), nasopharynx (C11), nasal cavity and middle ear (C30) and accessory sinuses (C31) have the lowest incidence of HNC, therefore were not analysed separately but included in the overall HNC figures.

Incident rates are reported as number of new cases per 100,000 person-years and are age-standardised according to the 2013 European Standard population. The ESP

is an artificial population structure which allows weighting of incidence or mortality data to produced age-standardised rates. This provides an estimate of what the incidence rate would be if the age-distribution was the same as the ESP, which allows comparison between countries with different population structures. The study population was categorised according to age, region of residence, gender and cancer sub-types.

2.3.1 Statistical Analysis

Poisson regression models were used to examine time trends in the overall incidence of HNCs and time trends in the five-year age categories, region of residence, gender and HNC subtypes, between 2002 and 2011. Poisson regression determines if changes occurring across a time series are significant, whilst adjusting for an independent variable such as age. The dependent variable is 'incidence of head and neck cancer' (or sub-category) and the independent variables were year, age category, region of residence and gender.

The Poisson regression equation can be written as

$$P(y_i|x_i;\beta) = \frac{\exp(-exp(x_i'\beta))\exp(x_i'\beta)^y}{y!}$$

where y_i is the incidence of HNC and x_i is an independent variable (age, region or gender). β represents the coefficient associated with the independent variable, x.

Stata statistical software (StataCorp. 2013 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) was used to analyse the data and p-values <0.05 were considered statistically significant.

2.4 Results

In the period 2002-2011, 71,457 HNC's were reported (69% men, 31% women). 30,651 were oral cancers, 12,849 were OPSCC and 17,496 were laryngeal cancers. 62.8% of HNC patients were 60 years or older.

The number of cases of HNC and the incidence, in 2002 and 2011, are displayed in Table 2.2; full data for each year are in Appendix 1. The results are displayed graphically in Figure 2.1 for HNC and each sub-type (oral cancer, oropharyngeal cancer and laryngeal cancer).

The average annual incidence in HNC increased by 30.3% from 2002-2011, from 12.2 to 15.9 per 100,000. There was a 27% increase in males (17.4 to 22.1 per 100,000; p=0.003) and 32% increase in females (7.4-9.8 per 100,000; p=0.004).

The incidence of OPSCC cancer increased by 45.5% from 1.8 to 3.3 per 100,000 between 2002-2011 ($p<0.001$). In males, the increase was 47.1% (2.7 to 5.1 per 100,000; p=0.003) and in females 37.5% (1.0 – 1.6 per 100,000; p=0.003).

Oral Cavity cancer showed a 24.6% increase from 5.2 to 6.9 per 100,000. For males, the increase was 24.1%, from 6.6 to 8.7 per 100,000 (p=0.005) and for females there was an increase of 25.5% (3.8 to 5.1 per 100,000) (p=0.004).

The incidence of laryngeal cancer was stable in comparison, increasing by only 2.9% from 3.4 to 3.5 per 100,000 (p=0.32).

Table 2.2. Incidence and number of cases of HNC in England from 2002 to 2011 (see Appendix 1 for full data). P-values for significance of the trend in incidence are presented, with <0.05 considered statistically significant.

Year	Men			Women		
	2002	2011		2002	2011	
Number of Cases						
Head and Neck	4215	5788		1867	2636	
Oral	1611	2271		971	1376	
Oropharyngeal	654	1338		245	434	
Larynx	1374	1506		300	342	
Incidence per 100,000			p value			p value
Head and Neck	17.4	22.1	**0.003**	7.4	9.8	**0.004**
Oral	6.6	8.7	**0.005**	3.8	5.1	**0.004**
Oropharyngeal	2.7	5.1	**0.003**	1.0	1.6	**0.003**
Larynx	5.7	5.8	**0.400**	1.2	1.3	**0.400**

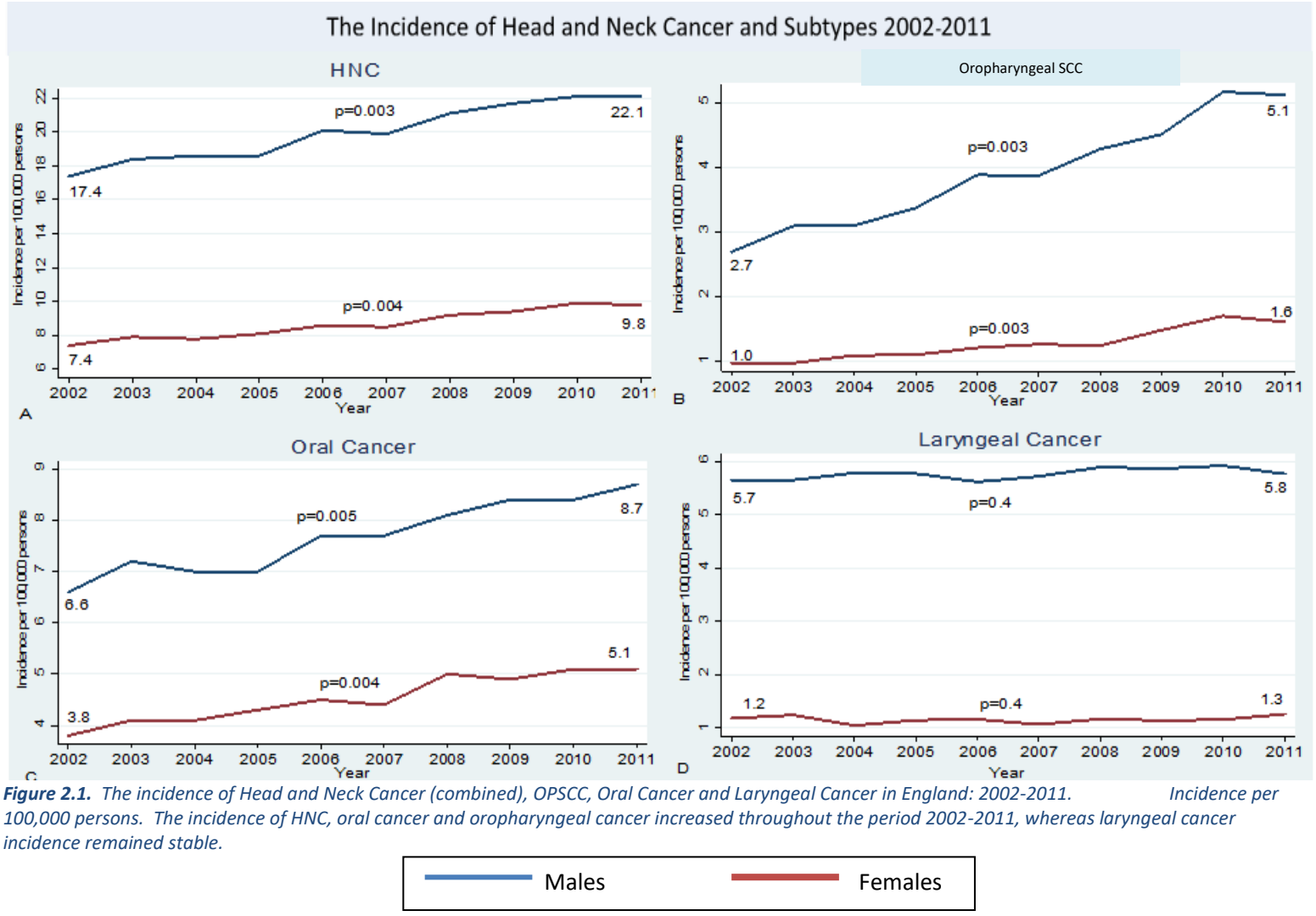


Figure 2.1. *The incidence of Head and Neck Cancer (combined), OPSCC, Oral Cancer and Laryngeal Cancer in England: 2002-2011. Incidence per 100,000 persons. The incidence of HNC, oral cancer and oropharyngeal cancer increased throughout the period 2002-2011, whereas laryngeal cancer incidence remained stable.*

2.4.1 Age

Figure 2.2 compares incidence rates of HNC and the subtypes, for males and females, aged over 40 years, in five-year age-categories between 2002 and 2011. Age is presented in 5-year groups by the ONS and this method of categorisation has been used in several other epidemiological studies (76, 77).

96% of patients with HNC were aged forty years or older (range 96.0-96.7%). 53% of cases occurred in persons aged 55 to 75 years. The highest incidence of HNC occurred in those aged 80 years and older (67.3 per 100,000 males and 30.0 per 100,000 females) but the highest average number of cases occurred in the 60 to 64-year age category (males: n=783; females: n=279). (See Figure 2.2 "HNC").

Oral Cancer also had highest incidence in males and females aged 80-years and older (25.4 and 18.7 per 100,000 respectively). The greatest number of oral cancer cases occurred in males aged 55-65 years (n=299) and in females aged 65-75 years (n=136), with 31% and 23% of oral cancer cases occurring in these age groups respectively. Incidence continued to rise sharply through all age categories for females, whereas for males there was no significant increase in incidence beyond 80 years. (See Figure 2.2 "Oral Cancer").

Laryngeal cancer incidence was highest in males and females aged 75 to 85 years (24.2 and 4.1 per 100,000 persons respectively), although the greatest number of cases was found in those aged 60-70 years (males: n=236 and females: n= 45), with 20.7% and 32.4% of cases occurring in these age groups respectively. After a sharp increase in incidence between 45 and 74 years, there is a slight decrease in incidence in the oldest age categories, although this is non-significant. (See Figure 2.2 "Laryngeal Cancer").

The incidence and total number of OPSCC were highest in males and females age 55 to 65 years (incidence 11.9 and 3.6 per 100,000 and n=349 and 110 respectively). There is a sharp rise in incidence between ages 40 and 60 years, followed by a statistically significant decrease in incidence from age 60 years upwards, for both

males and females (p=0.002). 16.4% of cases were in the 40 to 49-year age category (range 14.2-18.3%), compared to 9.3% (8.7-9.7%) for oral cancer. (See Figure 2.2 "Oropharyngeal SCC").

2.4.1.1 Trends within Age Categories

From 2002 to 2011, there was a significant increase in incidence of HNC for males in all age categories from 25 to 75 years, although this was most marked for males aged 55-74 years (incidence increased from 49.7 to 63.6 per 100,000 males). The largest increase was seen in the 55-59-year age category, particularly the second half of the ten-year period, with incidence of 41.4 in 2002, 45.0 in 2006 and 67.3 per 100,000 in 2011. (See Table 2.3).

Significant increases were also seen in females aged 30 to 40 (Appendix 2) and 50 to 85 years (Table 2.3), with the largest increase in incidence found in females aged 65-84 years: the incidence increased from 21.6 to 29.2 per 100,000 females between 2002 and 2011. The largest percentage increase was found in females aged 65-69 (17.4 to 25.5 per 100,000); however, the largest change in incidence was found in the 80-84-year age category (25.1 to 33.3 per 100,000).

For OPSCC, in males there was a significant increase in incidence over the ten-year period for those aged 40 to 79 years and for females aged 35 to 79 (Table 2.3 and Appendix 2). The incidence more than doubled in males aged 55-59 years (8.3 to 17.6 per 100,000) and 65-69 years (6.2 to 13.6 per 100,000), which was the highest percentage increase for any age group and any HNC subsite. Incidence almost doubled in females aged 65-69 years (2.0 to 3.9 per 100,000).

For oral cancer, the incidence increased significantly for females aged 50 to 84 years and males aged 50 to 74 years (Table 2.3). The highest percentage increase in the ten-year period was seen in males aged 60-64 years (18.1 to 26.5 per 100,000) and females aged 65-69 years (8.3 to 13.6 per 100,000).

No statistically significant increase or decrease was found in any age category for laryngeal cancer, for either females or males. Incidence rates remained relatively stable throughout the ten-year period (Appendix 2).

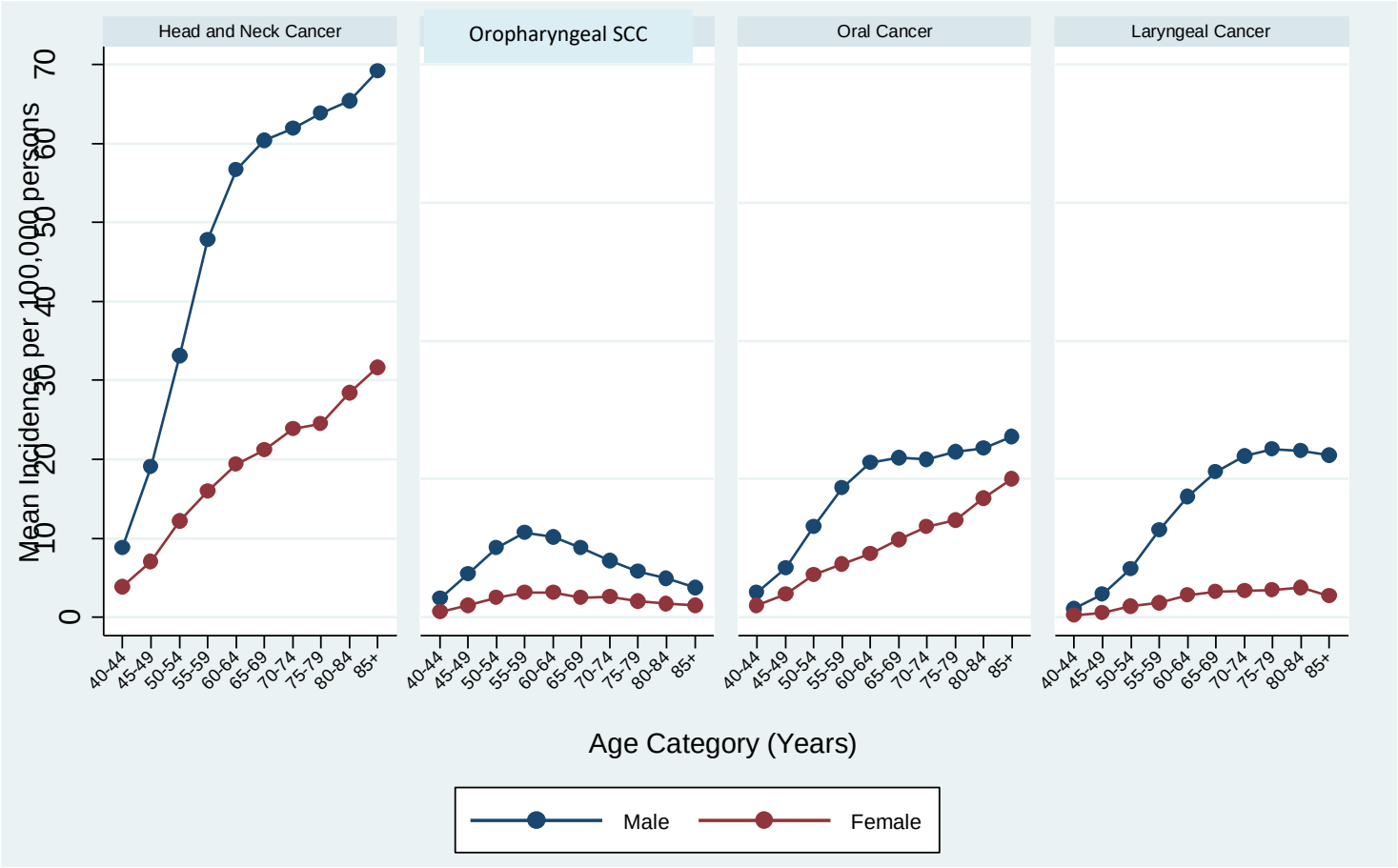


Figure 2.2. *Mean incidence, by age category, of Head and Neck Cancer, Oral Cancer, OPSCC and Laryngeal Cancer (per 100,000 persons). (mean of incidence per year from 2002-2011). Incidence of HNC (combined) and oral cancer increases with increasing age. For oropharyngeal caner the incidence decreases, after peaking in the 55-59y age category. The incidence of laryngeal cancer increases markedly, in males, up to the age of 75-70y and reduces slightly in the older age categories.*

***Table 2.3**. Incidence of Head and Neck, Oral, OPSCC and Laryngeal Cancer in 5 year age-categories, from 2002-2011.*

Significant p values are highlighted in bold. Significant increases in incidence are seen for HNC, oral cancer and OPSCC. The incidence of laryngeal cancer in stable in all age categories.

Age Category	Gender	Head and Neck			Oral			OPSCC			Laryngeal		
(years)		2002	2011	p value	2002	2011	p value	2002	2011	p value	2002	2011	p value
40-44	M	8.1	8.7	**0.035**	3.5	3.4	0.410	2.1	2.8	**0.027**	1.2	1.0	>0.05
	F	3.0	3.5	0.076	1.2	1.4	0.159	0.5	0.9	**0.014**	*0.4*	*0.2*	>0.05
45-49	M	18.5	21.3	**0.015**	7.6	8.5	0.220	5.2	7.3	**0.006**	3.2	3.3	>0.05
	F	5.6	7.3	0.129	2.6	3.1	0.674	1.2	2.0	**0.005**	0.5	0.8	>0.05
50-54	M	29.8	33.4	**0.022**	12.4	13.1	**0.027**	6.6	12.5	**0.005**	*7.5*	*5.2*	>0.05
	F	9.8	14.3	**0.006**	4.5	7.1	**0.032**	2.2	3.5	**0.010**	***1.2***	***1.7***	>0.05
55-59	M	41.4	57.3	**0.004**	16.2	22.3	**0.007**	8.3	17.6	**0.004**	13.5	12.6	>0.05
	F	13.7	19.1	**0.009**	6.1	8.8	**0.005**	2.9	5.2	**0.009**	2.8	1.8	>0.05
60-64	M	48.2	63.1	**0.012**	18.1	26.5	**0.008**	7.7	16.2	**0.005**	18.1	15.6	>0.05
	F	15.9	20.6	**0.006**	8.4	10.3	**0.029**	2.6	4.8	**0.022**	2.6	3.2	>0.05

Table 2.3 continued

Age Category (years)	Gender	Head and Neck			Oral			OPSCC			Laryngeal		
		2002	**2011**	**Pvalue**	**2002**	**2011**	**pvalue**	**2002**	**2011**	**pvalue**	**2002**	**2011**	**pvalue**
65-69	M	51.9	64.7	**0.008**	19.5	24.0	**0.018**	6.2	13.6	**0.003**	20.8	20.9	>0.05
	F	17.4	25.5	**0.010**	8.3	13.6	**0.004**	2.0	3.9	**0.010**	4.1	4.1	>0.05
70-74	M	57.0	69.3	**0.018**	18.9	26.9	**0.015**	6.0	12.5	**0.007**	24.8	22.7	>0.05
	F	22.0	29.1	0.018	11.6	15.9	**0.029**	3.1	3.5	0.076	4.2	4.6	>0.05
75-79	M	55.4	66.6	0.120	19.8	24.7	0.207	5.4	7.9	**0.022**	22.9	24.7	>0.05
	F	21.8	29.0	**0.006**	12.8	17.1	**0.010**	1.3	2.6	**0.032**	3.7	4.6	>0.05
80-84	M	65.0	67.5	0.370	25.7	25.8	0.410	4.6	5.9	0.076	23.4	24.0	>0.05
	F	25.1	33.3	**0.014**	14.8	20.9	**0.012**	1.9	2.3	0.571	5.0	4.7	>0.05
85+	M	68.9	79.7	0.546	28.7	30.0	0.596	5.6	4.8	0.499	18.6	26.2	>0.05
	F	26.8	32.5	0.076	15.7	19.7	0.096	2.2	1.8	0.784	3.2	3.3	>0.05

2.4.2 Gender

Between 2002 and 2011, on average, 69% of HNC patients were male, giving a male:female ratio of 2.1:1. The ratio of males to females did not change significantly between 2002 and 2011 (range 2.1:1 – 2.2:1). The percentages of male oral cancer patients, OPSCC patients and laryngeal cancer patients were 61% (M:F = 1.6:1), 72% (2.6:1) and 82% (4.6:1) respectively. Values quoted relate to patients aged 40 years or over.

Figure 2.3 shows the percentage of male and female cases in each age category for each of the HNC types; the mean percentage for 2002-2011 for each age category has been used.

The ratio of males:females with HNC, in terms of total number of cases, increases with age up to 55-59 years and then gradually decreases until the oldest age category, where there are fractionally more female cases than males (n=234 and 228 respectively). This trend is more marked for oral cancer, where the proportion of males peaks in the 55-59-year age category (70%) and gradually falls, with increasing age, to 36.6% in the 85 years and over category, giving a female:male ratio of 1.7:1 (n=149 and n=85 for females and males respectively). Laryngeal cancer is the only subtype of HNC analysed that did not display a significant decrease in the proportion of male:female cases in the older age categories.

Although the relative number of males affected falls in the older age categories for HNC, OPSCC and Oral Cancer, the incidence in males remains higher throughout all age categories (Figure 2.3).

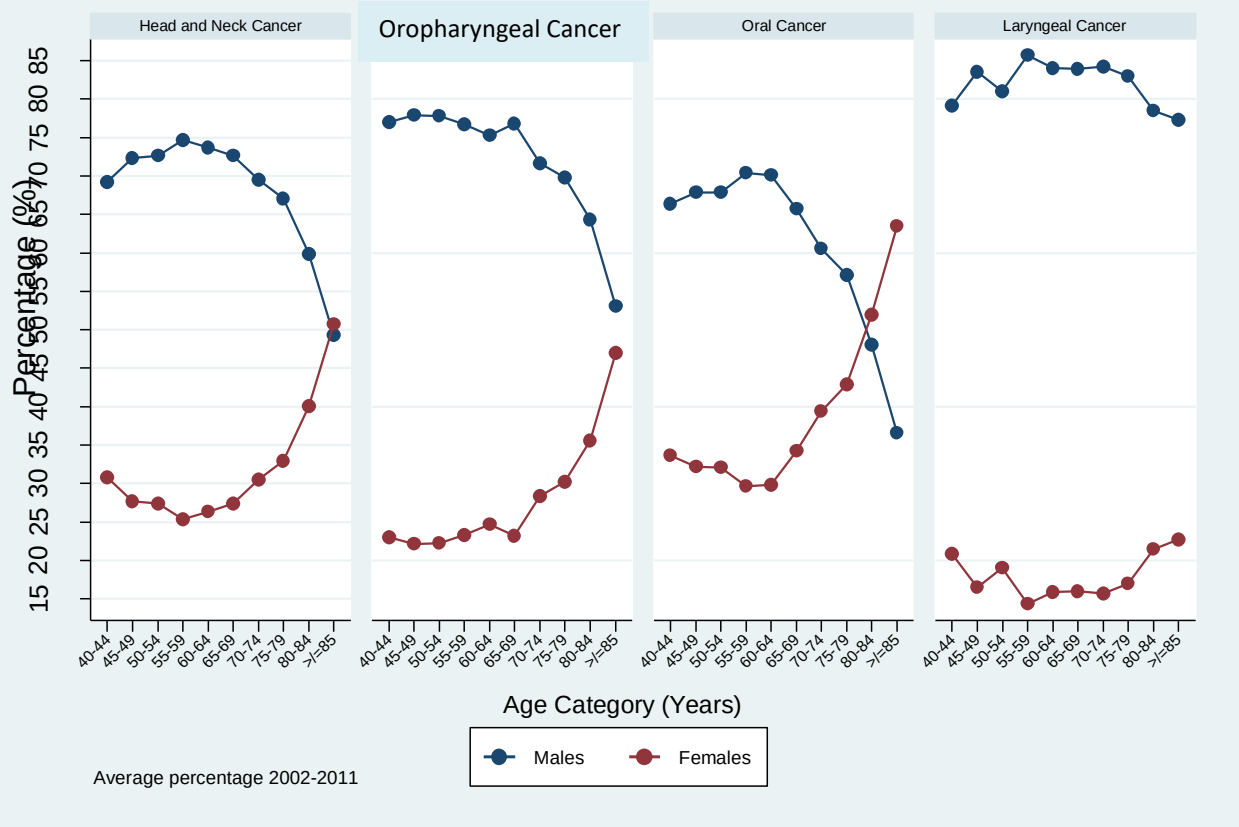


Figure 2.3. Percentage of Male and Female cases in each age category for HNC, OPSCC, Oral cancer and Laryngeal cancer; results show a decline in the male:female ratio with increasing age. There are more females than males with oral cancer in those aged 80y and over.

2.4.3 Regional Variation

Table 2.4 contains incidence data for all Regions of England. The North East of England has the highest incidence of HNC in England; in 2011 the incidence was 27.6 and 10.2 per 100,000 for males and females respectively, compared to the lowest incidence in London of 17.3 per 100,000 males and 6.8 per 100,000 females. The North East also recorded the highest incidence for the subtypes analysed (OPSCC, oral and laryngeal cancers).

The North West consistently records the second highest incidence of HNC (24.1 per 100,000 males and 9.9 per 100,000 females). The greatest number of cases of HNC in England are recorded in the North West; an average of 813 male and 348 female cases of HNC were recorded each year from 2002-2011, compared to 325 and 132 respectively in the North East.

Table 2.4. *Mean Incidence of HNC and each sub-type, per 100000 persons, by Region of England. (Mean of values from 2002-2011). The North East and North West have the highest incidence of HNC and all sub-groups.*

Region	Head and Neck		OPSCC		Oral		Laryngeal	
	Male	Female	Male	Female	Male	Female	Male	Female
North East	26.0	10.0	4.8	1.6	10.2	4.8	8.3	1.8
North West	24.1	9.9	4.7	1.4	9.2	5.1	7.4	1.7
Yorkshire&Humber	20.5	8.8	3.9	1.1	7.7	4.5	6.5	1.4
East Midlands	19.7	9.3	3.7	1.3	7.7	4.9	5.8	1.2
West Midlands	19.5	8.1	3.8	1.3	7.6	4.5	5.9	1.2
East	17.2	8.0	3.7	1.2	6.3	4.3	4.9	0.9
London	16.4	6.8	3.1	1.1	6.4	3.6	4.8	0.9
South East	17.3	8.2	3.4	1.2	6.7	4.5	4.7	0.8
South West	20.6	9.0	4.0	1.3	7.8	4.7	5.7	1.0

From 2002-2011, there was a significant increase in the incidence of HNC in all Regions of England. Figure 2.4 shows the incidence of HNC in the Regions of England from 2002-2011, with p-values for significance of the trend. The most consistent increases were found in the South West and Yorkshire & Humber for males, with an average annual percentage increase of 3.7% and 3.1% respectively. The East Midlands and North West reported the most consistent increases for females (average APC 8.1% and 4.3% respectively).

The North East showed a statistically significant decrease for Laryngeal cancer in males from 2002-2011 (incidence 9.2 per 100,000 to 7.6 per 100,000). However, the East Midlands report a statistically significant increase in incidence for females, from 0.8 to 1.5 per 100,000. All other regions display non-significant trends, indicating that the incidence of laryngeal cancer is relatively stable.

The incidence of Oral Cancer increased significantly in all regions except Yorkshire & Humber and the North East, for males and females. There was no significant increase in the East of England for female oral cancers. The East Midlands and South West displayed the most consistent increases each year for males and females respectively, with average annual percentage change of 5.1% (incidence increased from 6.2 to 9.2 per 100,000 from 2002-2011) and 5.7% (incidence increased from 3.5 to 5.6 per 100,000).

The incidence of OPSCC significantly increased in males and females in all regions except for females in the East and London. The East Midlands and Yorkshire & Humber display the most consistent increases in incidence, in males, between 2002 and 2011 with average APC of 14.3% (incidence increased from 1.9 to 5.9 per 100,000) and 8% (incidence increased from 2.6 to 5.1 per 100,000). In females, the most consistent increase was found in the South West, with average APC of 14.1%; incidence increased from 0.9 to 2.1 per 100,000 between 2002 and 2011.

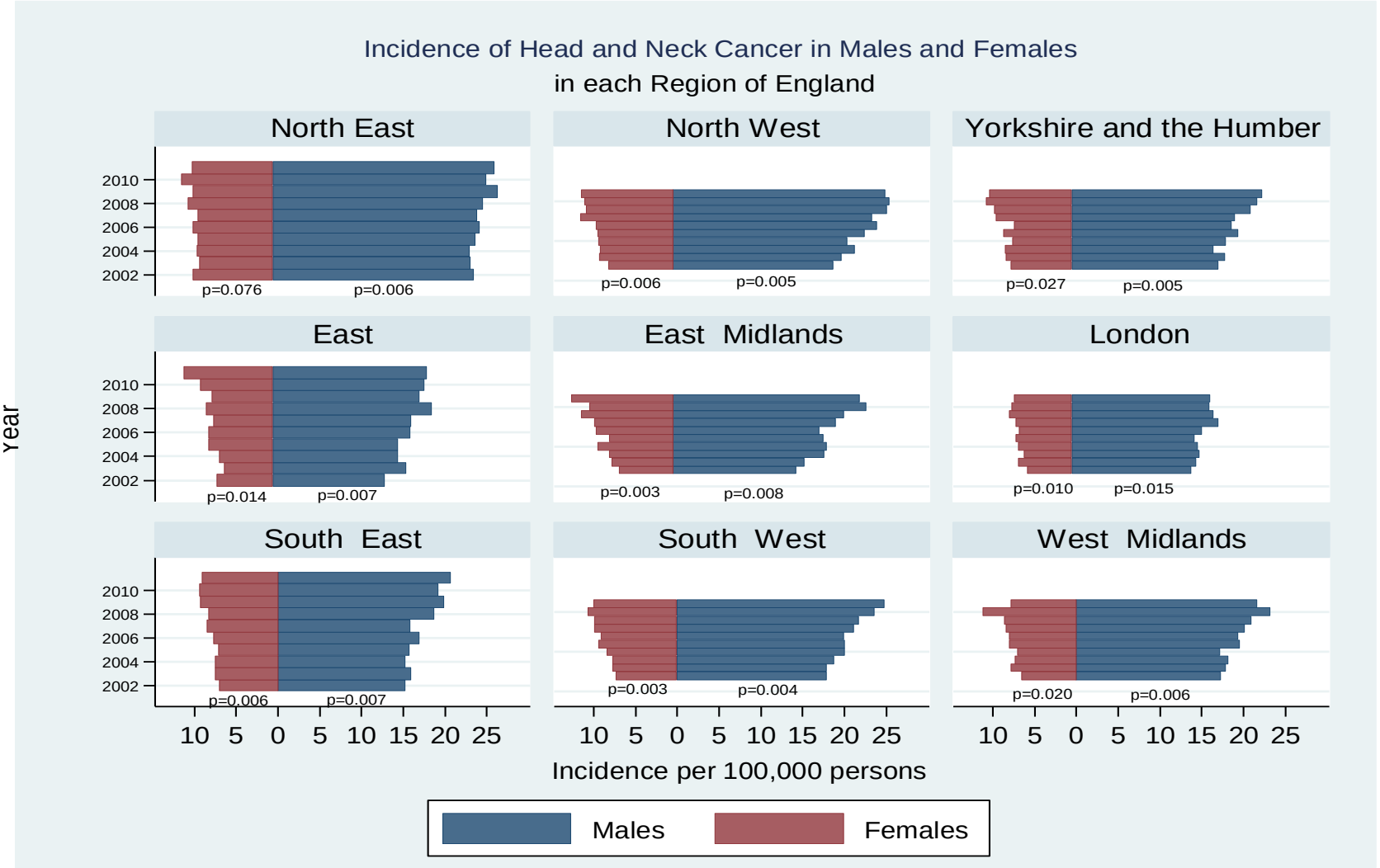


***Figure 2.4**. Incidence of Head and Neck Cancer in each Region of England from 2002-2011 with p values for significance of trend. All regions show a statistically significant increase in incidence of HNC for males. All regions except the North East display a statistically significant increase in incidence of HNC in females.*

2.5 Discussion

Results of an increasing trend in the incidence of HNC in England, between 2002 and 2011, have been presented in section 2.4.

Over 96% of patients were aged over 40 years and 68% of HNC patients were male, which is similar to figures reported in other studies from England and internationally (1, 9, 10, 12, 15, 78).

The incidence of HNC increased significantly during the study period, as did the incidence of OPSCC and oral cancer. These findings were also observed by Dobaree *et al* in their study of HNC in the South East of England between 1995 and 2004 (1). Conway *et al* observed an increase in oral and pharyngeal cancer rates (C00-C06, C09, C10) in England between 1990 and 1999, with incidence in males increasing from 6.5 to 8.3 per 100,000 and in females from 2.6 to 3.6 per 100,000 (79). Although our results cannot be directly compared due to differences in classification, the trend appears to be similar over the two decades.

There was no significant increase in the incidence of laryngeal cancer between 2002 and 2011; this finding is also reported by the Oxford Cancer Intelligence Unit in a report detailing the profiles of HNC in England. They found that the incidence of laryngeal cancer reduced by 20%, from 3.6 per 100,000 to 3.0 per 100,000, between 1990 and 2006 but stabilised in the latter five years (73). This is supported by Coupland *et al*, who found that incidence has decreased from the early 1990's, particularly in those aged over 70 (80). A reduction in laryngeal cancer incidence in males and stable incidence in females has been reported in France, Finland, Norway, Denmark, Spain and the Netherlands (10, 17, 71). The highest incidence of laryngeal cancer was found in 75-84 year olds, which is similar to findings reported from the Netherlands that 21% of patients are in the 75-85 year age group and 32% are in the 60-70 year age group (17).

2.5.1 Age

Over half of all HNC patients in England, between 2002-2011, were in the 55-75 year age group. Dobaree *et al*. reported that 60% of HNC patients in South East England were aged 40-69 years between 2000 and 2004 whereas Germany report a slightly higher age at diagnosis, with 50% of HNC patients aged 60-79 years (1, 15). The USA report mean age at diagnosis of 62 years (44).

Over the ten-year period studied, the most marked increases in HNC incidence were found in the 55-59 year age category for males and 65-69 year age category for females, which is mostly due to the increase in oropharyngeal, base of tongue and tonsil cancer as discussed below.

The highest incidence of oral cancer was found in the over 80's, for both males and females. The most significant increases in incidence of oral cancer were found in males aged 60-64years and females aged 65-69 years. Results from Portugal show that the highest incidence of oral cancer in females is in the over 75 year age group, whereas for males the 60-64 year age group has highest incidence, further supporting the concept that females with oral cancer tend to be older than males (12).

Oral cancer incidence is increasing in the Netherlands in females, however rates are stable in males, which are findings similar to those reported from France (17, 81). Other studies have reported reducing incidence of oral cancer; a reduction of 1.5% per year was found between 1995 and 2004 in the USA (81), however in the time period 2003-2010, there was an annual percentage increase in oral cancers in males of 0.2% (44). In fact, cancers of the tongue increased in males by 2.4% annually between 1999 and 2010 and in females by 0.6% annually between 1992 and 2010; therefore the trend may have been reversed (44). This is unlikely to be due to HPV, as oral cancers are less commonly associated with HPV infection than oropharyngeal cancers (82), and is more likely to be due to smoking and alcohol habits. The original reports of a declining incidence were for the USA as a whole, which is a vast, culturally and geographically diverse nation. Incidence within some states continued to rise

during the period of general decline in oral cancer incidence (83) and it may be that the increasing incidence in these states has now reversed the general trend.

2.5.1.1 Oropharyngeal SCC

Information on HPV-status was not available from the ONS. However, we classified oropharynx, base of tongue and tonsil as a sub-group (OPSCC) in order to study trends in incidence at these sub-sites, based on reports in the literature that between 36% and >80% of cancers at these sites are infected by HPV, implying, but not proving, causation (32). Studies have confirmed 50-55% of oropharyngeal cancers are HPV-infected (31) and HPV infection poses an increased risk of developing oropharyngeal cancer: OR 3.5 (95%CI 2.1 – 5.9) (84, 85).

OPSCC affect younger individuals, with the highest incidence found in those aged 55-65 years; it also affects proportionally more people aged 40-49 years than other head and neck cancers. Higher incidence in older age categories is noted in the other HNC sub-types, however incidence of OPSCC decreases in persons aged over 65 years. The incidence of OPSCC doubled in males aged 55-59 and 65-69 years, and almost doubled in females aged 65-69 years between 2002 and 2011. This is in agreement with National Cancer Information Service data, which shows that the incidence of oropharyngeal cancer doubled in England between 1990 and 2006 (73); this rise is thought to be due to HPV-infection. Forte *et al* have also reported a marked increase in tonsil and base of tongue cancer in Canada, again believed to be due to HPV infection (11). Forte *et al* report the largest increase in persons aged 50-59 years (incidence 4.4 to 8.9 per 100,000 between 1997 and 2009), which is similar to our findings in England. Monteiro *et al* reported that oropharyngeal cancer in men increased by 3.5% per year and in females by 2% per year between 1998 and 2007 in Portugal (12); the USA report increasing incidence of oropharyngeal and tonsillar cancer of 2.3% annually for males between 1992 and 2010 (13, 44). Interestingly, a 0.4% annual reduction in female oropharyngeal and tonsil cancers is reported in the USA in the period 1992-2010 (44); the reason for this is unclear. This HPV-epidemic is under intensive research, and cancer statistics will form an important part of public health campaigns and health-care planning.

2.5.2 Gender

The ratio of males:females remained relatively stable over the study period (approximately 2:1). The incidence of head and neck cancers in males is higher than females throughout all age groups, however the relative proportion of females affected increases in the older age categories, probably due to a larger female population. The male:female ratio is most consistent for cancers of the oral cavity; there are more female oral cancer patients over 80 years of age than male patients (58% and 42% respectively). Females have longer life-expectancy than males and as the population of females is much larger in this age group (1,564,400 and 920,700 respectively in 2011), it is reasonable to expect a higher number of oral cancer cases.

Laryngeal cancer had the highest ratio of male:female cancers (4.6:1) and this ratio is very similar throughout all age groups, even the most elderly, which is different to the trend observed with oral cancer: Coupland reports a male:female ratio of 4.8:1 for laryngeal cancer in the South East of England between 1985 and 2004 (80). In other countries, the ratio is much higher: Lithuania and Portugal have a male:female ratio of 25:1 and 36:1 respectively [(71)]. This is likely to be due to historical differences in smoking habits: 50% of men in Lithuania were smokers from the 1990's to 2002, whereas only 10-20% of women smoked (86). Alcohol consumption is also much higher in men in both Lithuania and Portugal (87).

The incidence in males varies widely from country to country, from 11.9 per 100,000 in Hungary to 1.8 per 100,000 in Sweden [(71)]. Smoking and alcohol are major risk factors for all HNC, however for laryngeal cancer the Population Attributable Risk (PAR) has been found to be 89% compared to 64% for oral cavity cancer. PAR is the proportion of the incidence of a disease in a population that can be attributed to a particular exposure, in this case smoking and alcohol. Males also have a higher PAR for smoking and alcohol compared to women (74% compared to 57% respectively) (88); this may help to explain the much higher incidence in males than females.

2.5.3 Region

The North East and North West have the highest incidence of HNC and all subtypes analysed, with incidence rates that are consistently above the national average.

For HNC overall (C00-14, C30-32), all Regions of England showed a significant increase in incidence in the period 2002-2011. Not all Regions had a statistically significant increase in Oral Cancer, but none displayed a decrease in incidence. Incidence of OPSCC increased in all Regions for males, particularly the East Midlands and Yorkshire & Humber; interestingly Yorkshire & Humber was one of the regions with no statistically significant increase in oral cancer incidence. For females, it was the South West with the most marked increase in OPSCC.

Laryngeal cancer incidence significantly decreased in the North East, although even with the decrease, the incidence is still the highest in the country. A previous report has found a decreasing incidence in laryngeal cancer from the North to the South of England, thought to be due to the changes in the industrial landscape and supporting the concept of the "North-South divide", which is a term used to describe gross differences in socio-economic status for individuals living in the North and South of England (73).

2.5.3.1 The Relationship between Social Deprivation, Smoking and Alcohol

It has previously been reported that there is increased incidence of HNC in lower socio-economic groups and a link with deprivation has been established (16). Smoking and alcohol are the two most significant risk factors for head and neck cancer, and differences in the rates of smoking and alcohol consumption could help to explain the regional variations in incidence of the disease. Smoking rates in the UK reduced dramatically between 1974 and 2011 (51% to 20% of men and 41% to 18% of women) but regional variations still exist: in 2011 smoking rates were higher in the North West (22%) than the rest of England (20%), although this is not statistically significant (89). Residential area deprivation is a strong independent predictor for smoking (OR 1.85 CI 1.57-2.13) and the North West contains over half of the 1% most deprived areas of England (90, 91). Social deprivation is also considered as a risk factor for HNC in Section 5.2.2.

Smoking is more prevalent in the routine and manual occupations than managerial and professional (29% vs 14% for males; 26% vs 12% for females) and the percentage of never smokers is lower. It is known that people in lower socio-economic groups

are not only more likely to take up smoking but generally start younger, smoke more heavily and are less likely to quit smoking, each of which increases their risk of HNC (89).

Heavy drinking on at least one day in the week (>8 units for men, >6 units for women) was most common in the North West and Yorkshire & Humber in 2011 (23% vs 18%). In contrast to smoking, regular alcohol consumption (at least 5 days per week) is more prevalent amongst the managerial/professional group than the routine/manual group (19% vs 13% for males) and in those who are in employment compared to the unemployed (15% vs 6% for males) (89).

Smoking and drinking are also closely linked: according to ONS data (2011), 14% of male smokers consumed greater than 12 units of alcohol on one day in the preceding week compared to 8% of non-smokers. It has also been found that amongst young people aged 11-15 years, occasional and regular smokers are much more likely to drink alcohol (OR 2.85 and 3.65 respectively) than non-smokers (92).

Ethnicity has also been considered as a risk factor, due to the marked differences in incidence of HNC around the world. Incidence of HNC is highest in South and South East Asia and the incidence of HNC amongst South East Asians living in the UK is higher than in other ethnic groups (3, 93); Csikar *et al* report incidence of 7.2 per 100,000 and 6.0 per 100,000 respectively. They conclude that in areas in which many South Asian women live, there may be a higher incidence of head and neck (particularly oral) cancer. However, London has the highest percentage of Indian, Bangladeshi and Pakistani persons in England (1.8% of the population) and our study shows the incidence of HNC was the lowest of all the Regions (16.4 per 100,000 males and 6.8 per 100,000 females) (Figure 2.4).

Smokeless tobacco use is highest in Bangladeshi women (16% of the Bangladeshi population) and this is thought to account for the higher incidence of oral cancer in this group (3). Interestingly, there appears to be no link with deprivation for either male or female South Asians, in terms of oral and pharyngeal cancer risk, which supports the concept that ethnic-specific risk factors account for the higher incidence of oral/HNC in this group of the population (93).

2.6 Conclusion

This study has confirmed that the incidence of HNC continues to rise in England. Between 2002 and 2011, incidence increased from 12.2 to 15.9 per 100,000. Oral cancer incidence is also increasing, in males and females, whereas incidence of laryngeal cancer is stable. The incidence of OPSCC doubled, in males and females in high-risk age-groups, in this ten-year period. Regional variation exists and further work is needed to establish the role of deprivation and socioeconomic status on HNC incidence. Cancer statistics form an important part of healthcare planning and this information may be used to inform researchers when planning studies and screening programmes in different Regions of England.

This work has demonstrated a significant increase in the incidence of oral cancers in older females, which justifies exploration of novel, female-specific, risk factors for HNC. Chapter 3 will explore female-specific risk factors for head and neck cancer, including age at menopause and hormone replacement therapy.

Chapter 3

Exploring Novel Risk Factors for Head and Neck Cancer

The work within this chapter was published in *Oncology Reports* (Appendix 8):

Age at Menopause and Hormone Replacement Therapy as risk factors for Head and Neck and Oesophageal Cancer. A systematic review.

McCarthy CE, Field JK, Marcus MW

Oncol Rep. 2017 Oct;38(4):1915-1922. doi: 10.3892/or.2017.5867. Epub 2017 Aug 1

3.1 Introduction

Chapter 2 explored the increasing incidence of HNC in England between 2002 and 2011 and identified an increasing incidence in older females. This chapter will explore novel female-specific risk factors for HNC, using a systematic review of the literature.

3.2 Background

The ratio of male: female cases of HNC in persons aged 50-60 years is close to 3:1, however the gender disparity reduces in the elderly population, with a male:female ratio of 1.5:1 in the over-eighties (94). For oesophageal SCC, the male:female ratio is lower, at 1.1:1.

There have been reports of young women with no classic risk factors, developing oral cancer (95, 96) and some efforts have been made to explore this (96). A review of risk factors in young adults (<45years) was conducted in the INHANCE consortium (a collaboration of HNC researchers, including over 40 member studies) in 2015; a lower attributable fraction for smoking and alcohol was detected (19.9% for women <45y vs 48.9% for women >45y). There were proportionally more female HNC cases with tongue cancer who were never smokers and never drinkers, across all age categories (97). This contrasts with the commonly accepted fact that smoking and alcohol account for most cases of HNC (see Section 1.2.1).

Hormones are known to play an important role in several cancers, such as breast, ovarian and uterine, endometrial, prostate, testis and thyroid cancers. There have also been reports of hormone-related risk factors for squamous cancers, such as oesophageal, cervical and lung cancer (98). Whilst hormone-replacement therapy (HRT) is a known risk factor for certain cancers (e.g. breast cancer), a recent meta-analysis found that use of HRT is protective against oesophageal squamous cell carcinoma (SCC) (99). Early-menopause has also been linked to increased risk of oesophageal SCC (RR 1.32 (95% CI 1.11-1.56) per 5 years younger at menopause) (100). Another meta-analysis suggested decreased risk of lung cancer in never-smoker females who use Hormone Replacement Therapy (HRT) (OR 0.86 (95% CI 0.75-0.99)) (101).

This leads to the hypothesis that hormone levels have a role as a risk factor for squamous cancers. There is uncertainty surrounding the role of female hormones and the risk of head and neck oesophageal SCC; no systematic review has been conducted to address this uncertainty.

3.3 Aims

The aim of this review is to explain the role of female hormones in relation to the risk of head and neck and oesophageal SCC.

The squamous histology and strong similarities in their epidemiology and aetiology justify their combination in this project (102-105), which will address two specific questions:

(i) Is early menopause a risk factor for HNC or oesophageal SCC?

(ii) Is Hormone Replacement Therapy protective against HNC or oesophageal SCC?

3.4 Methods

3.4.1 Search Strategy

Electronic databases Medline, Web of Science, Embase and Cochrane were searched up to February 11, 2016. Search strategies were developed using medical subject headings (MeSH): ("head and neck neoplasms"[MeSH Terms] OR ("head"[All Fields] AND "neck"[All Fields] AND "neoplasms"[All Fields]) OR "head and neck neoplasms"[All Fields] OR ("head"[All Fields] AND "neck"[All Fields] AND "cancer"[All Fields]) OR "head and neck cancer"[All Fields] OR "HNC"[All Fields])) AND "oesophageal cancer"[All Fields] OR "esophageal neoplasms"[MeSH Terms] OR ("esophageal"[All Fields] AND "neoplasms"[All Fields]) OR "esophageal neoplasms"[All Fields] OR ("esophageal"[All Fields] AND "cancer"[All Fields]) OR "esophageal cancer"[All Fields] AND "hormone replacement therapy"[MeSH Terms] OR ("hormone"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "hormone replacement therapy"[All Fields] AND ("female"[MeSH Terms] OR

"female"[All Fields]) AND ("hormones"[Pharmacological Action] OR "hormones"[MeSH Terms] OR "hormones"[All Fields] OR "hormone"[All Fields]) AND "early menopause"[All Fields]) and text words related to hormones and HNC or (o)esophageal cancer. Reference lists were also extensively searched and relevant papers obtained.

3.4.2 Eligibility Criteria

Randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs) or cluster trials, prospective and retrospective comparative cohort studies, case-control or nested case-control studies and cross-sectional studies, addressing the question of female hormones as a risk factor for HNC or oesophageal SCC, were considered. Studies were included if they:

(i) Examined the general adult population (age >18 years), specifically studies with at least 50 cases of HNC/oesophageal SCC and any number healthy controls.

(ii) Addressed the question of hormone replacement therapy or reproductive factors (menopause) and HNC/oesophageal SCC

(iii) Administered HRT as an intervention for prevention of cancer or being taken therapeutically due to symptoms of menopause.

(iv) Collected data on age at menopause, smoking, alcohol, age and socio-economic status or educational attainment.

(v) Reported odds ratios, risk ratios or incidence/prevalence of HNC or oesophageal SCC defined using the World Health Organisation (WHO) classification of diseases ICD-10 codes, C00-15 and C30-31 (see Section 1.1)

Cohort studies were only eligible if follow up time was at least 5 years. Case series and case reports were excluded. Only studies published in peer-reviewed journals, from 1948 to 2016, were considered. These criteria were applied to maximise the quality of the evidence considered.

3.4.3 Data Extraction

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors (Caroline McCarthy and Dr. Michael Marcus) to identify studies that potentially met the inclusion criteria outlined above. Studies combining HNC with oesophageal squamous cell cancers were considered but data were extracted separately for HNC and oesophageal cancer where possible. Data were extracted in all forms (e.g. dichotomous, continuous) as reported in the included studies. The full texts of these potentially eligible studies were independently assessed for eligibility by the same authors. Any disagreement over the eligibility of particular studies was resolved through discussion with a third reviewer. A data extraction form was developed to assess the characteristics and findings of the primary studies (Appendix 3).

3.4.4 Risk of Bias

The risk of bias in each study was assessed using the Newcastle-Ottawa Scale (NOS). The NOS evaluates risk of bias based on methods used to select patients, comparability of groups in the study, methods for assessing outcomes, proof of exposure and appropriate follow-up. Studies are categorised as low, medium, high or unclear risk of bias, using a star-based scoring system. 8 categories are considered in total (see Table 3.1) with one star allocated if the criteria are met (two stars are available for the “control” category, as indicated).

*Table 3.1. Categories for scoring studies using the Newcastle Ottawa Scale. One star is available for each category except 'Control' as indicated with *, where two stars are available. The maximum score is 9 stars.*

Newcastle Ottawa Scale Categories	Scores one star if criteria fulfilled
Selection	
1. Representativeness of the exposed cohort	Truly OR somewhat representative
2. Selection of controls	Drawn from same community as cohort
3. Ascertainment of exposure	Secure record OR structured interview
4. Demonstration that outcome of interest was not present at start of study	Yes
Comparability	***two stars available if general plus disease-specific factors included as control
5. Study includes control for confounders	
Outcome	
6. Assessment of outcome	Independent blind assessment OR record linkage
7. Was follow-up long enough for outcomes to occur	Yes
8. **Adequacy of follow-up cohorts**	Complete follow-up OR those lost to follow up unlikely to introduce bias: description of those lost suggests no different from those followed up OR <20% loss to follow up

A maximum of 9 stars are available; the higher the number of stars the lower the risk of bias. For ease of interpretation, a score of 7 or greater is considered 'low-risk' of bias, 4-6 is 'medium-risk' and 3 or below is considered 'high-risk' of bias.

3.5 Results

The search identified 13 potentially eligible studies following the review of titles and abstracts identified from the initial search. One study considered HNC and Oesophageal cancer separately, therefore this paper was included in both arms of the review. Five papers were excluded, based on insufficient number of cases (n=2), failure to report an effect estimate/confidence intervals (n=2) and lack of categorisation by histopathological subtype (n=1). Eight studies met the inclusion criteria, 3 for HNC and 6 for oesophageal cancer, with one being in both arms (100, 106-112). The literature search results and selection process are presented in Figure 3.1 and 3.2, for HNC and Oesophageal cancer respectively.

Figure 3.1. Flow diagram of literature search results and selection process: Head and Neck Cancer

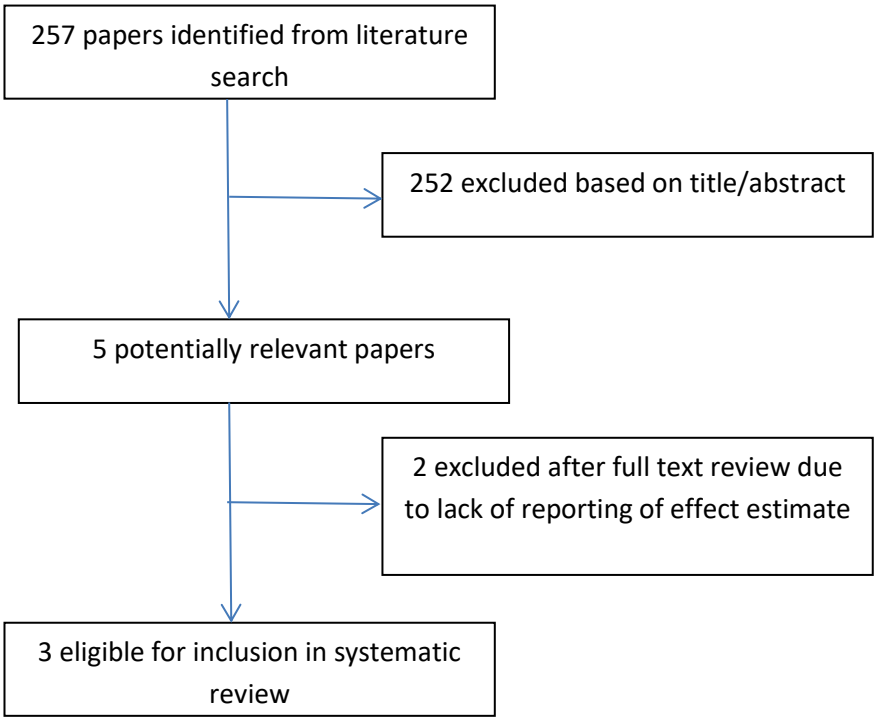
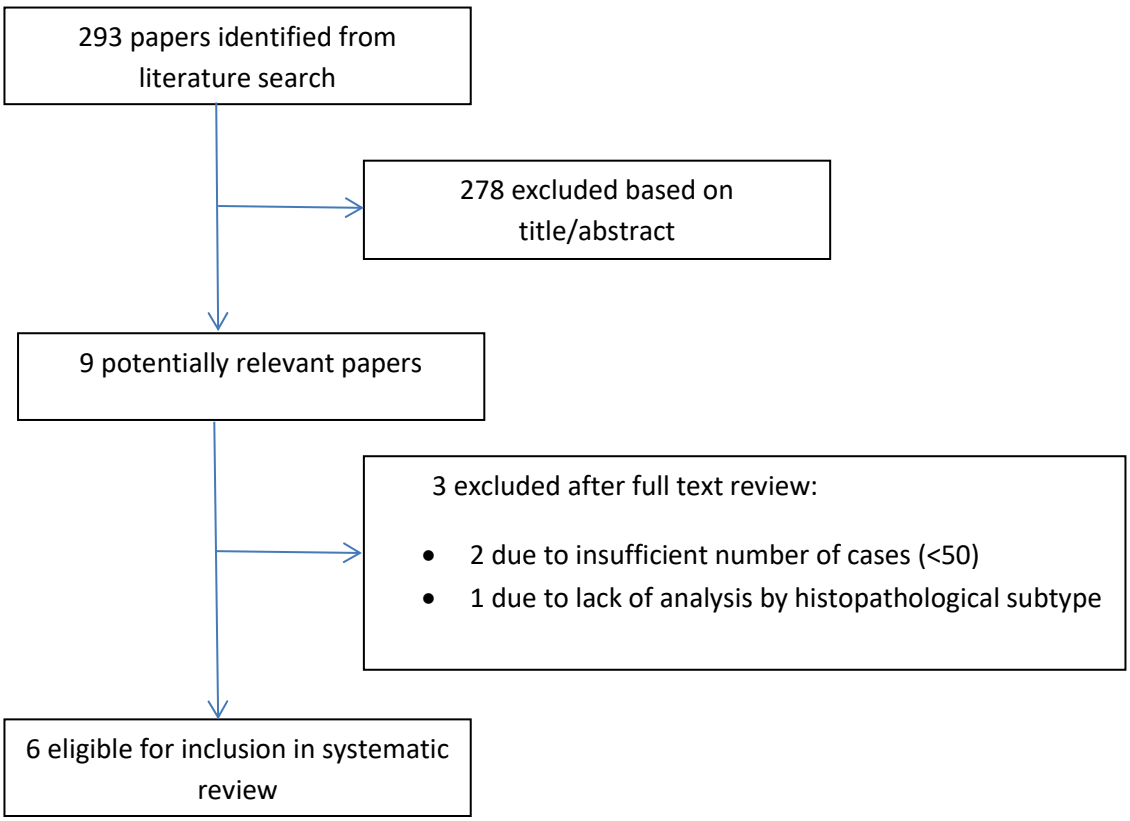


Figure 3.2. Flow diagram of literature search results and selection process: Oesophageal Cancer



The systematic review includes two cohort studies (one oesophageal/HNC and one oesophageal cancer only) (100, 106) with follow-up time of 7.5 and 9.1 years respectively. Six case-control studies (four oesophageal cancer and two HNC) (107-112) were also included. Studies covered the UK (100, 112), USA (106, 107), European continent (108, 113) and China (110, 111).

The mean number of cases per study for the HNC papers was 214 (range 149-297). For oesophageal cancer, the mean case number per study was 163 (range 56-578). A summary of the demographic data for each study is presented in Table 3.2.

A summary of the findings regarding use of hormone replacement therapy and risk of HNC/Oesophageal SCC is shown in Table 3.3. Table 3.4 summarises the findings regarding age at menopause.

Table 3.2. Demographic characteristics of the studies included in the Systematic Review of Hormone Replacement Therapy and Early Menopause, as risk factors for Head and Neck Cancer (HNC) and Oesophageal Cancer.

Cancer Type Studied	Author (Year)	Country	Study Type	Participant demographics	Time period
HNC/Oesophageal	Freedman (2010)	USA	Cohort	NIH-AARP Diet and Health Study Cohort, aged 50-71years (median follow up 7.5 years)	1995-2003
HNC	Langevin (2011)	USA	Case-Control	Cases of primary HNC and complaint-free hospital controls attending ENT department, University of Pittsburgh Medical Center.	2006-2010
HNC	Bosetti (2000)	Italy/Switzerland	Case-Control	Cases of histologically confirmed oral/pharyngeal cancer age <75 years attending hospitals in Italy/Switzerland and hospital controls with acute, non-neoplastic conditions	1984-1997
Oesophageal	Lindblad (2006)	UK	Nested Case-Control	UK General Practice Research Database (UK GPRD) Cohort aged 50-84 years	1994-2001
Oesophageal	Gallus (2001)	Italy/Switzerland	Case-Control	Cases aged < 79years of histologically confirmed oesophageal SCC admitted to study hospitals; hospital controls admitted to the same hospitals for acute, non-neoplastic conditions	1984-1999
Oesophageal	Yu (2011)	China	Case-Control	Cases of histopathologically confirmed oesophageal SCC; hospital based controls confirmed not to have oesophageal cancer.	2008-2010
Oesophageal	Chen (2011)	China	Case-Control	Cases of newly diagnosed primary oesophageal cancer; Hospital controls with no history of cancer	2004-2010
Oesophageal	Green (2012)	UK	Cohort	Million Women Study Cohort (women aged 50-64 years) with mean 9.1 years follow up	1996-2008

*Table 3.3. Results for Hormone Replacement Therapy as a risk factor for HNC and Oesophageal cancer. Significant Odds Ratios or Hazard Ratios are shown in **bold**.*

Outcome of Interest	Author (Year)	Type of Study	Number of cases	Relative Effect (Odds Ratio (OR) or Hazard Ratio (HR))	95% Confidence interval	Risk of Bias (Newcastle Ottawa Scale)
HNC	Freedman (2010)	Cohort	297	**HR 0.78**	0.61 – 0.99	Low (8/9)
HNC	Langevin (2011)	Case-Control	149	OR 0.47	0.20 – 1.08	Medium (6/9)
HNC	Bosetti (2000)	Case-Control	195	OR 0.88	0.45 – 1.72	Medium-High (4/9)
Oesophageal SCC	Lindblad (2006)	Nested Case-Control	74	OR 0.93	0.40 - 2.16	Low (9/9)
Oesophageal SCC	Gallus (2001)	Case-Control	114	OR 0.32	0.09 – 1.13	Medium-High (4/9)
Oesophageal SCC	Freedman (2010)	Cohort	56	HR 0.74	0.42 – 1.26	Low (8/9)
Oesophageal SCC	Yu (2011)	Case-Control	88	OR 0.94	0.53 – 1.70	Medium-high (4/9)

*Table 3.4. Age at menopause and risk of HNC and Oesophageal cancer. Significant Odds Ratios and Hazards Ratios are shown in **bold.***

Outcome of Interest	Author (Year)	Type of Study	Number of cases	Age	Relative Effect	95% Confidence interval	Risk of Bias (Newcastle Ottawa Scale)
HNC	Freedman (2010)	Cohort	297	>55 years	HR 0.92	0.50-1.71	Low (8/9)
HNC	Bosetti (2000)	Case-Control	195	> 50 years	**OR 0.46**	**0.30 – 0.70**	Medium-High (4/9)
Oesophageal SCC	Gallus (2001)	Case-Control	114	> 50 years	**OR 0.43**	**0.22 – 0.83**	Medium-High (4/9)
Oesophageal SCC	Freedman (2010)	Cohort	56	increasing age	**P trend = 0.019**		Low (8/9)
Oesophageal SCC	Yu (2011)	Case-Control	88	<45 years	**OR 2.27**	**1.03 – 4.97**	Medium-high (4/9)
Oesophageal SCC	Green (2012)	Cohort	578	Per 5 years younger	**RR 1.32**	**1.11 – 1.56**	Low (7/9)
Oesophageal SCC	Chen (2011)	Case-Control	68	>48 years	OR 0.94	0.31-2.85	Medium (5/10)

3.5.1 Hormone Replacement Therapy (HRT)

3.5.1.1 Head and Neck Cancer

Three papers (one cohort study and two case-control studies) addressed the question of the use of HRT and incidence of HNC. Only the Freedman *et al* study (8) was considered at 'low-risk' of bias, with a Newcastle Ottawa score of 7/9 stars. This was a cohort study conducted in the USA, using the NIH-AARP Diet and Health Cohort of 125 887 women. 297 cases of HNC were identified with mean follow-up of 7.5 years. The risk of HNC was 22% lower for people who had ever used HRT (HR 0.78;95% CI 0.61-0.99). 44.1% of cases (n=127) had ever used HRT compared to 54.6% of controls (n=106934).

Further analysis by hysterectomy status revealed that the risk reduction was greatest for women with an intact uterus who were current users of HRT for >5 years (HR 0.23;95% CI 0.09-0.57). Interestingly, use of HRT other than oestrogen-alone or oestrogen-progesterone therapy conferred a greater risk of HNC (HR 2.31;95% CI 1.15-4.65); however, this analysis was based on only 9 cases who used an alternative HRT.

Two case-control studies were considered at medium/high risk of bias; they reported a non-significant reduction in risk of HNC for ever-users of HRT (107, 108).

3.5.1.2 Oesophageal SCC

Four studies analysed HRT use and risk of oesophageal SCC. Two were considered low-risk of bias (106, 112) and two were medium/high risk of bias (109, 110). Although all studies reported an effect estimate of <1 for users of HRT, implying a protective effect, none of the results were statistically significant.

3.5.2 Age at Menopause

3.5.2.1 Head and Neck Cancer

Two studies (106, 108) assessed the link between age at menopause and risk of HNC. Bosetti *et al* (108) found a protective effect of later age at menopause (>50 years), with an OR of 0.46 (95% CI 0.30-0.70), although the study was medium-high risk of bias (NOS 4/9 stars). Freedman *et al* (106) found no significant effect on risk of HNC with later age at menopause (>55 years) and this study was scored as low risk of bias (7/9 stars).

3.5.2.2 Oesophageal SCC

Four out of five studies reported a significant effect of age at menopause and risk of oesophageal SCC. The method of reporting varied: Gallus *et al* (109) reported an OR of 0.43 (95% CI 0.22-0.83) for age at menopause of >50 years vs menopause at age <45 years. Yu *et al.* (110) reported an increased risk of oesophageal SCC for women entering menopause at <45 years (OR 2.27;95% CI 1.03-4.97) and for 45-49 years (OR 2.16; 95% CI 1.14-4.78) compared to menopause at age >50 years. Both of these studies were scored as medium-high risk of bias (NOS 4/9 stars). Green *et al* (100) reported increased risk of oesophageal SCC for every 5 years younger a woman was at time of menopause (RR 1.32;95% CI 1.11 – 1.56). Although Freedman *et al* (106) found no significant effect for individual age categories, they did observe a significant trend (p=0.019) for lower risk of oesophgeal SCC with older age at menopause. Green (100) and Freedman's (106) studies were considered low risk of bias, with NOS scores of 7/9 and 8/9 respectively (see Table 3.4). Chen *et al* (111) (NOS score 5/9; medium risk of bias) observed no significant effect for age at menopause, although these authors classified older age at menopause as >48 years.

3.6 Discussion

This systematic review has considered evidence from a total of eight studies investigating the risk of HNC or oesophageal SCC in relation to age at menopause and use of hormone replacement therapy: five papers investigated oesophgeal SCC, two papers investigated HNC and one paper included both cancers.

3.6.1 Early Menopause

The evidence suggests that earlier age at menopause is associated with a higher risk of oesophageal cancer, based on 4 studies with a total of 836 cases of oesophageal SCC.

Most women experience the menopause between the ages of 45 and 55 years; the median age at menopause is 47.2 years, according to a prospective cohort study of over 5000 women enrolled on the Royal College of GP's Oral Contraception study (114). Menopause is 'early' in women aged 40-45 years (~5% of women) and 'premature' in women <40years (~1% of women) (115).

3.6.1.1 Risk Factors for Early Menopause

Early menopause is more frequent in women with certain genetic or autoimmune disorders, infections or a history of chemotherapy/radiotherapy or surgery to remove the ovaries (115). Mean age of menopause for smokers is significantly lower than non-smokers (45.6 years vs 46.9 years) (114). Women with early natural menopause are more likely to be smokers, ever-users of the oral contraceptive pill, undergone tubal ligation, have at least one episode of endometriosis and are less likely to use HRT. No association with alcohol, BMI, physical activity or parity (number of children) is reported (114).

Women with diabetes have also been found to be at risk of early menopause (OR 2.76;95% CI 1.32-5.66) (116). In a pooled analysis of case-control studies, diabetes diagnosed at age < 50 years conferred a greater risk of HNC (OR 1.37;95% CI 1.07-1.74) when analysing 6448 cases of HNC and 13747 controls (117), but no link with age at menopause was considered in this study.

3.6.1.2 Early Menopause and Oesophageal Cancer

A recent systematic review and meta-analysis by Zhu *et al* of oesophageal squamous cell carcinoma and reproductive factors also found a protective effect for older age at menopause (RR=0.70; 95% CI 0.51-0.95) (118). The authors concluded that "properly extending the time of menstruation for pre-menopausal women is a possible way to reduce the risk of oesophageal SCC" (118). However, this meta-analysis was only able to consider evidence from case-control and cohort studies, several of which did not report adjusted risk ratios, therefore the authors calculated crude risk ratios from the reported data, which may have introduced bias.

Another meta-analysis, by Wang *et al*, of eight oesophageal SCC studies, found menopausal status was associated with higher risk of oesophageal SCC (RR 1.66; 95% CI 1.12-2.48) but age at menopause was not significant (6).

3.6.1.3 Early Menopause and HNC

Hashim *et al* published a pooled analysis of hormone factors in female HNC in 2017(119). They used data from 11 studies from around the world, including 1572

cases of HNC and 4343 controls. They report a 69% increased risk for all HNC for menopause at less than 52 years (OR 1.69 95% CI 1.06 – 2.71) compared to menopause over the age of 52 years, which conferred a non-statistically significant increased risk of HNC (OR 1.54 95%CI 0.93 – 2.57).

3.6.2 Hormone Replacement Therapy (HRT)

Hormone replacement therapy is long-established in the management of symptoms of the menopause and has also been shown to reduce risk of osteoporotic fractures, cardio-vascular disease, Alzheimer's, depression, stroke, and colon cancer. Approximately 30% of UK women aged 50-74 years used HRT in 2001-2002 (120). Following this, a large US-based trial (Women's Health Initiative - WHI) was prematurely stopped due to concerns over evidence of increased risk of breast cancer, coronary heart disease, stroke and pulmonary embolism amongst users of HRT (121). The UK-based Million Women Study (MWS) also reported increased risk of breast cancer with HRT in 2003 (122). Following media coverage of the results of these trials, use of HRT declined steadily in the UK for the next 3-4 years. In 2005, only 10-11% of menopausal women were using HRT (120).

However, concerns have been raised by some authors surrounding the reporting of the WHI and MWS trial results and the fact little coverage was given to the evidence of reduced incidence of osteoporotic fractures and colon cancer (123). Both trials recruited women aged over 50 years, therefore the results cannot be applied to women who undergo premature menopause (124). HRT for women with premature menopause (primary ovarian insufficiency), prescribed up to the age of natural menopause (~51 years), is endorsed by the British Menopause Society and NICE guidelines. The NICE guidelines also recommend the development of a collaborative 'primary ovarian insufficiency' registry to allow data collection to clarify, amongst other factors, the long-term risk of cancers in this group (125).

3.6.2.1 HRT and Oesophageal Cancer

The systematic review in this chapter did not find evidence of a significant risk reduction for oesophageal cancer amongst users of HRT. However, all effect

estimates were <1 and the studies included contained only modest numbers of oesophageal cancer cases: the Freedman *et al* cohort study included 297 cases of HNC and was the only study to report a significant relative risk reduction for HNC in users of HRT (HR 0.78; 0.61-0.99).

In a recent meta-analysis of oesophageal cancer and reproductive factors, the authors reported a 33% relative risk reduction with HRT use (RR 0.67; 95% CI 0.56-0.81) (118). Similar results were reported for reduced risk of gastric cancers (RR 0.77; 95% CI 0.64-0.92) (126).

3.6.2.2 HRT and HNC

The review presented in this chapter found a protective effect of HRT for HNC but this was based on one study at low risk of bias (106); Freedman *et al* report a 22% protective effect (HR 0.78;95% CI 0.61-0.99) for ever-users of HRT.

Hashim et al (119) reported a striking protective effect of HRT for HNC, in their pooled analysis (described in 3.6.1.3). For HNC they report a 42% protective effect (OR 0.58 95% CI 0.34-0.77) when considering a total of 626 cases and 1,351 controls who had ever used HRT.

The relationship between HRT and female HNC is assessed using the UK Biobank data, in Section 5.2.11.

3.6.2.2 HRT: Confounding Factors

Confounding factors must be considered: users of HRT tend to be of higher socio-economic status and have higher levels of education. Both factors would reduce risk of HNC. To address this, only studies controlling for a measure of SES or education were eligible for inclusion in the review presented in this chapter. Freedman *et al* (8) controlled for education, alcohol, BMI, tobacco smoking, physical activity and diet (fruit and vegetable intake), although residual confounding could still be relevant.

3.6.3 The Role of Oestrogen deficiency

3.6.3.1 The Female Survival Advantage

Females have been found to have survival advantage in head and neck cancer, oesophageal, gastric and pancreatic cancer, as well as cancers at 11 other sites. For all cancers combined, women have a 5% lower risk of death than men; for head and

neck cancer, 12% improved survival is reported (39). This finding is consistent across all European regions in the EUROCARE-4 cohort of 1.6 million population-based cancer cases (127). The advantage is most pronounced in younger women and declines with age, with a marked decline beyond the age of menopause. It is possible that female hormones play a part in this 12% improvement in survival.

3.6.3.2 Oestrogen and Cancer

Oestrogen is known to promote cancer in oestrogen-responsive tissues, such as breast, endometrium and cervix, however evidence from mouse models suggests that oestrogen has an inhibitory role in oesophageal SCC growth (128). Oestrogen receptors have been found in oesophageal SCC tissue samples and HNCs (128-130). Oesophageal SCC cells with oestrogen receptors have been shown to be inhibited by oestrogen exposure and this may initiate apoptosis (131). Oestrogen appears to have both tumour-promoting and anti-tumour properties, depending on the tissue and presence of oestrogen receptors. Head and neck cancer cell lines, from males and females, have been found to contain oestrogen receptors, and laboratory studies appear to show that oestrogen promotes growth of HNC cells (132, 133).

3.6.3.3 Cumulative Oestrogen Exposure

If oestrogen is responsible for inhibiting the growth of some cancer cells, oestrogen deficiency could be considered a risk factor for certain cancers. A woman who undergoes premature menopause has less oestrogen exposure over her lifetime and this may increase risk of cancers such as oesophageal SCC or HNC. However, further high-quality basic science studies are required to confirm the role of oestrogen in HNC and oesophageal SCC.

3.6.4 Limitations

The studies included in this review were all assessed for risk of bias, using the Newcastle Ottawa scale. Only three of the eight papers included were low risk for bias. This does limit the significance of our findings and is an indication of the need for further, high quality studies addressing the issue of female hormones and squamous cancers.

We have only included studies that control for significant potential confounding factors, such as smoking and socio-economic status, however, the risk of residual

confounding remains. Smokers are at risk of early menopause, so this is something that needs to be properly controlled for in future studies in this area. Equally, users of HRT are likely to be of higher socio-economic status, which is a protective factor for HNC; studies should collect data on deprivation so that this might be controlled for.

The rationale for combining head and neck cancer and oesophageal squamous cell carcinoma is based on the strong similarities in their epidemiology and aetiology. We have deliberately excluded oesophageal adenocarcinomas as these cancers have quite different aetiology. One of the papers included in our review by Bosetti *et al* (9) fails to clarify the histology of the oral/pharyngeal cancer cases included, which introduces a potential source of bias. However, over 90% of oral cancers and more than 80% of pharyngeal cancers are of squamous histology (46), therefore the bias is unlikely to be significant.

3.7 Conclusion

Earlier age at menopause is a risk factor for oesophageal squamous cell carcinoma, with women entering menopause at <45 years having double the risk of those entering menopause age >50 years. Similar, but less striking, results were observed for HNC. Hormone replacement therapy was found to reduce the risk of HNC/Oesophageal SCC but the evidence is not conclusive.

Strict eligibility criteria were used and only studies that controlled for other risk factors were considered, however there is still risk of residual bias.

Data on reproductive factors and exposure to HRT should be collected, as routine practice, in future epidemiological and clinical studies of these cancers. The concept of oestrogen deficiency as a risk for HNC/oesophageal SCC deserves further exploration in appropriate laboratory and clinical studies. Chapters 2 and 3 have demonstrated an increasing incidence of HNC in England and explored novel, female-specific risk factors. Chapter 4 describes the methodology used to develop and validate a risk prediction model for HNC, using the UK Biobank dataset.

Chapter 4

Methodology for developing the first risk prediction model for Head and Neck Cancer

4.1 Introduction

Chapters 2 and 3 have presented results on the increasing incidence of HNC in England and explored novel risk factors for female HNC. The role of risk modelling in cancer prediction was discussed in Chapter 1 (section 1.3 and 1.4). This chapter will describe the methodology used to develop the first risk prediction model for absolute risk of HNC, using data from the UK Biobank. Study design is considered in 4.3 and the UK Biobank dataset is described in 4.3.2. Methods for data cleaning and handling of missing data are discussed in 4.3.3, as well as the issue of handling of continuous predictors (section 4.3.5). Logistic regression is discussed in 4.4.4 and the issue of number of events per variable (EPV) is considered in 4.4.5.2. Methods for assessment of model performance are briefly covered in 4.5 and expanded later in Chapter 6.

Finally, the TRIPOD guidelines (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) are discussed in 4.6 as an essential framework for ensuring that this HNC risk prediction model is robustly developed, validated and presented (134, 135).

4.2 Research Question

The aim of this study is to develop an internally and externally validated prognostic model for predicting an individual's risk of developing HNC. This would inform the

organisation of future screening programmes for HNC to ensure their efforts and finances are focussed on the highest risk individuals.

The question being addressed is: “Can a large-scale dataset, containing data from 500,000 individuals, be used to create a risk prediction model, which will accurately predict an individual’s risk of developing head and neck cancer?”

4.3 Research Design

4.3.1 Options for Study Design: Observational Studies

Observational studies are frequently used to study risk factors and for predicting risk of disease. Randomised controlled trials are not feasible for this type of project as it would be unethical to expose people to harmful risk factors (e.g. smoking) in order to determine which diseases they develop. Equally, due to strict inclusion and exclusion criteria, the population enrolled may not be representative of the general population (136).

Prospective cohort studies, case-control studies and cross-sectional studies are all valid types of observation study, through which to collect data for development of a risk prediction model (137). Time available, budget and rarity of the disease will influence the type of study chosen to collect the necessary data. As pre-existing databases can be used for developing a risk prediction model, these considerations are not relevant, rather it is the quality of the study used to develop the database that should be considered.

4.3.1.1 Prospective Cohort Studies

Prospective cohort studies have an advantage that participants are disease-free at recruitment, therefore the researcher knows that the exposure of interest precedes the outcome. This allows calculation of incidence, rather than simply prevalence (as is the case with cross-sectional studies) (137). The researcher is also able to determine cause and effect, rather than simply reporting an ‘association’ between a risk factor and a disease, although one must be aware of the risk of confounding, even with prospective cohort studies. Prospective studies also allow the study of rare exposures and allow examination of multiple effects of a single exposure (137); for

example, one can study the effect of smoking on incidence of cardiovascular disease, lung cancer and HNC.

However, prospective cohort studies are often not appropriate when studying rare diseases or those with a long latency period, such as head and neck cancer (138) ; to develop a dataset with enough numbers of individuals with the outcome of interest, to provide an appropriately powered study, would take many years (137). Prospective studies are time-consuming and expensive and there is often an issue of differential loss to follow up between those who develop disease and those who do not, which introduces bias (139, 140).

4.3.1.2 Retrospective Cohort Studies

Retrospective cohort studies involve going back to existing data, developing a cohort within this and determining which risk factors were present in those who developed the disease. As the study will have been designed without the present question in mind (for example risk factors for HNC), it is possible that the dataset will not contain all relevant information related to the disease in question, which means that potentially relevant risk factors may not be included in the model (136, 141); however, retrospective cohort studies are preferred to case-control studies as the risk of recall bias is reduced (137). Recall bias describes the situation whereby those with a disease are more likely to remember exposure to risk factors than those without the disease.

4.3.1.3. Case-Control Studies

Case-control studies compare separate groups of cases and controls retrospectively and seek to identify predictors of outcome. They are particularly useful when studying rare diseases, when a cohort study would take too long. New hypotheses can be generated with the findings of case-control studies, which can be tested in future prospective studies. Cases are recruited from a particular population, for example patients attending a head and neck cancer clinic; controls may be recruited from the general population but are often recruited from hospital patients who do not have the disease in question. This introduces selection bias as they may not be representative of the general population. Controls are usually matched to cases in terms of age and sex to reduce confounding. Case-control studies are cost-efficient

and allow calculation of odds ratios; they examine the relative importance of a predictor (risk factor) in relation to the presence or absence of disease. A case-control study is often the only feasible option when there is a long latency period between the exposure and outcome (142), e.g. smoking and head and neck cancer.

4.3.1.4 Nested Case-Control Studies

Nested case-control studies provide an alternative study design when developing risk prediction models. The 'nested' design, whereby the case and control groups are nested within an existing cohort database, overcomes some of the disadvantages of case-control studies and has some of the advantages of cohort studies (143, 144). Those who have developed the disease are 'cases' and those who have not are used as 'controls'. This should mean the cases and controls are more representative of the population, when compared to recruiting from a single centre, for example (145). The issue of recall bias is also reduced as the data were collected prospectively; however, some 'cases' may have already had the disease at recruitment. As with retrospective cohort studies, the problem of incomplete data or failure to record details of all pertinent risk factors could be a problem with nested case-control studies (141).

4.3.1.5 Existing Databases

Pre-existing databases are a convenient source of data (141); data has been collected by people other than the researcher and independently of any hypothesis, thereby reducing observer bias and standardising data collection. The main disadvantage is that the type of data collected may not be ideally suited to the current hypothesis (141).

4.3.2 The UK Biobank Dataset: a nested case-control study

To answer the research question posed ("Can we reliably predict an individuals' risk of developing head and neck cancer?"), a nested case-control study design is used here. The case-control study is nested within the UK Biobank dataset, a prospective cohort study of over 500,000 individuals.

The UK Biobank is a UK-based project, which has involved collecting large amounts of data from over half a million people from the general population of the United Kingdom. It provides a uniquely rich resource for the study of risk factors, with the

aim of helping researchers to understand the causes of diseases and to find better ways of preventing and treating many conditions.

The UK Biobank recruited over 500,000 persons aged 40-69 years between 2006 and 2010. These participants have provided detailed information about themselves and have agreed to have their health followed; this will develop a powerful resource for scientists to discover why some people develop diseases and others do not. Data on a wide range of exposure and health-related outcomes have been collected.

The UK Biobank was established by the Wellcome Trust (www.wellcome.ac.uk) and is supported by many other charities, government bodies and the NHS. The biobank links to several electronic records, including cancer registries, death registers, hospital episode statistics and general practice records. As time goes on, more health events will occur, and the resource will become increasingly valuable.

Researchers can apply to have access to the dataset for a clearly-defined research programme and can select which information they receive from several categories (e.g. genetic data, population characteristics, health-related outcomes etc.) The application is a two-stage process, preliminary and main application, including a lay summary, scientific rationale for the project, feasibility, security protocols for the data, funding details and a timeframe for the project. The application is reviewed by the UK Biobank application sub-committee and when approved, charges must be paid in full.

4.3.2.1 Data Protection

Prior to release of anonymised data to researchers, the principal investigator, their institution and any collaborators are required to complete a Material Transfer Agreement. This details the specific purpose for which the data will be used and standard terms relating to the dissemination and exploitation of results. See Appendix 4.

In this case, the application process took over one year up to the point the data were released, and the cost was £2500,

4.3.2.2 Participants

Researchers within UK Biobank planned to recruit 500,000 participants from the UK; this number was based on power calculations, assuming the dataset would mainly be used for nested case-control studies. Further details of the power calculations can be found in the UK Biobank Protocol (146).

Eligible participants were identified from population-based registers, held by the NHS. 35 assessment centres were set up around the UK, with 10 million eligible people living within 10 miles of an assessment centre. The importance of good transport links, disabled access and availability of evening appointments were considered when setting up the assessment centres. A pilot study of 300 individuals was conducted to allow refinement of the protocol. Based on this, it was estimated that around 5 million primary invitations would need to be sent to achieve recruitment of 500,000 individuals.

4.3.2.3 Data Collection and Validity of Data

Participants first completed the consent process via a touch-screen electronic system, allowing for direct data entry. A touch-screen self-administered questionnaire was used to collect most data, which has ensured good response-rates to sensitive questions, as privacy is maintained when compared to interview.

A subsequent computer-assisted personal interview was completed, based on 'screening' questions asked as part of the touch-screen questionnaire; for example, patients who indicated they had a particular medical condition would be asked follow-up questions during the interview. The full assessment lasts around 90 minutes.

Questions can be divided into the following categories:

- Sociodemographic factors
- Smoking and alcohol
- Family history and early life exposures
- General health and disability
- Environmental factors
- Dietary habits
- Physical activity
- Psychological and cognitive state

The findings of a review of questionnaires used in previous scientific studies and trials, as well as consultation with international experts in each area, were used to develop the questionnaire used in UK Biobank (146).

Baseline physical measurements were also recorded by trained staff at the recruitment centres; the measurements were chosen based on relevance, reliability and resources: blood pressure, weight, height, waist and hip circumference, bio-impedance (body-fat), hand-grip strength and bone densitometry were measured (146).

4.3.3 Data Cleaning

Due to the large file size (1.7GB), it was necessary to access the dataset via a University of Liverpool virtual machine. The dataset was imported to R statistical software (147). The UK Biobank dictionary of variables (n=7,800) was then reviewed to determine which variables could be removed from the outset, using prior clinical knowledge. Variables that are very unlikely to be risk factors for HNC, for example 'number of falls in the last year' and 'plays computer games – yes or no' were removed.

4.3.3.1 Missing Data

The remaining variables were then assessed for amount of missing data. Many of the questions were only asked to a smaller number of participants, based on answers to

previous questions, e.g. specific smoking-related questions were only asked to participants who disclosed they had previously smoked. For this reason, it was not possible to create a rule whereby variables were discarded based on amount of missing data; variables had to be assessed individually to determine their relevance to the research question, based on clinical knowledge and literature. Missing data is discussed in more detail in section 4.4.3.

As this study requires only baseline characteristics, rather than repeated measures, it was necessary to drop a large number of variables representing repeated measures; it was noted that these variables had a large amount of missing data (over 90%) in some cases and therefore would have added little to the analysis.

A working dataset containing 233 variables, with some relevance to HNC and with less than 20% missing data, was created by discarding variables as described. The full list of variables included in the development dataset is presented in Appendix 5. The rationale for retaining these variables in the dataset is discussed in Chapter 5.2.

4.3.3.2 Inconsistencies in the Data

Data were assessed for inconsistencies and outliers. Cancer Registers often have the same cancer registered twice, with slightly different/updated information. Many of the HNC cases within the dataset appeared to have had two HNC at the same anatomical site, days apart; obvious errors like these were corrected by removing the details of the 'second' HNC. The rules applied for managing variables are presented in Appendix 6.

4.3.4 Identification of Head and Neck Cancer cases

International Classification of Disease-10 codes (148) were used to identify patients within the dataset who had HNC. ICD-10 codes C00-C14 and C30-31 were used to represent HNC. Laryngeal cancer was excluded from the initial model; it would be useful to consider building a separate model for this disease, due to the differences in epidemiology and risk factors. The male:female for laryngeal cancer ranges from 4:1 (80) up to 36:1 (71) , compared to 2:1 for oral cancer (149) (see sections 2.4.2 and 2.5.2). Smoking and drinking alcohol account for 90% of cases compared to 64% for

oral cavity (88). There have also been differences identified at the molecular level, in the pathway of carcinogenesis, when comparing laryngeal cancer and oral cancer (150). Laryngeal lesions are not visible via oral examination, therefore General Dental Practitioners (GDPs) are not involved in the detection of laryngeal cancer. Given that the model will be aimed at GDPs it would not be appropriate to include laryngeal cancers in this context. As described, oral and OPSCC have a mixed-aetiology, whereas laryngeal cancer has a high PAR for smoking and alcohol, therefore it is possible that other relevant risk factors for oral and OPSCC would be masked by including laryngeal cancers in the model. For these reasons, a separate model for laryngeal cancer can be considered in the future.

4.3.5 Handling of Continuous Variables: Categorisation and Fractional Polynomials

One of the assumptions of a logistic regression model is that the relationship between the log odds of the predictor variable and the outcome variable is linear (151). There are three main options for addressing a non-linear relationship: variables can be categorised at arbitrary cut-off points, or fractional polynomials or cubic splines can be used (152). Categorisation of continuous variables reduces power through loss of information and can lead to serious bias (153). Several authors have recommended avoiding categorisation or dichotomising of continuous variables (154-156), as models developed using categorised variables display poorer performance (157). Royston and Altman developed the concept of fractional polynomials as a flexible way of modelling a non-linear relationship between predictor and outcome variables (158). Using multivariable fractional polynomials allows us to test for deviation from linearity using fractional polynomials to model non-linear effects. This first involves transforming the variable to ensure the value is not less than zero and then applying a power function from a pre-determined set of (-3, -2, -1, 0, 1, 2, 3) (159).

The output of the logistic regression analysis when using fractional polynomials can be obscure and difficult to interpret (152). For this reason, FPs are not used in building the logistic regression model for HNC (in Chapter 6) as an easily-interpreted output is considered more important than a slight improvement in model performance (157).

However, categorisation of continuous variables has been avoided to prevent loss of data. Categorisation results in poorer model performance (157) and is thought to be unnecessary, biologically implausible and an inefficient use of data (154, 157). However, in some cases clinical interpretation is simplified by categorisation: the 'Townsend deprivation index' (160) is presented as a continuous variable, with the score commonly categorised into quintiles; one is most deprived and five is least deprived, to allow for more meaningful analysis and interpretation of results.

4.4 Model Development

4.4.1 Descriptive Analysis

Individual variables were assessed using descriptive statistics. Data are presented for cases and controls and separated by gender.

Histograms were used to view data from continuous variables as a crude check for normality. In cases of normally distributed data, a mean and standard deviation is presented and a two-sided students t-test was completed. For skewed data, median and interquartile range is presented, along with results of a Mann-Whitney U test of significance at the 5% significance level.

For categorical data, numbers and percentages are shown in each category. A chi-squared test was completed where appropriate with a Fisher's Exact test used when the number per cell dropped below 5. Again a 5% significance level was used.

4.4.2 Planning Model Validation: Splitting the Dataset

An important part of model development is internal and external validation of model performance and this is discussed in more detail in Sections 4.5, 6.6.2, and 6.6.3. It involves quantifying a model's performance (based on discrimination and calibration of the model) initially internally, i.e. within the data used to develop the model, followed by external validation in data not used to develop the model. This accurate estimation of model performance allows us to draw meaningful conclusions regarding the model's predictive accuracy (161).

This can involve testing the *reproducibility* of the developed model on different samples from the same or similar populations, for example data collected from the same population at a different point in time or at a different geographical location.

Another form of external validation tests the *transportability* of the model into different populations; in this case a completely independent dataset is used, often including patients from entirely different populations.

In order to be classed as completely external, the validation should be carried out on completely independent data, by researchers who did not develop the original model. Completely independent data with sufficient numbers of events and containing information on all relevant predictors is difficult to find, thus many models that are developed are not tested externally (162).

With very large datasets, such as the UK Biobank, splitting the dataset into development and validation sets is a recognised way of allowing the model to be tested 'externally'. The validation dataset should have a minimum of 100 events (163) and ideally closer to 200 (164). A non-random split in the data is recommended, e.g. data could be split based on geographical location, sex, smoking-habits, or based on presence of particular diseases e.g diabetes (163).

4.4.2.1 Geographical Split of the Dataset

The UK Biobank data was collected at 22 main assessment centres around the UK. The prevalence of HNC is variable around the UK, therefore it was decided to split the dataset into development and validation datasets based on geographical location of assessment centres. The data from assessment centres in the North West (Manchester, Liverpool, Bury and Stockport) were separated to become the 'validation dataset', containing 157 cases of HNC. Data from other centres were retained for the development dataset. The North West is known to have a high prevalence of HNC, therefore it is useful to validate the prediction model in this subset of the population (149). It is recognised that the North East also has a high incidence of HNC (see Section 2.4.3), however, the number of cases from this part of England within the dataset (n=92) is less than the North West (n=157) and does not reach the minimum 100 cases recommendation (163) (discussed in Section 4.4.2) for the validation dataset.

4.4.3 Multiple Imputation

Missing data is a problem common to many studies. It is possible to simply omit the data from the analysis (complete case analysis) but this risks losing potentially useful information. If the data are not missing completely at random, i.e. there is an underlying reason for the missingness, one risks severely biasing the results by omitting observations with missing data (165).

Multiple imputation (MI) is a method for mitigating this loss of information, which allows the retention of all available information, potentially reduces bias and improves efficiency in parameter estimation (166). MI is a simulation-based procedure; each missing value is replaced by $m>1$ reasonable values, creating m complete datasets, which are then analysed using standard statistical procedures(166). The model is developed on each imputed dataset and the model estimates and fit statistics are combined using Rubin's rules (167, 168).

4.4.4 Developing the Risk Prediction Model: Logistic Regression Analysis

Risk prediction models are used to predict the risk of a future health outcome, in the case of HNC, in a presently healthy individual. To examine the research question, a regression analysis is used. If data are available on time-to-event, a Cox Regression can be used. However, where data regarding time are not available, logistic regression is the preferred statistical tool for developing a prediction model.

A binary logistic regression will be conducted to assess if the independent variables predict the dependent variable, "development of head and neck cancer – yes or no". Binary logistic regression is an appropriate statistical analysis when the purpose of research is to assess if a set of independent variables predict a dichotomous dependent variable (151). This type of analysis can be used when the independent variables (predictors) are continuous, discrete, or a combination of continuous and discrete. This method of analysis evaluates the odds of membership in one of the two outcome groups, based on the combination of predictor variable values.

Binary logistic regression analysis overcomes many of the assumptions of linear regressions. For example, linearity between dependent and independent variables, normality and equal variances are not assumed, nor is it assumed that the error term (residuals) variance is normally distributed. The major requirement is that the outcome variable must be dichotomous. There should be no multicollinearity among the independent variables (i.e. the predictor variables should not be highly correlated with each other), there should be no outliers, and there should be a linear relationship between the log odds and the independent variable (151).

4.4.5 Variable Selection

4.4.5.1 Clinical Significance of Variables vs Univariable Screening

Univariable screening is not recommended (169, 170); it involves testing all predictors individually, i.e. running a logistic regression model for each predictor variable, one at a time. The statistical significance of each predictor is assessed and a decision is made whether or not to include the predictor in the final model (see below).

Simply excluding all non-significant variables can wrongly rule out important predictors (171) but it is important to acknowledge that including non-significant variables may lead to reduced precision of estimation other effects, without necessarily adding validity. In our case, lack of significance will not prevent the variable being included in the model, rather the clinical significance of the variable will be considered in conjunction with the statistical significance. Highly correlated variables will not be included to avoid bias within the model (151). Variables will be selected for the model if there is robust evidence of a causal association between the risk factor and HNC. Evidence from meta-analyses, systematic reviews or large observational studies, published in peer-reviewed journals, will be considered.

4.4.5.2 Events per Variable (EPV)

The relative number of cases (“Events”) to number of regression coefficients estimated (excluding the intercept) is known as the ‘Events Per Variable’ ratio. This has been shown to be a key predictor of model performance (134). When EPV is low,

the association between predictors and the outcome estimated by logistic regression can be inaccurate and biased (too extreme) (172, 173). Models built within small datasets suffer the same problem (174). 10 EPV has been adopted as a minimum for performing binary logistic regression analysis (135) although more recent work shows that the evidence for this figure of 10 is weak as it is based on only three EPV simulation studies (173, 175, 176). The risk of finite sample bias (over-optimistic estimates of the true association between predictor and outcome) is higher when small datasets are used to estimate logit coefficients (177). This can be overcome by increasing the total sample size, whilst keeping EPV constant i.e. increasing the number of non-events or 'controls' (177).

We ensured a minimum of ten events per variable (EPV) in order to reduce bias and increase reliability of parameter estimates(175). We also used a minimum of 10 controls per case.

4.4.5.3 Variable Selection for the Final Model

Selection of variables for the final model can be achieved through various methods, when developing a risk prediction model. Fitting the full model, i.e. with no prior variable selection is one method. More commonly, an element of automatic selection, either forward, backwards or stepwise selection is used (151).

The aim is to develop a model that accurately predicts an individuals' risk of developing head and neck cancer, using a parsimonious multivariable model. This means only including variables (predictors) that improve the fit of the model.

4.4.5.3.1 Forwards Selection

Forward selection involves starting with no variables in the model and adding the most significant variable (from univariable analysis) first. One then continues to add one variable at a time and test to see if they improve the fit of the model (151, 178).

4.4.5.3.2 Backwards Selection

Backwards selection involves starting with the full model then removing the least significant variable (from univariable analysis) and retesting to determine the impact on model fit. This process is repeated until the parsimonious model is achieved. This method evaluates each predictor after accounting for other variables (179).

4.4.5.3.3 Stepwise Selection

Stepwise selection is a method that allows moves in either direction, dropping or adding variables at the various steps. *Backward stepwise selection* involves starting off in a backward approach and then possibly adding variables back in if they later appear to be significant. The process is one of alternation between choosing the least significant variable to drop and then re-considering all dropped variables (except the most recently dropped) for re-introduction into the model. This means that two separate significance levels must be chosen for deletion from the model and for adding to the model. The second significance must be more stringent than the first (151, 178).

4.4.5.3.4 Forward Stepwise Selection

Forward stepwise selection is also a possibility, though not as common. In the forward approach, variables once entered may be dropped if they are no longer significant as other variables are added (178, 180).

The results of applying data-driven approaches may not be reproducible; it is important to always consider the clinically relevant variables for inclusion in the model, even if they do not appear to be significant (178).

4.5 Model Validation

Assessment of model validity is a key requirement of a risk prediction model; it indicates the usefulness of the model in clinical practice. This is discussed in detail in chapters 6 and 7.

4.5.1 Apparent Validation

Apparent validation involves using statistics, such as the Area under the Receiver Operating Curve (AUROC) (see 6.6.1) and calibration curve (see 6.6.2) to assess the performance of the model (discrimination and calibration) in the data in which it was developed.

4.5.2 Internal Validation

Internal validation involves assessing model performance within the existing dataset. There are different methods commonly used for internal validation: split-sampling/cross-validation and bootstrapping are discussed in detail in 6.6.3.1 and 6.6.3.2.

Briefly, cross-validation involves splitting the dataset into development and validation sets, then developing the model in the development set and validating it in the validation set. This process can be repeated several times, taking new random subsamples each time, to improve the stability of the cross-validation process (181).

Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, of the same size as the original data set (182). Models may be developed in bootstrap samples and tested in the original sample or in those subjects not included in the bootstrap sample (183). This method has been shown to result in more accurate estimation of model performance (184, 185).

4.5.3 External Validation

External validation tests the model on completely independent data and indicates how well the model adapts to different clinical situations. In our case, the dataset has been split into development and validation sets based on geographical region. The model was built using the development dataset, which contains 702 cases of HNC and validated within the validation set, containing 157 cases of HNC from the North West of England.

4.6 TRIPOD Guidelines

The TRIPOD guidelines have been developed by a collaborative group of academics and clinicians, with the aim of improving the reporting of risk prediction models (134). Moons *et al* (135) cited 49 papers as examples of poorly-reported risk models, to demonstrate the need for guidelines. Transparent reporting of the model development and validation process is vital to ensure the risk of bias can be accurately assessed and the usefulness of the model can be determined by researchers external to the development process (135). This will also help policymakers decide whether to recommend the use of the model when developing clinical practice guidelines (135). The TRIPOD checklist comprises 22 items covering the entirety of the publication of the model: title, abstract, introduction, methods, results, discussion, supplementary information and funding (134). The checklist encourages publication of coefficients for predictor variables (rather than simply odds ratios), so that the model can be tested in external data, by authors not involved with the development of the model. TRIPOD guidelines have been followed in the development and validation of the model presented in Chapters 6 and 7. The TRIPOD checklist is in Appendix 7, with links to the relevant sections of this thesis to demonstrate compliance with the guideline.

4.7 Conclusion

This chapter has described the methodology that is used in the development of a risk prediction model for predicting absolute risk of HNC. The dataset is split based on

geographical region (Section 4.4.2.1) to allow for subsequent external validation of the model (Chapter 7). The risk model is developed using logistic regression analysis and univariable screening and automated variable selection methods are avoided (Section 4.4.5.1). Methods for assessment of model performance are discussed in more detail in Chapter 6.

The next chapter (Chapter 5) describes details of the UK Biobank dataset and presents descriptive statistics for each of the predictor variables considered relevant to HNC.

TRIPOD guidelines are followed throughout the development, validation and reporting of this risk prediction model.

Chapter 5

Results: Descriptive Statistics

5.1 Introduction

The previous chapter described the methodology used to handle the large, UK Biobank, dataset and produce a working dataset for development of an HNC risk prediction model. Section 4.4.2 also described how the dataset was split, based on geographic region, into development and validation datasets. This is so that the final model may be validated in data from a cohort from the North West of England, which was not used to develop the model.

This chapter contains a description of why these variables were selected, using clinical evidence and summary statistics to compare HNC cases with controls (section 5.2). A detailed description of the HNC cases can also be found in 5.3, with a breakdown of subtypes and outcome. The variables considered for the risk model can be placed into the following categories:

- Demographic information (section 5.2.1)
- Social Deprivation (section 5.2.2)
- Smoking (section 5.2.3)
- Alcohol (5.2.4)
- Diet and Exercise (5.2.5 and 5.2.6)
- Medical History (5.2.7 and 5.2.8)
- Sexual History (5.2.12)
- Hormone-related (females only) (5.2.11)
- Other risk factors (5.2.9, 5.2.10 and 5.2.12)

5.2. The Results

Sections 5.2.1 to 5.2.13 consider differences in demographic data, socio-economic status, smoking, alcohol, diet, exercise, medical history, baseline measures of current

health, engagement with screening programmes, breastfeeding, female-specific hormone risk factors, sexual history and other novel risk factors.

5.2.1 Demographic Information

The dataset contains 859 cases of Head and Neck Cancer (HNC) and 501,788 controls. Table 5.1 summarises the differences in demographics and socioeconomic factors between HNC cases and controls.

534 cases are male (62.2%) and 325 are female (37.8%).

228,644 controls are males (45.6%) and 273,144 are females (54.4%).

Male to female ratio of cases is 1.64:1 and for controls 0.82:1 ($p<0.001$).

The mean age of the cases is 58.6 years (female) and 58.8 years (male). Controls were significantly younger: 56.3 years (female) and 56.7 years (male); $p<0.001$ for both genders.

Most cases (90.8%) and controls (91.1%) were born in the UK, with less than 10% of participants born elsewhere.

The UK Biobank contains both prevalent and incident cases of HNC: 552 (64.3%) were diagnosed prior to recruitment and 307 (35.7%) were diagnosed post-recruitment. The mean time to diagnosis post recruitment was 2.5 years (range 0 – 6.8 years). The mean time between diagnoses and recruitment for prevalent cases was 7.14 years (range 0 to 37.9 years).

The average period at risk per subject was calculated from date of birth to 7 years post-recruitment (the most recent available update on cancer registry linkage). Total person-time-at-risk was 31,932,329 years with a total of 859 cases. This gives a rate of 0.027 per 1000 person-years. The average period at risk was 63.5 years.

5.2.2 Socio-Economic Deprivation

Socio-economic deprivation has been strongly linked with male risk of HNC (35). One marker of area-level deprivation is the Townsend Deprivation Score (160). This score

is calculated from several measures of individual deprivation, from consensus data, such as car ownership, education, employment, number of persons per household and income. It has the benefit that it can be calculated from routinely collected data (area postcode). However, it has disadvantages over collecting individual measures of deprivation as the data used to calculate the Townsend score is often calculated from census data that may be over 12 years old (186). It also assumes that persons living within the same electoral ward are socio-economically homogenous, which is unlikely to be true (186). This makes the Townsend Score particularly inaccurate for mobile, inner-city populations. In a study of alternative measures of health in relation to deprivation, annual household income and National Statistics Socio-Economic Class (NS-SEC) (formerly Socio-Economic Group) were found to be two measures which account for the largest variation in self-reported health (186).

Lower level of education has previously been found to confer increased risk of HNC in the INHANCE consortium (an international combined cohort study containing 23,964 cases of HNC); OR 1.34 (1.04-1.73) (35). Conway *et al*. also found that those with the lowest income had a 56% increased risk of HNC, when controlling for smoking, alcohol, diet, age and gender (OR 1.56 (1.29-1.88)) (35).

Table 5.1 presents the socio-economic data for this UK Biobank data, separated by HNC cases and controls and gender. Within the UK Biobank, 14% of male cases (n=76) live in the most deprived areas of the UK (Townsend Deprivation Quintile 5), compared with 9% of male controls (n=21,230) ($p<0.001$).

There was no statistically significant difference in level of education between cases and controls for females or males, although male cases left full time education at a statistically significantly younger age than controls (see Table 5.1). There was a significant difference in the employment status between cases and control, with significantly more males and female cases being retired and unable to work due to illness, compared to controls. This is likely to be explained by the older age of cases vs controls and the fact they have diagnosis of HNC.

In the current study, 30% of male cases (n=138) reported an annual household income of <£18,000 in comparison to 20% of controls (n=41,652) ($p<0.001$). Figures

are similar for female cases and controls, with 33% (n=86) of female cases living in households with <£18,000 annual income, compared to 24.8% (n=55,350) of controls. The lower income could be attributed to the fact cases tend to be older and are more likely to be retired or unable to work due to their illness, although other studies support lower income as a risk factor for HNC (35).

Table 5.1. Demographic and Socio-economic Data: Differences between HNC Cases and Controls in the UK Biobank. p value <0.05 is considered statistically significant. ***Bold*** *indicates a significant result.*

Variable		**Head and Neck case**				**Control**				**p-value**	
		Male		**Female**		**Male**		**Female**			
Number		534		325		228,644		273,144		**<0.001**	
	%	62.2		37.8		45.6		54.4			
Age at recruitment (mean years (SD))		58.8 (6.86)		58.6 (6.82)		56.7 (8.20)		56.3 (8.00)		Males	**<0.001**
										Females	**<0.001**
Townsend Deprivation Quintile		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
	1	173	32.4	113	34.8	82,341	36.1	97,981	35.8	Males	**<0.001**
	2	107	20.0	75	23.1	53,724	23.5	65,897	24.2	Females	0.61
	3	86	16.1	62	19.1	39,835	17.4	49,157	24.2		
	4	92	17.2	41	12.6	31,218	13.7	37,335	13.7		
	5	76	14.2	34	10.5	21,230	9.3	22,443	8.1		
Average total annual household income											
£ (before tax)	< 18,000	138	30.3	86	33.2	41,652	20.7	55,350	24.8	Male	**<0.001**
	18,000 - 30,999	112	24.5	90	34.8	49,253	24.4	58,746	26.3	Female	**<0.001**
	31,000 - 51,999	113	24.8	44	17.0	53,909	26.7	56,727	25.4		
	52,000 - 100,000	74	16.2	33	12.7	44,577	22.1	41,608	18.7		
	>100,000	19	4.2	6	2.3	12,190	6.1	10,719	4.8		

Table 5.1 continued. Demographic and Socio-economic Data: Differences between HNC Cases and Controls

Variable	Head and Neck case				Control				p-value	
	Male		**Female**		**Male**		**Female**			
Country of Birth	N	%	N	%	N	%	N	%		
England	398	74.5	243	75.0	179,177	78.7	210,782	77.4	Males	**0.04**
Wales	30	5.6	15	4.6	10,135	4.4	11,903	4.4	Females	0.33
Scotland	60	11.2	28	8.6	17,996	7.9	22,105	8.1		
Northern Ireland	3	0.6	5	1.5	1,438	0.6	1,660	0.6		
ROI	7	1.3	5	1.5	2,112	0.9	2,842	1		
Elsewhere	36	6.7	28	8.6	16,883	7.4	22,972	8.4		
Education and Employment										
Age completed full-time education median (IQR)	16 (15 - 17)		16 (15 - 17)		16 (15 - 17)		16 (15 - 18)		Male Female	**<0.01** 0.32
Qualifications	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
University/College degree	149	37.9	86	35.7	76,502	41.4	84,475	38.1		
A/AS levels or equivalent	38	9.7	38	15.8	23,283	12.6	31,976	14.4		
GCSE's/O-levels	107	27.2	66	27.4	41,976	22.7	63,074	28.4		
CSE or equivalent	25	6.4	13	5.4	12,269	6.6	14,588	6.6		
NVQ/HND/HNC	49	12.5	13	5.4	20,516	11.1	12,159	5.5		
Other professional qualifications	25	6.4	25	10.4	10,134	5.5	15,626	7.1		
Employment Status										
In paid employment or self-employed	250	47.3	136	42.6	137,739	61	149,112	55.2	Males	**<0.01**
Retired	187	35.3	149	46.7	71,242	31.5	95,436	35.3	Females	**<0.01**
Looking after home/family	1	0.2	9	2.8	1,283	0.6	12,619	4.7		
Unable to work due to sickness/disability	75	14.2	21	6.6	9,304	4.1	7,436	2.8		
Unemployed	16	3.0	0	0.0	5,360	2.4	2,890	1.1		
Doing unpaid/voluntary work	0	0.0	4	1.3	656	0.3	1,668	0.6		
Full or part-time student	0	0.0	0	0.0	461	0.2	883	0.3		

5.2.3 Smoking

Smoking is the single largest risk factor for cancers of the head and neck. 66.1% (n=353) male HNC cases in the UK Biobank are ever smokers (defined as current or former smokers). 50.7% (n=115,892) of male controls are ever smokers; p<0.001 56% (n=182) of female cases are ever smoker's vs 40.1% (n=109,664) of controls; p<0.001. Full data are in Table 5.2.

Consistent with previous reports, HNC cases report smoking more cigarettes per day than controls. Current male smokers with HNC report smoking a mean of 20.7 cigarettes per day compared to 17.1 for controls.

Male and female HNC cases, who were smokers, began smoking at a younger age than controls, with males beginning around one year earlier (age 16.2 years) and females around three years earlier (age 15.8 years).

Former smokers with HNC stopped at an older age than former smokers in the control group pointing to an overall increased duration of smoking among cases.

Smoking duration was calculated as a new variable by subtracting age stopped smoking from age started smoking for former smokers. For current smokers age at baseline – age started smoking was used to calculate smoking duration.

Pack Years has been used as a measure of smoking exposure for many years, however, more recently smoking duration is believed to be a more accurate predictor of disease (187, 188). Peto explains that a 55 year old person who begins smoking at age 15 and smokes 0.5 packs per day for 40 years has a greater risk of cancer than if they begin smoking at 45 years later but smokes 2 packs per day, even though they have smoked for 20 pack years (189). In this study, pack years of smoking was significant, between cases and controls, in males and females. Male cases had smoked for 37.5 pack years vs 25.9 in controls (p<0.001) and females 23.8 vs 20.1 pack years; p=0.013.

5.2.3.1 Involuntary Smoking

Involuntary, or passive, smoking has been difficult to study in relation to HNC due to difficulties in assembling large enough studies including sufficient numbers of never smokers. Lee *et al* have published the findings from 6 case-control studies from within the INHANCE consortium, which contains 542 HNC who are never smokers and 2,197 never-smoker controls. They found an increased risk of head and neck cancer for those who were exposed to passive smoking in the home for greater than 15 years (OR 1.60; 1.12 -2.28; p-value<0.01). The effect was only seen with this long duration of exposure and there was no overall increased risk for 'ever exposure' to passive smoke. There have been other reports of an increased risk of HNC in adults who were exposed to passive smoke as children (190). Troy *et al*. studied 858 cases and 806 controls and found a 28% increased risk for head and neck cancer (OR 1.28 (95% CI 1.01 – 1.63)) when controlling for current smoking and other commonly accepted risk factors (190). The study may be subject to recall bias due to the nature of the retrospective data collection. Our study found no difference in number of hours of smoke exposure at home or work, for non-smokers. We did find a significant difference between male cases and controls in terms of number of smokers per household, however there were only 8 cases who reported >1 smoker in the household so the results are unreliable.

Table 5.2. ***Smoking Related statistics for HNC cases and controls in the UK Biobank Dataset****. t-tests are used to test differences between continuous, normally distributed variables and chi-2 tests for categorical variables (with Fischer's Exact where indicated). Significant p-values are shown in* ***bold (<0.05 is considered statistically significant)***

	All		**Head and Neck Cases**				**Controls**				***p*-value**	
	n= 502,647		n=859				n=501,788					
			Male		**Female**		**Male**		**Female**			
			N 534		325		228,644		273,144		<0.001	
			% 62.2		37.8		45.6		54.4			
Smoking Status	N	%	n	%	n	%	n	%	N	%		
Never smoker	273,604	54.8	176	33.0	140	43.5	111,320	49.0	161,968	59.6	**males**	**<0.001**
Current Smoker	52,989	10.6	102	19.0	35	10.9	28,515	12.5	24,337	9.0	**females**	**<0.001**
Previous smoker	173,102	34.6	251	47.0	147	45.6	87,377	38.5	85,327	31.4		
No of smokers/household												
0	411,489	81.7	386	72.3	260	80.0	186,617	81.6	224,226	82.0	**males**	**0.04**
1	41,294	8.2	48	9.2	27	8.2	16,890	7.4	24,329	8.9	females	0.94
>1	5,373	1.1	8	1.5	3	0.8	2,294	1.0	3,068	1.1		
Hours of smoke exposure at home (for non-smokers)												
mean (SD)	0.5	(4.5)	0.7	(4.1)	0.5	(3.7)	0.5	(4.4)	0.6	(4.6)	males	0.43
N	463,475		441		289		203,372		247,269		females	0.81
Hours of smoke exposure outside the home (for non-smokers)												
mean (SD)	0.5	(2.6)	1.3	(5.6)	0.3	(1.0)	0.6	(3.0)	0.4	(2.1)	males	0.4
N	463,475		409		264		191,847		229,253		females	0.81

Table 5.2 continued. Smoking-related Statistics for HNC cases and controls

All			Head and Neck Cases				Controls				*p*-value	
n= 502,647			n=859				n=501,788					
			Male		Female		Male		Female			
	N	%	n	%	n	%	n	%	N	%		
Smoked at least 100 cigarettes in lifetime (occasional smokers only)												
Yes	60,475	44.0	65	66.3	38	51.4	29,392	49.1	29,949	41.7	**males**	**0.002**
No	71,261	51.8	33	33.7	36	48.6	30,423	50.9	41,800	58.3	females	0.09
Don't know	5,793	4.2										
Type of tobacco smoked												
Current Smokers												
Manufactured Cig	27,336	69.8	36	43.4	23	76.7	11,545	56.5	15,732	84.4	**males**	**0.04**
Hand-rolled cig	9,158	23.4	36	43.4	7	23.3	6,326	31.0	2,789	15.0	females	0.41
Cigars or pipes	2,668	6.8	11	13.2	0	0.0	2,552	12.5	105	0.6		
Former Smokers												
Manufactured Cig	107,507	88.8	159	74.3	99	94.3	54,247	82.8	53,002	96.4	**males**	**<0.001**
Hand-rolled cig	7,996	6.7	40	18.7	5	4.7	6,066	9.3	1,885	3.4	females	0.206
Cigars or pipes	5,326	4.4	15	7.0	1	1.0	5,190	7.9	120	0.2		
None of above	138	0.1										
Prefer not to answer	34	0.0										

Table 5.2 continued. Smoking-related Statistics for HNC cases and controls

All			Head and Neck Cases				Controls				*p*-value	
n= 502647			n=859				n=501788					
			Male		Female		Male		Female			
Age started smoking												
Current Smokers												
mean (SD)		17.9	16.2	(5.2)	15.8	(2.5)	17.5	(5.7)	18.3	(5.9)	**males**	**0.04**
n		39,416	83		30		20,253		18,409		**females**	**0.02**
Former Smokers		17.3	17.1	(4.7)	18	(4.0)	16.9	(3.5)	17.8	(3.84)	males	0.43
n		122,239	211		104		65,306		54,729		females	0.51
No. cigs/per day												
	mean											
Current Smokers	(SD)	15.5	20.7	(11.3)	13.6	(6.6)	17.1	(9.2)	14.1	(7.37)	**males**	**0.00**
	n	52,989	70		30		17,657		18,407		females	0.71
	mean											
Former Smokers	(SD)	19.1	24.6	(12.6)	17.4	(8.6)	21.2	(11.6)	16.7	(8.5)	**males**	**<0.001**
	n	173,102	197		102		59,850		54,473		females	0.38
Age Stopped Smoking												
	mean											
	(SD)	39.8 (11.6)	45.8	(12.4)	42.7	(11.9)	40.1	(11.6)	39.6	(11.8)	**males**	**<0.001**
	n	122,239	212		104		65,258		54,739		**females**	**0.01**
Ever Stopped for 6 months	n	%	n	%	n	%	n	%	n	%		
No	67,005	55.8	127	61.7	62	59.0	37,356	58.3	29,460	54.6	males	0.33
Yes	51,262	42.7	79	38.3	43	41.0	26,693	41.7	24,447	45.4	females	0.37
Don't know	1,787	1.5										

Table 5.2 continued. Smoking-related Statistics for HNC cases and controls

All			**Head and Neck Cases**				**Controls**				***p*-value**	
n= 502,647			n=859				n=501,788					
			Male		**Female**		**Male**		**Female**			
Time from waking to first cigarette												
	n	%	n	%	n	%	n	%	n	%		
<5 mins	5,212	14.0	15	24.6	5	17.3	2,838	16.1	2,263	12.4	**males**	**0.05**
5-15 mins	13,648	36.8	25	41.0	17	58.6	6,478	36.9	6,781	37.2	female	0.08
30m-1h	10,140	27.4	10	16.4	3	10.3	4,750	27.1	5,082	27.9		
1-2h	3,626	9.8	7	11.4	2	6.9	1,752	10.0	1,750	9.6		
>2h	4,218	11.4	4	6.6	2	6.9	1,729	9.9	2,343	12.9		
Don't know	221	0.6										
Total	37,065											
Smoking now compared to ten years previous												
More now	6,548	16.7	19	22.9	6	20.0	2,943	14.4	3,580	19.2	males	0.09
About the same	15,661	40.1	31	37.3	14	46.7	8,511	41.7	7,107	38.2	females	0.56
Less now	16,917	43.2	33	39.8	10	33.3	8,955	43.9	7,920	42.6		
Total	39,126											
Pack Years of Smoking												
mean (SD)	23.4	(18.6)	37.5	(27.4)	23.8	(16.3)	25.9	(20.5)	20.1	(15.3)	**males**	**<0.001**
n	150,126		206		105		65,641		62,493		**females**	**0.01**

5.2.4 Alcohol

Alcohol is known to increase permeability of the oral mucosa and may, therefore, increase exposure to smoke carcinogens. Alcohol and smoking act synergistically to increase risk of oral cancer and this is discussed in the Introduction Chapter 1 (section 1.2.1). Alcohol alone is a risk factor for HNC; in non-smokers drinking 3 or more alcoholic drinks per day doubles an individual's risk of HNC (OR 2.04 (95% CI 1.29-3.21)) (191). Purdue *et al* showed similar odds ratios for heavy drinkers of beer, wine or liquor, implying that quantity rather than type of alcohol is most relevant to risk of HNC (192). In contrast to smoking, it appears that a high intake of alcohol over a shorter period confers greater risk of HNC compared to a low intake (1 drink per day) over a longer period (192).

In the present study, 30% (n=163) of male cases report to drink alcohol on a daily basis compared to 25% (n=57,751) of male controls ($p<0.001$). In contrast to this, 12% of male cases report complete abstinence vs 6% of controls; this could be due to the effects of treatment for HNC or a decision to stop drinking following the diagnosis. Results are similar but not statistically significant, for females.

Amongst male non-drinkers, 84% (n=54) report to be former alcohol-drinkers vs 55% of controls. This supports the assumption regarding the diagnosis of HNC having an influence on the current alcohol status. The majority of male and female cases report drinking less alcohol now compared to ten years previously and this was statistically significant between cases and controls; $p<0.001$ males and 0.031 for females.

When the type of alcohol was studied, male cases were found to drink less wine ($p=0.001$) and more beer than controls. Males cases consumed an average of 7.7 pints of beer per week compared to 5 pints for controls ($p<0.001$). Cases also consumed a greater number of measures of spirits per week compared to controls (3 vs 2; $p=0.001$). Male cases were also less likely to drink alcohol with meals (44% vs 58%; $p<0.001$).

These results are displayed in Table 5.3.

Table 5.3. ***Alcohol: Differences between HNC Cases and Controls, in terms of alcohol status, frequency and type of alcohol consumed, in the UK Biobank****. Significant p-values are shown in* ***bold*** *(<0.05 is considered statistically significant).*

Variable	Head and Neck Cancer Cases				Controls				*p*-value	
	Male		Female		Male		Female			
Alcohol Status	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Never	11	2.1	13	4	6,458	2.9	16,065	5.9	**Males**	**<0.001**
Previous	54	10.1	26	8	8,074	3.6	9,961	3.7		
Current	469	87.8	286	88	213,350	93.5	246,377	90.4	**Females**	**<0.001**
Alcohol Frequency (Current)										
Daily or almost daily	163	30.5	56	17.1	57,751	25.2	43,822	16	**Males**	**<0.001**
3-4 times per wk	109	20.4	71	21.9	59,443	26	55,840	20.3		
1-2 times wk	123	23	72	22.2	59,011	25.8	70,117	25.7	Females	0.39
1-3 times per month	33	6.2	36	11.1	20,326	8.9	35,479	13		
Special occasions only	41	7.7	51	15.7	16,819	7.4	41,119	15.2		
Never	65	12.2	39	12	14,532	6.4	26,026	9.5		
Missing	0	0	0	0	762	0.3	741	0.3		

Table 5.3 continued. Alcohol-related statistics comparing differences between HNC cases and controls

Variable	Head and Neck Cancer Cases				Controls				*p*-value	
	Male		**Female**		**Male**		**Female**			
Alcohol usually taken with meals										
(only asked to those who drink alcohol)	N	%	N	%	N	%	N	%		
No	161	55.9	40	26.1	50,744	42.4	30,721	23.4	**Males**	**<0.001**
Yes	127	44.1	113	73.9	68,869	57.6	100,784	76.6	Females	0.42
Alcohol now compared to 10 years previously										
More now	44	9.4	38	13.4	28,039	13.2	47,504	19.5	**Males**	**<0.001**
About the same	134	28.6	120	42.4	78,088	36.8	94,371	38.7	**Females**	**0.04**
Less now	291	62	125	44.2	106,107	50	102,131	41.8		
Former Alcohol Drinker (never drinkers only)										
No	10	15.6	13	33.3	6,397	44.2	15,975	61.6	**Males**	**<0.001**
Yes	54	84.4	26	66.7	8,074	55.8	9,961	38.4	**Females**	**<0.001**

Table 5.3 continued. Alcohol-related statistics comparing differences between HNC cases and controls

Variable		Head and Neck Cancer Cases		Controls		*p*-value	
		Male	Female	Male	Female		
For those who drink at least once per week:							
Weekly number of glasses red wine (125mL)	mean(sd)	3.39 (5.7)	3.59 (5.8)	4.43 (6.3)	3.38 (4.7)	**Males**	**<0.01**
	N	394	197	174,936	168,874		
						Females	0.51
Weekly no. of glasses of white wine or champagne (125mL)	mean (sd)	1.71 (4.0)	3.18 (5.2)	2.01 (4.4)	3.32 (5.0)	Males	0.18
	N	393	197	174,858	168,687		
						Females	0.71
Weekly pints of beer or cider	mean (sd)	7.70 (9.2)	1.04 (3.1)	5.31 (6.9)	0.62 (1.8)	**Males**	**<0.01**
	N	393	198	175,495	169,071		
						Females	**<0.01**
Weekly number of measures of spirits (25cl)	mean (sd)	3.03 (7.9)	2.38 (7.5)	2.22 (6.4)	1.47 (4.0)	**Males**	**0.01**
	N	392	198	174,775	168,471		
						Females	**<0.01**
Weekly glasses of fortified wine (62.5mL)	mean (sd)	0.47 (3.8)	0.27 (1.0)	0.20 (1.3)	0.28 (1.2)	**Males**	**<0.01**
	N	392	197	175,199	169,133		
						Females	0.97
Weekly glasses of other alcohol	mean (sd)	0.0 (0.0)	0.1 (0.3)	0.0 (0.6)	0.0 (0.5)	Males	0.48
	N	121	58	59,200	56,313		

Table 5.3 continued. Alcohol-related statistics comparing differences between HNC cases and controls

Variable		Head and Neck Cancer Cases		Controls		*p*-value	
		Male	**Female**	**Male**	**Female**		
For those who drink maximum 3x/month:							
Average number of glasses of red wine per month (125mL)	mean (sd)	0.45 (1.3)	0.86 (1.3)	1.17 (2.1)	0.91 (1.7)	Males	0.09
	n	26	29	13,309	26,963		
						Females	0.89
Average number of glasses of white wine/champagne per month (125mL)	mean (sd)	0.15 (0.5)	0.72 (1.1)	0.76 (1.4)	1.11 (1.7)	**Males**	**0.03**
	n	26	29	13,300	26,918		
						Females	0.23
Average number of pints of beer/cider per month	mean (sd)	4.00 (6.7)	0.41 (1.0)	2.21 (3.5)	0.42 (1.2)	**Males**	**0.01**
	n	25	29	13,324	27,078		
						Females	0.99
Average number of measures of spirits per month (25cl)	mean (sd)	0.36 (0.8)	0.58 (1.1)	0.84 (2.9)	0.70 (1.8)	Males	0.41
	N	25	29	13,273	26,925		
						Females	0.73
Average number of glasses of fortified wine per month (62.5mL)	mean (sd)	0.04 (0.2)	0.38 (1.2)	0.14 (0.8)	0.17 (0.9)	Males	0.52
		26	29	13,341	27,066		
						Females	0.20
How many glasses of other alcoholic drinks per month?	mean (sd)	0.00 (0.00)	0.00 (0.00)	0.09 (0.6)	0.12 (0.7)	Males	0.48
	n	26	29	13,354	27,098		
						Females	0.32

5.2.5 Diet

Diet is known to be a risk factor for HNC. Chuang *et al* have published evidence of the protective effect of fruit and vegetables on the risk of HNC (193). This study used the international INHANCE consortium of studies with 14,520 cases and 22,737 controls; Consuming fruit 7 or more times per week offered a protective effect of 48% (OR 0.52 (95% CI 0.43 – 0.62)) and vegetables OR 0.66 (95% CI 0.49 – 0.90). In contrast, increased intake of red and processed meat conferred a greater risk of HNC: eating red meat on 7 or more occasions per week confers a 40% increased risk of HNC (OR 1.40 (95% CI 1.13 – 1.74)), similar to processed meat (OR=1.37 (95% CI 1.14-1.65)).

The data (Table 5.4) show that cases consume less fruit and raw salad/vegetables compared to controls. On average, cases consumed less than two portions of fruit per day compared to controls, who reportedly consumed greater than two portions per day. Over a week this equates to a difference of around 3 portions. This was statistically significant for males and females.

Male cases are more likely to report never eating oily fish, beef or lamb than male controls. Male cases are more likely to always add salt to their food (9.8%; n=52) compared to controls (5.2% n=11,818).

5.2.6 Exercise

Hashibe *et al*, in their study of risk factors for HNC within the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer cohort (n=101,182), showed that physical activity for more than three hours per week offered a protective effect against HNC of around 40% (OR 0.58 (95%CI 0.35-0.96))(194).

The INHANCE consortium have reported similar effects, with a risk reduction of 22% with moderate physical activity compared to none (OR 0.78 (95%CI 0.66-0.91), in the 2,283 cases and 5,674 controls studied (195).

Moderate physical activity is defined, by the World Health Organisation, as 3-6 Metabolic Equivalents (METs): “One MET is defined as the energy cost of sitting

quietly and is equivalent to a caloric consumption of 1kcal/kg/hour. It is estimated that compared with sitting quietly, a person's caloric consumption is three to six times higher when being moderately active (3-6 METs) and more than six times higher when being vigorously active (>6 METs)" (196).

The present study confirms a difference between male cases and controls in terms of the number of days of moderate exercise per week. 20% of male cases report no moderate exercise compared to 13% of controls; p=<0.001. Results are mixed, with the majority of male cases completing either no moderate exercise or exercising seven days per week (20% and 19.4% respectively). Results for females were not statistically significantly different. Results are presented in Table 5.4.

Table 5.4. Diet and Exercise: Differences between HNC Cases and Controls in the UK Biobank Dataset

Variable	Head and Neck Cancer Case				Control					
	Male		Females		Males		Females		p-value	
Salt added to food	n	%	n	%	N	%	n	%		
Never	253	47.6	205	63.3	121,881	53.4	155,668	57.1	Males	**<0.001**
Sometimes	146	27.4	79	24.4	64,550	28.3	75,881	27.8	Females	0.1
Usually	81	15.2	25	7.7	29,824	13.1	28,487	10.5		
Always	52	9.8	15	4.6	11,818	5.2	12,554	4.6		
Beef										
Never	68	12.9	54	16.7	18,459	8.1	37,068	13.7	Males	**<0.001**
<1/week	195	37.1	144	44.4	101,233	44.6	125,602	46.3	Female	0.6
1/week	171	32.5	90	27.8	78,160	34.4	80,325	29.6		
2-4/week	89	16.9	35	10.8	28,288	12.5	28,028	10.3		
5-6/week	1	0.2	1	0.3	579	0.3	330	0.1		
At least daily	2	0.4	-	-	224	0.1	175	0.1		
Bread (number of slices per week)										
median (IQR)	12 (7 - 20)		8 (4.5 - 14)		14 (8 - 20)		10 (5 - 14)		Males	**<0.001**
									Females	0.0
Bread type	n	%	n	%	n	%	n	%		
White	202	41.4	67	22.3	73,221	33.0	54,614	20.8	Males	**<0.001**
Brown	56	11.5	31	10.3	30,643	13.8	29,874	11.6	Females	0.7
Wholemeal	219	44.9	189	63.0	111,054	50.1	160,206	62.2		
Other	11	2.1	13	4.4	6,844	3.1	13,726	5.3		

Table 5.4 continued. Diet and Exercise: differences between HNC cases and controls in the UK Biobank dataset

Variable		Head and Neck Cancer Case				Control					
		Male		Females		Males		Females		p-value	
Cereal (number of bowls per week)											
	median (IQR)	5 (2-7)		6 (3 -7)		5 (2-7)		5 (3-7)		Males	0.2
										Females	**0.0**
Cheese		n	%	n	%	N	%	n	%		
	Never	21	4.1	12	3.8	6,531	2.9	7,010	2.6	Males	0.4
	<1/week	70	13.6	61	19.1	32,324	14.6	52,318	19.7	Females	0.4
	1/week	112	21.8	72	22.6	46,092	20.7	58,552	22.1		
	2-4/week	253	49.0	127	39.8	106,018	47.7	114,255	43.1		
	5-6/week	43	8.3	37	11.6	22,844	10.3	23,581	8.9		
	At least daily	17	3.3	10	3.1	8,423	3.8	9,400	3.6		
Coffee (number of cups per day including decaf)											
		2 (1-4)		2 (1-3)		2 (1-3)		2 (0 - 3)		Males	0.8
										Females	**0.0**
Coffee Type											
	Decaf	53	13.4	55	22.3	27,379	15.3	46,913	22.9	Males	0.4
	Instant	243	61.4	143	57.9	106,286	59.4	108,328	52.9	Females	0.3
	Ground	91	23.0	44	17.8	42,450	23.7	45,376	22.1		
	Other	9	2.3	5	2.0	2,760	1.5	4,373	2.1		

Table 5.4 continued. Diet and Exercise: differences between HNC cases and controls in the UK Biobank dataset

Variable	Head and Neck Cancer Case				Control					
	Male		Females		Males		Females		p-value	
Cooked Vegetables (number of tbsp per day)										
median (IQR)	2 (2 - 3)		2 (2 -3)		2 (2 -3)		3 (2 - 3)		Males	0.9
									Females	0.0
Oily Fish intake	n	%	n	%	n	%	n	%		
Never	79	15.2	33	10.2	25,716	11.4	29,033	10.7	Males	**0.0**
<1/week	182	34.9	107	33.0	78,377	34.6	86,266	31.8	Females	0.8
1/week	172	33.0	117	36.1	82,456	36.4	105,796	39.0		
2-4/week	77	14.8	63	19.4	37,226	16.4	48,058	17.7		
5-6/week	7	1.3	3	0.9	1,945	0.9	1,639	0.6		
At least daily	4	0.8	1	0.3	712	0.3	495	0.2		
Non-oily fish intake										
Never	39	7.4	16	4.9	10,199	4.5	13,249	4.9	Males	**0.0**
<1/week	156	29.6	87	26.9	67,683	29.8	76,958	28.4	Females	0.9
1/week	238	45.1	170	52.5	112,835	49.8	135,216	49.8		
2-4/week	90	17.1	50	15.4	34,364	15.1	44,374	16.4		
5-6/week	3	0.6	1	0.3	1,190	0.5	1,194	0.4		
At least daily	2	0.4	0	0.0	369	0.2	438	0.2		

Table 5.4 continued. Diet and Exercise: differences between HNC cases and controls in the UK Biobank dataset

		Head and Neck Cancer Case				Control					
		Male		Females		Males		Females		p-value	
Processed Meat											
	Never	45	8.5	47	14.5	12,367	5.4	34,368	12.6	Males	**0.0**
	<1/week	101	19.1	118	36.3	48,674	21.4	103,488	38.0	Females	0.8
	1/week	152	28.7	93	28.6	67,777	29.8	78,050	28.7		
	2-4/week	198	37.4	62	19.1	83,941	36.9	51,158	18.8		
	5-6/week	24	4.5	5	1.5	11,689	5.1	3,952	1.5		
	At least daily	10	1.9	-	-	3,079	1.4	1,016	0.4		
Salad and Raw Vegetables (no. heaped tbsp/day)											
	mean (sd)	1.8	(1.9)	2.2	(1.8)	2.0	(2.2)	2.5	(2.1)	Males	**0.0**
	n	484		318		210,386		260,166		Females	**0.0**
Fruit	Mean no. pieces per day (SD	1.69 (1.45)		2.10 (1.36)		2.11 (1.62)		2.44 (1.58)		Males	**<0.001**
	N	501		317		217,226		265,479		Females	**<0.001**
Lamb		n	%	n	%	n	%	n	%		
	Never	102	19.4	74	22.9	32,921	14.6	55,618	20.5	Males	**<0.01**
	<1/week	244	46.4	168	52.0	128,399	56.7	152,982	56.5	Females	0.6
	1/week	156	29.7	75	23.2	56,388	24.9	55,716	20.6		
	2-4/week	22	4.2	6	1.9	8,321	3.7	645	2.4		
	5-6/week	1	0.2	-	-	196	0.1	125	0.1		
	At least daily	1	0.2	-	-	136	0.1	105	0.0		

Table 5.4 continued. Diet and Exercise: differences between HNC cases and controls in the UK Biobank dataset

Variable		Head and Neck Cancer Case				Control					
		Male		Females		Males		Females		p-value	
Type of Milk		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
	Full cream	95	17.9	28	8.6	20,913	9.2	13,584	5.0	Males	**<0.01**
	Semi-skimmed	314	59.1	195	60.2	154,758	67.1	167,705	61.5	Females	**<0.01**
	Skimmed	85	16.0	67	20.7	36,683	16.3	63,795	23.4		
	Soya	14	2.6	15	4.6	5,592	2.5	14,035	5.2		
	Other	9	1.7	7	2.2	2,671	1.2	3,819	1.4		
	Never have milk	14	2.6	12	3.7	7,157	3.7	9,553	3.5		
Pork											
	Never	106	20.2	74	23.1	31,173	13.8	55,158	20.4	Males	**<0.001**
	<1/week	251	47.4	176	54.8	129,164	57.0	153,250	56.5	Females	0.5
	1/week	147	28.2	67	20.9	55,748	24.6	55,180	20.4		
	2-4/week	19	3.3	4	1.3	9,885	4.4	7,228	2.7		
	5-6/week	1	0.2	0	0.0	327	0.1	142	0.1		
	At least daily	1	0.2	0	0.0	154	0.1	93	<0.1		
Poultry											
	Never	45	8.5	29	8.9	8,822	3.9	16,759	6.2	Males	**<0.01**
	<1/week	71	13.4	35	10.8	25,849	11.4	28,011	10.3	Females	0.4
	1/week	188	35.0	112	34.5	84,290	37.1	95,091	34.9		
	2-4/week	212	40.0	143	44.0	103,370	45.4	126,091	46.3		
	5-6/week	90	1.7	5	1.5	4,497	2.0	5,464	2.0		
	At least daily	5	0.9	1	0.3	702	0.3	771	0.3		
Water											
(no. glasses/day)	**Median (IQR)**	2 (1 - 4)		3 (2 -4)		2 (1 -4)		3 (2 -4)		Males	**< 0.01**
	n	499		306		207,634		256,058		Females	0.4

Table 5.4 continued. Diet and Exercise: differences between HNC cases and controls in the UK Biobank dataset

Variable	Head and Neck Cancer Case				Control					
	Male		Females		Males		Females		p-value	
Moderate Exercise for at least 10 minutes										
(number of days per week)										
0	100	20.0	45	14.6	28,813	13.2	32,221	12.6	Males	**<0.001**
1	25	5.0	30	9.7	18,657	8.5	19,578	7.7	Females	0.2
2	72	14.4	39	12.6	31,701	14.5	37,988	14.8		
3	54	10.8	53	17.2	30,585	13.9	40,815	16.0		
4	46	9.2	38	12.3	20,571	9.4	26,546	10.4		
5	65	13.0	43	13.9	35,677	16.3	35,657	13.9		
6	42	8.4	15	4.9	14,412	6.6	11,967	4.7		
7	97	19.4	46	14.9	38,187	17.4	51,176	20.0		

5.2.7 Medical History

5.2.7.1 Diabetes

The percentage of cases and controls with diabetes did not differ significantly, for males (6.8-7%) or females (3.1 -3.8%). However, female cases with diabetes were diagnosed with diabetes at a significantly older age than female controls (61years vs 54 years; n=8). The low number of females with HNC and diabetes (n=8) limits the significance of this finding (see Table 5.5)

Diabetes is associated with several other chronic health problems including an increased risk of cancers. A pooled analysis of 12 case-controls studies within the INHANCE consortium (117) showed an increased risk of HNC for women with diabetes, particularly never smokers (OR 1.70 95% CI (1.25 – 2.32); n=39). Overall, a diagnosis of type two diabetes conferred increased risk of 33% (OR 1.33; 95%CI 1.02 – 1.73; n=118), when controlling for age, sex, education, centre, smoking, alcohol, BMI and race. Information on treatment of diabetes was not available but it is known that around 80% of patients diagnosed with diabetes receive treatment, therefore the authors concluded that the effect of diabetes in the absence of treatment (i.e. undiagnosed diabetes) might be stronger than that observed in their study.

Around 90% of patients with newly diagnosed diabetes in the UK are treated with the drug Metformin (197). A recent systematic review has examined the effect of Metformin on the incidence of HNC and concluded that metformin reduces incidence of HNC, reduces recurrence of disease and improves overall survival of HNC patients (198, 199).

The incidence of diabetes has doubled in the last twenty years. It is estimated that 1 million people are living with undiagnosed Diabetes in the UK. Although the numbers of females with diabetes and HNC in our study are small (n=8), one could hypothesise that their later age at diagnosis implies they have lived with untreated disease for longer than the female controls, therefore being exposed to the damaging effects of uncontrolled hyperglycaemia for longer. To investigate this, a prospective study would be required with blood glucose levels measured at intervals.

5.2.7.2 Cardiovascular Disease

Male cases had a higher percentage of cases of heart attack (14.9% vs 11.8%), stroke (7.9% vs 4.4%) and angina (11.6% vs 8.8%) than male controls (see Table 5.5). This is most likely to be due to increased age as there are no reports of an association between cardiovascular disease and increased risk of head and neck cancer. It is known, however, that patients newly diagnosed with HNC have a higher cardiovascular risk score (Framingham) compared to the general population, mainly due to a lack of secondary prevention which could be achieved by treatment of hypercholesterolemia (200). This may be due to shared risk factors between HNC and CVD, such as smoking and poor diet.

We observed no statistically significant difference in systolic or diastolic blood pressure, or pulse, between cases and controls (see Table 5.5).

5.2.8 Baseline Measures of Current Health

5.2.8.1 BMI and Body Fat

Body Mass Index has been investigated in relation to HNC risk, with mixed results (201). A pooled analysis of 17 international studies appeared to show a protective effect of higher BMI against HNC amongst smokers and consumers of alcohol (BMI of >30; OR 0.38; 95% CI 0.30-0.49). This protective effect was not observed for never smokers (OR 0.95 (95% CI 0.47 – 1.91) (201). A similar tendency for leanness has been noted in other smoking-related malignancies such as lung and oesophageal (202).

Within the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, 177 individuals developed HNC. BMI was extensively analysed, using current BMI and BMI at ages 50 years and 20 years; there was no association with HNC risk (194).

In the present study, both BMI and body fat were statistically significantly lower in cases than controls (see Table 5.5). Male cases had a mean BMI of 26.5 compared to 27.8 in controls. Female cases had a mean BMI of 26.1 compared to 27.1 for controls.

It is unclear if the BMI and body fat have reduced in cases due to difficulty eating secondary to development of oral cancer; to prove causation, a prospective study would be required.

5.2.9 Engagement with Screening Programmes

There were no statistically significant differences in reported engagement with bowel, prostate, breast and cervical screening between cases and controls (see Table 5.6). This is contrary to other data regarding screening behaviours; amongst the most socially deprived individuals, uptake of screening is known to be poor. Only 35% of those living in the most deprived areas engage with bowel cancer screening compared to 66% or persons living in affluent areas (203). The UK Biobank questions asked if people had "ever" attended for screening, so it may be that people have attended on a small number of occasions but do not routinely participate.

5.2.10 Breastfeeding

The benefits of being breastfed as an infant are well documented (204, 205). There is evidence of improved cognitive function, reduced risk of allergy (particularly asthma) and reduced risk of obesity. However, despite reports of a reduced incidence of childhood leukaemia (206), a large meta-analysis of 5,000 subjects revealed no link between being breastfed as an infant and cancer incidence later in adulthood (RR 1.07 (95% CI 0.89-1.28)), except for pre-menopausal breast cancer (RR 0.88 (95%CI 0.79 – 0.98)) (207).

The present study reveals no statistically significant difference between reports of being breastfed as an infant between cases and controls, although in male cases the rate was higher than controls (79.8 vs 75.5%; p=0.057) (see Table 5.7).

Table 5.5. ***Diabetes and Cardiovascular Status and BMI: Differences between HNC Cases and Controls****. p<0.05 indicates a statistically significant result; significant results are shown in* ***bold***

Variable	Head and Neck Cancer Case				Control				p-value	
	Males		Female		Male		Female			
Medical Conditions	n	%	N	%	N	%	n	%		
Diabetes										
Yes	36	6.8	10	3.1	15,968	7	10,394	3.8	Males	0.82
No	495	93.2	314	96.9	211,266	93	261,547	96.2	Females	0.49
Age diabetes diagnosed										
Median (IQR)	53 (47 - 60)		61 (56 - 64.5)		54 (46 - 60)		54 (46- 60)		Males	0.69
N	34		8		15,615		8,943		Females	**0.02**
Vascular/heart problems n(%)										
Heart Attack	32	6.0	2	0.6	9,277	4.1	2,298	0.8	Male	**<0.001**
Angina	25	4.7	7	2.2	6,910	3.0	4,397	1.6	Female	0.38
Stroke	17	3.2	3	0.9	3,488	1.5	2,712	1.0		
HTN	141	26.4	86	26.5	59,070	25.8	60,889	22.3		
Age hypertension diagnosed										ranksum
median (IQR)	54 (46.5 - 58)		52 (45- 58)		52 (45-58)		52 (45-58)		Males	0.23
N	168		69		64,463		56,525		Females	0.80
Age angina diagnosed										rank sum
median (IQR)	56 (51.1 - 59)		52 (50 - 60)		54 (48 - 59)		55 (50 - 60)		Males	0.20
N	36		7		10,209		4,758		Females	0.66
Age heart attack diagnosed										ranksum
median (IQR)	56 (50 - 60)		42 (42-42)		53 (57-59)		55 (49-60)		Males	0.13
N	30		1		9,017		2,151		Females	0.16

Table 5.5. continued. ***Diabetes and Cardiovascular Disease: Differences between HNC Cases and Controls****. P-values <0.05 are considered statistically significant and are shown in* ***bold.***

Variable		Head and Neck Cancer Case		Control		p-value	
		Males	Female	Male	Female		
Blood Pressure							
Systolic	mean (sd)	144.2 (21.46)	138.5 (22.03)	142.7 (18.53)	137.2 (20.29)	Male	0.07
	N	483	297	213,161	254,246	Female	0.29
Diastolic	mean (sd)	83.7 (11.63)	80.3 (11.14)	84.0 (10.57)	80.7 (10.57)	Male	0.55
	N	483	297	213,168	254,252	Female	0.54
Pulse	mean (sd)	68.7 (12.04)	72.1 (11.67)	67.9 (12.04)	69.9 (11.07)	Male	0.41
	N	163	99	78,158	92,363	Female	**0.05**
BMI	mean (sd)	26.5 (4.40)	26.1 (5.08)	27.8 (4.25)	27.1 (5.20)	Male	**<0.001**
	N	530	323	227,002	271,687	Female	**<0.001**
Body fat percentage							
	mean (sd)	24.4 (6.26)	35.7 (7.55)	25.3 (5.81)	36.6 (6.91)	Male	**<0.001**
	N	522	317	223,370	269,028	Female	**0.03**

*Table 5.6. Differences in uptake of Screening between HNC Cases and Controls in the UK Biobank Dataset; p<0.05 indicates a statistically significant result. Significant results are shown in **bold.***

Variable		Head and Neck Cancer Case				Control					p-value
		Males		Female		Male		Female			
Attitudes to Screening		n	%	n	%	n	%	n	%		
Ever had bowel cancer screening (60y)											
	Yes	134	49.8	82	49.4	52,992	52.7	56,943	50.4	Males	0.32
	No	135	50.2	84	50.6	47,274	47.3	56,103	49.6	Females	0.80
Ever had PSA test (males only)											
	Yes	169	34			66,002	30.6			Males	0.10
	No	328	66			149,786	69.4				
Ever had Breast screening (females >=50y only)											
	Yes			274	96.5			199,474	95.9		
	No			10	3.5			8,517	4.1	Females	0.63
Ever had cervical smear (females only)											
	Yes			321	99.1			265,543	97.7		
	No			3	0.9			6,344	2.3	Females	0.09

Table 5.7. ***Differences between HNC Cases and Controls in terms of Breastfeeding in infancy****; p<0.05 is considered statistically significant.*

Variable	**Head and Neck Cancer Case**				**Control**					
	Males		Female		Male		Female			
	n	%	N	%	n	%	n	%		
Breastfed as baby										
Yes	288	79.8	179	72.8	122,743	75.5	154,452	70	Male	0.06
No	73	20.2	67	27.2	39,927	24.5	66,085	30	Female	0.35

5.2.11 Female – specific Risk Factors

The role of hormones, including hormone replacement therapy and menopause has been extensively reviewed in Chapter 3.

Earlier age at menopause is a risk factor for oesophageal SCC. When controlling for smoking, however, the evidence for a role in HNC is less clear (99, 118). There is some evidence for a protective role of hormone replacement therapy in HNC, but further evidence is needed (106). In the present study, female cases were older than controls which may explain why there was a significantly higher percentage of cases who were post-menopausal (86.4 vs 72.1%) (see Table 5.8).

This study showed no statistical difference between cases and controls for age at menarche, age at menopause, age at first live birth, number of lives births, use of oral contraceptive pill, use of hormone replacement therapy or experience of hysterectomy or bilateral oophorectomy. Data on lactation history were not available; however, no studies investigating links between lactation history and HNC could be found, so this is unlikely to be relevant to the current study.

The data are presented in Table 5.8. Hormone replacement therapy had been taken by 39.7% of cases and 38.2% of controls, for an average of 6 years. This study suggests there is no protective effect of HRT in HNC (see Table 5.8).

The concept of oestrogen deficiency as a risk factor for female HNC remains interesting as Bosetti showed a protective effect of later age at menopause (OR 0.40 (95%CI 0.30-0.70)) (108); equally Hashim *et al* found that menopause at less than 52 years conferred greater risk of HNC (OR 1.69 95%CI 1.06 – 2.71; n=476) compared to no history of menopause, when controlling for age, education, smoking, alcohol, BMI) (119).

However, this UK Biobank study does not support a role for early menopause as a risk factor for HNC as there was no difference in age at menopause between cases and controls. Given the differences between males and female cases with HNC (females tend to be older and there are more cases in never smokers), efforts to identify female-specific risk factors should continue.

Table 5.8. ***Female-specific Hormone-related Factors: differences between HNC cases and controls in the UK Biobank Dataset.*** *Significant p-values (<0.05) are shown in* ***bold.***

Variable	Head and Neck Cases		Controls		*p*-value
Age at recruitment					
mean (range)	58.6 (40-70)		56.4 (39-71)		**<0.001**
N	325		273,144		
Menstruation					
Age at menarche (mean (SD))	12.92		12.97		0.58
N	314				
Menopause					
Post-menopausal	N	%	N	%	
Yes	242	86.4	165,202	72.1	
No	38	13.6	64,057	27.9	**<0.001**
Age at menopause					
Mean (std dev)	49.3		49.7		0.36
N	228		154437		
Pregnancy					
Age at 1st live birth					
Mean (std dev)	27.8	6.55	29	6.34	0.18
N	56		36,360		
Number of live births					
Mean (std dev)	1.82		1.82		0.99
N	324		272,321		

Table 5.8 continued. Female-specific hormone-related risk factors: Differences between HNC cases and controls

Variable	Head and Neck Cases		Controls		*p*-value
Medications					
Ever taken oral contraceptive pill (OCP)	N	*%*	N	%	
Yes	269	82.8	220,235	78.2	
No	56	17.2	51,489	18.9	0.47
Ever used Hormone Replacement Therapy (HRT)					
Yes	129	39.7	103,824	38.2	
No	196	60.3	167,744	61.8	0.63
Age Started HRT					
Mean (std dev)	47.5		47.4		0.87
N	115		91,563		
Number of years on HRT					
Mean (std dev)	6.2		6.3		0.81
N	94		73,347		
Operations					
Hysterectomy	N	%	N	%	
Yes	25	8.6	19,900	8.3	
No	266	91.4	221,084	91.7	0.92
Age at hysterectomy					
Mean years (std dev)	44.3 (7.68)		43.9 (8.0)		0.73
Bilateral Oophrectomy	N	%	N	%	
Yes	26	8.2	21,781	8.1	
No	291	91.8	246,767	91.9	1

5.2.12 Sexual History

HPV infection accounts for over half of oropharyngeal cancers and almost all cervical cancers (31, 208). In the USA, the incidence of oropharyngeal cancer now exceeds cervical cancer (209).

Sexual behaviour is the main risk factor associated with oral HPV infections; lifetime number of sexual partners and age of sexual debut <18 years are strong indicators of risk of HPV infection (210-212). The earliest evidence of infection has been found 2 months following onset of sexual activity, and 62% of females were infected after 48 months (212), which suggests vaccination would be most effective prior to the onset of sexual activity. Gillison et al studied prevalence of HPV infection in the US population (n=5,579) and reported 6.9% of participants, aged 14-69 years, had oral HPV infection, with 1% carrying the high-risk strain HPV-16. Age, male gender, number of sexual partners and positive smoking history were all independent risk factors for HPV infection (213). Number of oral sexual partners has also be linked to higher risk of HPV infection (>10 oral sexual partners OR 5.2 (95% CI 1.1 – 25.0)) (214).

In the UK, a vaccination programme for pre-adolescent girls has been in place since 2008 and on 24th July 2018 the UK Government announced that this programme would be extended to adolescent males (215). The Joint Committee on Vaccination and Immunisation commented that vaccination of boys would not be cost-effective if current NICE guidelines on assessment of cost-effectiveness of health interventions were applied. However, using a system that reflects the long-term benefits of the programme did make vaccination of boys cost-effective. The benefits of this wider vaccination programme will not be realised for at least 30 years but should contribute to a decline in the numbers of HPV-related oropharyngeal cancers (216).

In this study, age at first sexual activity was statistically significantly lower in male cases (18.2 years vs 19.2 years; p<0.001) and male cases had a higher median number of sexual partners (6 vs 4; p<0.001) (see Table 5.9). (Data were not available on number of oral sexual partners). It is not immediately obviously why cases would have a higher number of sexual partners than controls. However, age at sexual debut has been explored in relation to a number of factors related to socioeconomic status (217-219). Sexual debut before 16 years is more frequent in people with no academic

qualifications than with academic qualifications and more frequent in those in lower occupations than managerial and professional occupations (220).

Low parental educational attainment was significantly associated with earlier age at sexual debut (OR 2.58 95%CI 1.49 – 4.46), as was absence of either Mother (OR 2.43 95% CI 1.22 – 4.83) or both parents (OR 2.28 95%CI 1.04 – 5.00) during childhood. Household income was not statistically significantly associated with age at sexual debut (218).

The model development dataset contains 159 cases of oropharyngeal/tonsillar cancer/base of tongue cancer, out of a total 702 cases (22.6%). Data are not available on HPV status of the HNC cancers in our dataset, however, based on estimates from the literature (31), around 83 (52% of 159) of these may be due to HPV infection, 12% of the total number of cases of HNC. This justifies the consideration of sexual history in our model, however differences in sexual history are only evident in males and this will be considered when selecting variables for the final model.

Table 5.9. ***Sexual History: Differences between HNC Cases and Controls in the UK Biobank Dataset.*** *P-values <0.05 are considered statistically significant and are shown in* ***bold.***

Variable		Head and Neck Cancer Cases				Controls				*p*-value	
		Male		**Female**		**Male**		**Female**			
Age first had Sexual Intercourse (years)											
	mean (sd)	18.2 (3.8)		19.0 (3.1)		19.2 (4.3)		19.1 (3.6)		Male	**<0.001**
	n	452		285		199,406		235,378		Female	0.65
Number of sexual partners											
	median (IQR)	6 (3 - 15)		3 (1 -6)		4 (2 - 9)		3 (1 -5)		Male	**<0.001**
	n	387		264		183,545		220,997		Female	0.47
Ever had same-sex sex		N	%	N	%	N	%	N	%		
	Yes	27	5.8	7	2.4	8,870	4.3	6,920	2.9		chi2
										Male	0.10
	No	435	94.2	281	97.6	197,325	95.7	235,063	97.1	Female	0.66
Number of same-sex partners										Mann-Whitney U	
	Median (IQR)	1 (1-8)		2 (1-7)		4 (1-18)		2 (1-3)		Male	**0.04**
	n	23		7		6,718		6,613		Female	0.46

5.2.13 Other Risk Factors for HNC

Other risk factors for HNC have been less well-investigated. Air pollution, sleep deprivation and snoring have been linked with other diseases including cancers.

5.2.13.1 Snoring

In this study, there was a statistically significant difference in self-reported snoring between cases and controls for both genders; cases were less likely to snore than controls (see Table 5.10).

Snoring is a marker for sleep apnoea or Sleep-Disturbed Breathing (SDB). Persons with SDB have an increased risk of dying from cancer than normal controls but a causation has not been proven (221): Data from the Wisconsin Sleep Cohort Study, of 1,522 adults with 22 years follow up, found an increased risk of dying from cancer (HR 4.8) for those with severe SDB (7.3 per 1000 per years vs 1.54 per 1000 person years in the normal group) (221). The authors controlled for age, BMI, smoking and deprivation but acknowledge the small numbers in the severe SDB group. Although this study is only exploring risk factors for HNC, rather than risk factors for mortality from HNC, these findings appear to be in contrast to our results, which show that cases are less likely to snore than controls.

5.2.13.2 Air Pollution

In the present study, there was no statistically significant difference in air pollution in the areas inhabited by HNC cases and controls ($p>0.05$), which appears to support the findings of Weinbayr *et al* (222) (see below); see Table 5.10.

Air pollution is a risk factor for cancers, as identified in 2013 by the International Agency for Research on Cancer (223). Weinmayr *et al* (222) have shown a link between long term exposure to $PM_{2.5}$-Sulphates and Gastric Cancer, in a combined study of 10 European Cohorts in the ESCAPE study. 227,044 individuals were included, with 14.9 years follow up. There were 763 cases of Upper Aerodigestive Tract Cancers (UADT), which included head and neck and oesophageal cancers and 633 cases of gastric cancer. The authors found no association with UADT but found

an increased risk of gastric cancer with increased exposure to $PM_{2.5}$-Sulphates with a HR of 1.93 (95% CI 1.13 – 3.27) for every increase of 200ng/m^3.

Although air pollution is not implicated in as many cancers as more commonly accepted risk factors, such as smoking, the entire population is exposed therefore it may have a significant global effect. Exposure to particulate matter of < 2.5 x 10^{-6} m in diameter ($PM_{2.5}$) is an established risk factor for lung cancer and are classified as a class I carcinogen (224).

5.2.13.3 Sleep Deprivation

The Office for Disease Prevention and Health Promotion has established a programme entitled "Healthy People 2020"; one of four core areas included in this programme is "Sleep Health"(225). They have set a target that 70% of adults aged 22 years or over should have 7 hours or more sleep in 24 hours. This is in response to findings that lack of sleep confers increased risk of chronic diseases, including cancers. Von Reusten *et al* published findings from the EPIC study (European Prospective Investigation into Cancer and Nutrition) which revealed that those sleeping for less than 6 hours per night have a 43% increased risk of cancers compared to those sleeping 7-8 hours per night (HR 1.43 (95% CI 1.09-1.87)). This study included 23,630 individuals with average follow-up of 7.8 years (226).

Our findings were contrary to this: sleep duration was slightly longer in male cases (7.2 hours) than controls (7.1 hours) (p=0.04). There was no statistically significance difference in duration of sleep between female cases and controls (see Table 5.10). Sleep is a multifactorial phenomenon: male cases tended to be older and were more likely to be retired than controls, which may account for the slightly longer sleep duration. Those with an established diagnosis of HNC may sleep longer as part of their recovery from treatment. Sleep duration will vary throughout life and will depend on work and family commitments. Consequently, this dataset is not ideally suited to assessing sleep deprivation as a risk factor for cancer and we are only provided with data at a single point in time, with no information of any history of chronic sleep deprivation.

Table 5.10. ***Other Potential Risk Factors for HNC: Exposure to air pollution and self-reported sleep duration and snoring in HNC Cases and Controls****. p<0.05 is considered statistically significant.* ***Bold*** *values indicate a statistically significant result.*

Variable	Head and Neck case				Control				p-value	
	Male		Female		Male		Female			
Air Pollution										
Nitrogen dioxide air pollution; 2010										
mean (SD)	27.35 (8.36)		27.03 (7.82)		26.8 (7.63)		26.7 (7.52)		Males	0.08
N	521		318		225216		269199		Females	0.40
Particulate matter air pollution (pm10); 2010										
mean (SD)	16.3 (1.90)		16.2 (2.04)		16.2 (1.90)		16.2 (1.89)		Males	0.25
N	464		292		210239		250325		Females	0.85
Particulate matter air pollution (pm2.5); 2010										
mean (SD)	10.07 (1.11)		10.04 (1.11)		10.0 (1.06)		9.98 (1.04)		Males	0.18
N	464		292		210,239		250,325		Females	0.40
Sleep Deprivation										
Sleep duration (average per night)										
mean number hours (SD)	7.23 (1.25)		7.28 (1.22)		7.13 (1.10)		7.17 (1.12)		Males	**0.04**
N	527		324		226,999		270,579		Females	0.08
Snoring										
Yes	161	32.5	56	18.1	102,339	47.7	70,850	28.3	Males	**<0.001**
No	334	67.5	253	81.9	112,418	52.3	179,174	71.7	Females	**<0.001**

5.3 Head and Neck Cancer Cases

The detail of number of cases of four sub-types of HNC is considered here in the risk prediction model: oral, salivary gland, oropharyngeal and sinus cancers. Sections 5.3.2-5.3.8 consider differences in age, smoking, lifetime number of sexual partners, household income, alcohol and exercise for these four sub-types. For the justification for exclusion of laryngeal cancer, see section 4.3.4.

Within the development dataset, there are 702 cases of HNC and 423,050 controls. Most cases are oral cancers (44.4%, n=311) followed by oropharyngeal/tonsil cancer (38.3%, n=269). 92 salivary gland cancers (13.1%) and 30 sinus cancers (4.2%) account for the remaining cases (see Table 5.11).

5.3.1 HNC Sub-type and Sex

The male:female ratio was elevated for oral and pharyngeal cancers but almost equal for salivary and sinus cancers. The trend for male predominance was particularly strong for pharyngeal cancers and has been noted in other large studies (227).

Table 5.11. ***Head and Neck Cancer Sub-types by Gender, within the UK Biobank Development Dataset***

Cancer Type	**Number of Cases**			
	Male n (%)	**Female n (%)**	**Total (%)**	**M: F**
Oral	185 (59.3)	127 (40.7)	311 (44.3)	1.45:1
Pharyngeal	193 (71.7)	76 (28.3)	269 (38.3)	2.54:1
Salivary	48 (52.7)	43 (47.3)	92 (13.1)	1.11:1
Sinus	14 (46.7)	16 (53.3)	30 (4.3)	0.88:1
			Total: 702	
Controls	191 897 (45.4)	231 153 (54.6)	423,050	0.83:1

5.3.2 Age at Diagnosis

Age at diagnosis was comparable for all sub-types of head and neck cancer (see Table 5.12). Over the last two decades, there has been a sharp rise in the incidence of oropharyngeal cancers in younger males, however in recent years it has been noted that this trend is slowing (31, 228). There are increasing numbers of older individuals developing the disease (228). There has been a drive to ensure treatment carries less morbidity than classic treatment for oral cancer, as survivors are likely to live with the consequences for longer due to their younger age at diagnosis. However, there have been recent calls to review these so-called "de-escalation" trials in favour of more robust treatments, in recognition of the older patients now being diagnosed with oropharyngeal cancer (228, 229).

Table 5.12 ***HNC Sub-types and Age at Diagnosis, by Gender*** *(within the UK Biobank Model Development Dataset).*

Type of Cancer	**Age at Diagnosis**	
	Male (mean/years)	**Female (mean/years)**
Oral	56.6	55.3
Pharyngeal	55.4	54.9
Salivary	52.6	50.0
Sinus	55.3	57.9

5.3.3 Smoking Duration amongst Ever Smokers

Smoking duration was significantly longer for patients with oral vs other HNCs (see Table 5.13). This is consistent with evidence that smoking is the major risk factor for oral cancers, whereas risk factors such as HPV infection may be more relevant for oropharyngeal cancers (192, 230, 231).

Table 5.13. ***Smoking Duration for each sub-type of HNC considered, using data from the UK Biobank Dataset***

Type of Cancer	Duration of Smoking (mean/years)
Oral	34.1
Pharyngeal	30.6
Salivary	26.5
Sinus	27.1

P-value (ANOVA) = **0.03**

5.3.4 Lifetime number of sexual partners

There is evidence to suggest a higher number of sexual partners increases risk for HPV-related oropharyngeal cancer (232). Our data reveal a median of 10 sexual partners amongst male pharyngeal cancer patients compared to 4 for male oral cancer patients. The difference is less notable amongst female head and neck cancer patients. See Table 5.14.

Table 5.14. ***Median Number of Sexual Partners for cases with each sub-type of HNC***

Cancer Type	**Median number of Sexual Partners (n)**		
	Sex		
	Male	**Female**	**Median (both genders)**
Oral	4	2	3
Pharyngeal	10	4	8
Salivary	3	3	3
Sinus	5.5	4.5	5

5.3.5 Household income

Household income can be used as a proxy for deprivation. It may be a more reliable marker of individual levels of deprivation than Townsend or IMD scores (186), which also require calculation from the patient's postcode. The highest levels of low income were seen amongst patient with Oral cancers, consistent with previous reports (227, 233) (see Table 5.15).

Table 5.15. ***Mean Annual Household Income for HNC cases, by anatomical sub-type.***

	Annual Household Income (£)				
Cancer Type	**n (%)**				
	< £18k	**£18 – 31999**	**£32-51999**	**£52-99999**	**>£100k/year**
Oral	93 (34.7)	77 (28.7)	57 (21.3)	36 (13.4)	5 (1.87)
Pharyngeal	60 (26.7)	62 (27.6)	53 (23.6)	37 (16.4)	13 (5.8)
Salivary	25 (32.9)	22 (28.9)	13 (17.1)	16 (21.1)	0 (0%)
Sinus	6 (20.7)	10 (34.5)	8 (27.6)	2 (6.9)	3 (10.3)
Controls	79798 (22.1)	90912 (25.1)	94907 (26.2)	75325 (20.8)	20784 (5.6)

5.3.6 Frequency of Alcohol Consumption

Reports of daily drinking were higher for all sub-types of HNC compared to controls, showing that this remains an important risk factor to consider in any risk prediction model. The percentage of never drinkers was higher for all sub-types of HNC (see Table 5.16). It is possible that patients decided to stop drinking following their diagnosis, as 88% of pharyngeal cancer patients and 60% of oral and salivary gland cancer patients claim to be previous drinkers (Table 5.17). See 5.2.4 for a more complete discussion of alcohol consumption in HNC.

Table 5.16. ***Frequency of Alcohol consumption by HNC Cases, by anatomic sub-type of HNC.***

Frequency of Alcohol	Type of Cancer				
	Oral	**Pharyngeal**	**Salivary**	**Sinus**	**Controls**
	N(%)	**N(%)**	**N(%)**	**N(%)**	**N(%)**
Daily	82 (26.3)	73 (27.1)	20 (22.0)	9 (30.0)	87,489 (20.7)
3-4/week	66 (21.2)	57 (21.2)	20 (22.0)	4 (13.33)	96,932 (23.0)
1-2/week	65 (20.8)	60 (22.3)	19 (20.8)	6 (20.0)	107,724 (25.5)
1-3/month	29 (9.3)	17 (6.3)	7 (7.7)	4 (13.33)	46,929 (11.1)
Special occasions only	34 (10.9)	23 (8.6)	15 (16.5)	3 (10.0)	48,320 (11.5)
Never	36 (11.5)	39 (14.5)	10 (11.0)	4 (13.33)	34,349 (8.1)

Table 5.17. ***Previous Alcohol Consumption in Current Never Drinkers****, for HNC Cases, by anatomic sub-type*

Former Drinker (if current never drinker)	Type of Cancer			
	Oral N(%)	**Pharyngeal N(%)**	**Salivary N(%)**	**Sinus N(%)**
No	10 (38.5)	4 (11.8)	4 (40)	2 (50)
Yes	26 (61.5)	34 (88.2)	6 (60)	2 (50)

5.3.7 Exercise

There are greater levels of complete inactivity (i.e. zero days of exercise) amongst pharyngeal cancer patients (21% compared to 12.6% in controls) (Table 5.18). Exercise is known to be beneficial in helping to protect against several cancers and this evidence of reduced levels of exercise could be interesting to explore in greater detail (194, 195, 234).

Table 5.18. Number of Days on which HNC cases participate in Moderate Exercise, by sub-type of HNC.

Moderate Exercise for at least 10 minutes (Number of Days per week)					
	Cancer Type				
	Oral N(%)	**Pharyngeal N(%)**	**Salivary N(%)**	**Sinus N(%)**	**Control**
0	44 (15.2)	53 (21.0)	13 (14.8)	4 (13.3)	50,599 (12.6)
1	19 (6.5)	15 (6.0)	6 (6.8)	2 (6.7)	32,461 (8.1)
2	43 (14.8)	30 (11.9)	16 (18.2)	3 (10.0)	59,111 (14.8)
3	36 (12.4)	28 (11.1)	10 (11.4)	5 (16.7)	60,335 (15.1)
4	28 (9.7)	28 (11.1)	11 (12.5)	7 (23.3)	40,085 (10.0)
5	41 (14.1)	32 (12.7)	13 (14.8)	4 (13.3)	60,274 (15.1)
6	22 (7.6)	17 (6.8)	8 (9.1)	1 (3.3)	22,317 (5.6)
7	57 (19.7)	49 (19.4)	11 (12.5)	4 (13.3)	75,330 (18.8)

5.4 Conclusions

Many potential risk factors have been explored here covering patient demographics, medical history, smoking and alcohol, sexual history, hormone-related factors, and diet and exercise. The evidence for the role of all the risk factors is discussed, however not all could be included in a risk prediction model. The strongest evidence exists for smoking and alcohol, closely followed by number of sexual partners for HPV-related oropharyngeal cancer, diet and exercise, and social deprivation. Low body mass index does not appear to represent a true risk factor for HNC but underlying reasons for the lower BMI of HNC patients are worthy of further investigation. We have identified differences between patients with subtypes of HNC and between males and females in almost all identified risk factors, showing that Head and Neck cancer is a heterogenous disease in terms of its aetiology.

Selection of variables for the final risk model will consider evidence from the literature as described, whilst maintaining the aim of developing a parsimonious model that can be utilised by general practitioners.

Table 5.19 provides a summary of the pertinent risk factors described, with data for HNC cases and controls from the model development dataset. Chapter 6 will describe the development of the risk prediction model for HNC.

Table 5.19. ***Summary of Differences in Risk Factors between HNC Cases and Controls, with descriptive statistics, by gender, in the Model Development Dataset, within the UK Biobank****.* *P-values of <0.05 are considered statistically significant and are shown in* ***bold.***

Variable	Head and Neck Cancer Cases		Controls		p-value
	Males	**Females**	**Males**	**Females**	
Total Number	440	262	191,897	231,153	
Age at Recruitment (mean years (SD))	58 (41-70)	59 (40-70)	56 (37- 72)	56 (39 – 71)	**<0.001**
Smoking Status N(%)					
Never Smoked	143 (32.9)	119 (45.9)	93,885 (49.2)	137,805 (60.0)	
Ex-smoker	201 (46.2)	113 (43.6)	73,365 (38.5)	72,021 (31.3)	
Current Smoker	91 (20.9)	27 (10.4)	2,3449 (12.3)	20,021 (8.71)	**<0.001**
Smoking Duration (Mean (SD))	32.8 (13.0)	29.3 (12.3)	26.5 (12.9)	25.2 (12.7)	**<0.001**
N	241	102	70,699	60,377	
Alcohol Status n (%)					
Never	9 (2.0)	12 (4.6)	5,421 (2.8)	13,846 (6.0)	
Previous	46 (10.5)	22 (8.4)	6,765 (3.5)	8,317 (3.6)	**<0.001**
Current	385 (87.5)	228 (87.0)	179,059 (93.3)	208,335 (90.1)	

Table 5.19 continued. ***Differences between HNC cases and controls with in the Model Development Dataset, within the UK Biobank.***

Variable	Head and Neck Cancer Cases		Controls		P-value
	Males	Females	Males	Females	
Current Alcohol Frequency n (%)					
Daily or almost daily	136 (30.9)	48 (18.3)	49,388 (25.8)	38,101 (16.5)	**<0.001**
3-4 times per week	92 (20.9)	55 (21.0)	49,714 (26.0)	47,218 (20.5)	
1 – 2 times per week	94 (21.4)	56 (21.4)	48,936 (25.6)	58,788 (25.5)	
1 – 3 times per month	28 (6.4)	29 (11.1)	17,033 (8.9)	29,896 (13.0)	
Special occasions	35 (8.0)	40 (15.3)	13,988 (7.3)	34,332 (14.9)	
Never	55 (12.5)	34 (13.0)	12,186 (6.4)	22,163 (9.6)	
N	440	262	191,245	230,498	
Body Mass Index (BMI); mean(SD)	26.4 (4.5)	26.1 (5.0)	27.8 (4.2)	27.0 (5.2)	**Males: <0.001 Females: 0.004**
N	436	260	190,545	229,959	
Fruit (no. of pieces per day; mean(SD))	1.7 (1.5)	2.1 (1.4)	2.1 (1.6)	2.4 (1.6)	**<0.001**
N	416	254	182,400	224,686	
Townsend Deprivation Quintile N (%)					
1 (least deprived)	142 (32.3)	90 (34.4)	69171 (36.1)	82,830 (35.9)	**Males: <0.001**
2	90 (20.4)	60 (22.9)	45201 (23.6)	55,750 (24.1)	Females: 0.62
3	69 (15.7)	47 (17.9)	33687 (17.6)	41,913 (18.2)	
4	77 (17.5)	37 (14.1)	26406 (13.8)	31,797 (13.8)	
5 (most deprived)	62 (14.1)	28 (10.7)	17166 (9.0)	18,563 (8.0)	
N	440	262	191631	230,853	

Table 5.19 continued. Differences between HNC cases and controls with in the Model Development Dataset, within the UK Biobank

Variable	Head and Neck Cancer Cases		Controls		P-value
	Males	Females	Males	Females	
Household Income per year (£) n (%)					
<18000	109 (28.4)	75 (35.1)	33,918 (19.8)	45,880 (24.1)	
18000-30999	100 (26.0)	71 (33.2)	41,177 (24.1)	49,735 (26.1)	
31000-51999	94 (24.5)	37 (17.3)	46,075 (26.9)	48,832 (25.6)	**<0.001**
52000-100000	64 (16.7)	27 (12.6)	38,807 (22.7)	36,518 (19.2)	
>100000	17 (4.4)	4 (1.9)	11,034 (6.5)	9,750 (5.1)	
N	384	214	171,011	190,715	
Moderate Exercise (at least 10 minutes) no. days/week					
0	80 (19.5)	34 (13.6)	23,823 (13.0)	26,776 (12.4)	
1	20 (4.9)	22 (8.8)	15,818 (8.6)	16,643 (7.7)	Females: 0.681
2	57 (13.9)	35 (14.0)	26,825 (14.6)	32,286 (14.9)	
3	41 (10.0)	38 (15.2)	25,771 (14.0)	34,564 (15.9)	**Males: <0.001**
4	41 (10.0)	33 (13.2)	17,353 (9.4)	22,732 (10.5)	
5	55 (13.4)	35 (14.0)	29,983 (16.3)	30,291 (14.0)	
6	35 (8.5)	13 (5.2)	12,135 (6.6)	10,182 (4.7)	
7	81 (19.8)	40 (16.0)	31,979 (17.4)	43,351 (20.0)	
N	410	250	183,687	216,825	

Chapter 6

Development of a multivariable risk prediction model for head and neck cancer in adults, using the UK Biobank

6.1 Introduction

The aim of this Chapter is to describe the development and performance of the first UK-based risk prediction model for head and neck cancer, using the UK Biobank dataset. TRIPOD guidelines on development, validation and reporting have been followed and a summary of compliance is presented in Appendix 7.

Chapter 5 described the study population and detailed descriptive statistics comparing over 230 candidate predictors. The evidence to support the consideration of these candidate predictors was also presented.

The methodology used to develop the model has been described in Chapter 4. Briefly, the model presented in this chapter has been developed using a nested case-control study within the UK Biobank, a cohort of over 500,000 adults recruited from around the UK (see section 4.3.2) (235). The outcome of interest is a diagnosis of head and neck cancer, with the model predicting absolute risk of head and neck cancer. The dataset contains 859 cases of HNC, as confirmed by linkage with the UK Cancer Registries. Given the large size of the dataset, the data obtained from the North West of England were split from the remainder, to allow geographical

validation of the model. This formed a development dataset with 702 cases of HNC and a validation dataset with 157 cases. (see section 4.4.2.1 for a detailed discussion of the rationale for this methodology).

The dataset contained some missing data and this was handled by multiple imputation using chained equations (166, 236). The model was developed using logistic regression analysis, first considering the candidate predictors in a univariable (unadjusted) analysis (section 6.3) and subsequently in a multivariable model (section 6.4). Automated selection methods were avoided to ensure the clinical relevance of the model (169, 170). The discrimination and calibration of the model is assessed in section 6.7 (179, 237).

6.2. Candidate Variables

From the initial list of 7,800 variables available within the UK Biobank dataset, a reduced list of 233 variables were considered to have some clinical relevance to HNC (Appendix 5). These variables were explored in Chapter 5 and the literature was assessed for existing evidence to support their role as risk factors for HNC (section 5.2). From this investigation, a final list of twelve variables was created, each of which were explored in the univariable analysis (see box 6.1).

Box 6.1. Variables considered in the Univariable Analysis

Age	Gender
Smoking Duration	BMI
Smoking Status	Alcohol (frequency of consumption)
Alcohol Status	Exercise (number of days per week)
Lifetime number of sexual partners	Townsend Deprivation Score (groups 1-5)
Annual Household Income	Fruit (number of pieces consumed per day)

6.3 Univariable Analysis

Each variable of interest was tested for an (unadjusted) association with the outcome, diagnosis of HNC. The step was performed to detect associations, not to aid in variable selection: variable selection using univariable analysis has been shown to be an unhelpful step in model development, as variables which could have helped to stabilise the model may be excluded, even if they are not statistically significant (169, 170). The results of the univariable analysis are shown in Table 6.1.

Table 6.1. Univariable analysis of risk factors for head and neck cancer. *Risk factors (variables) are shown with their corresponding Odds Ratio and 95% Confidence Interval, related to risk of Head and Neck Cancer. P-values are shown for each category, with <0.05 considered statistically significant.*

Variable	**Odds ratio (OR)**	**95% Confidence Interval**	***p-value***
Age	1.03	1.03 – 1.05	<0.001
Gender			
Female	1.00		
Male	2.02	1.74 – 2.36	<0.001
Smoking Status			
Never smoked	1.00		
Ex-smoker	1.91	1.62 – 2.25	<0.001
Current Smoker	2.40	1.93-2.98	<0.001
Smoking Duration	1.03	1.025 – 1.034	<0.001
Alcohol Status			
Never drinker	1.00		
Previous drinker	4.14	2.53 – 6.75	<0.001
Current drinker	1.45	0.93 – 2.24	0.093

Table 6.1 continued. Univariable analysis of risk factors for head and neck cancer

Variable	Odds ratio (OR)	95% Confidence Interval	*p-value*
Alcohol Frequency			
Daily	1.00		
3-4 times per week	0.72	0.58-0.90	0.003
1-2 times per week	0.66	0.53-0.82	<0.001
1-3 times per month	0.58	0.43-0.78	<0.000
Special Occasions	0.74	0.56-0.97	0.027
Never	1.23	0.96-1.59	0.107
BMI	0.95	0.93 – 0.97	<0.001
Fruit	0.79	0.76 – 0.84	<0.001
Townsend Groups			
1	1.00		
2	0.97	0.79 – 1.20	0.798
3	1.01	0.80 – 1.26	0.963
4	1.28	1.03 – 1.61	0.029
5	1.65	1.29 – 2.11	<0.001

Table 6.1 continued. Univariable analysis of risk factors for head and neck cancer

Variable	**Odds Ratio (OR)**	95% confidence interval	*p-value*
Household Income (£ per year)			
<18,000	1.00		
18,000 - 30,999	0.82	0.66 – 1.00	0.055
31,000 – 51,999	0.60	0.48 – 0.75	<0.001
52,000 - 100,000	0.52	0.40 – 0.67	<0.001
>100,000	0.44	0.28 – 0.69	<0.001
Moderate Exercise (at least 10 minutes; number days/week)			
0	1.00		
1	0.57	0.40 – 0.82	0.002
2	0.69	0.52 – 0.91	0.008
3	0.58	0.43 – 0.77	<0.001
4	0.82	0.61 – 1.10	0.183
5	0.66	0.50 – 0.87	0.004
6	0.95	0.68 – 1.33	0.788
7	0.71	0.55 – 0.92	0.010
Lifetime number of sexual partners	1.00	1.00 – 1.00	0.321

In the univariable analysis, the following variables are significantly associated (at the 5% level) with an increased risk of HNC (odds ratio >1): increasing age, male gender, past or current smoking, increasing smoking duration, being a previous alcohol drinker or a current alcohol drinker and living in an area categorised as deprived or very deprived (Townsend Groups 4 and 5).

Factors offering a statistically significant (5% level) protective effect (odds ratio <1) are: increasing consumption of fruit, higher BMI and an annual household income of greater than or equal to £32,000 (compared to <£18,000).

6.4 Multivariable Analysis

6.4.1 Multivariable Model Development

6.4.1.1 Selection of Variables

Annual household income and Townsend groups are both measures of deprivation. Annual household income is a measure of individual-level deprivation, whereas the Townsend score is a measure of area-level deprivation (186). Deprivation has been recognised as an important risk factor for head and neck cancer and has been discussed in Chapter 5 (section 5.2.2). However, including two variables to measure the same risk factor is not necessary. 59.2% of patients with HNC living in the most deprived areas (Townsend group 5) had an annual household income of <£18,000, compared to only 16% of those living in the most affluent areas (data not shown). Despite this, the variables are only weakly correlated, as demonstrated by a Spearman's correlation coefficient of 0.2086 ($p<0.001$). For simplicity, Townsend groups were not included in the multivariable model as they are not simply calculated with freely available software. Household income is self-reported by the patient and can be directly entered into the model.

Alcohol status was also removed from the final model, as this does not reflect level of alcohol consumption. Frequency of alcohol intake has been shown to be a reliable

and valid measure of alcohol consumption in a systematic review of population surveys (238) and avoids the need for the patient to recall exact numbers of drinks or calculate number of units. Asking patients about alcohol intake on the previous day has been shown to be a more accurate measure of alcohol intake than overall frequency, as patients tend to underestimate how often they drink (239). However, these data were not available in our dataset. The final multivariable model included variables for age, gender, smoking status, smoking duration, annual household income, frequency of alcohol consumption, BMI, exercise, number of pieces of fruit per day and lifetime number of sexual partners.

6.4.1.2 Multivariable Results

The data were split into North West (for model validation) and Rest of UK (for model development) (section 4.4.2.1). The development dataset contains 329,005 observations with 10 imputed datasets; section 4.4.3 discussed multiple imputation.

Table 6.2 shows the Odds ratios with 95% confidence intervals for each variable, from the multivariable model developed.

Table 6.2. Multivariable Model of Risk Factors for Head and Neck Cancer. *Odds Ratios and 95% confidence intervals are presented, with p-values (<0.05 is considered statistically significant).*

Variable	Odds Ratio	P value	95% Confidence Interval	
Model Intercept	**Coefficient: -6.094852**	<0.001	-7.12	-5.07
Age	1.03	<0.001	1.01	1.04
Male Gender	1.74	<0.001	1.44	2.10
Smoking Status				
Previous	1.15	0.257	0.90	1.47
Current	1.00	0.990	0.68	1.49
Smoking Duration	1.02	<0.001	1.01	1.03
Household income				
18,000 – 30,999	1.00	0.999	0.78	1.28
31,000 – 51,999	0.85	0.262	0.65	1.13
52,000 – 99,999	0.79	0.152	0.58	1.09
≥100,000	0.72	0.201	0.44	1.19

Table 6.2 continued. Multivariable model of Risk Factors for Head and Neck Cancer

Variable	Odds Ratio	p-value	95% confidence interval	
BMI	0.94	<0.001	0.93	0.95
Frequency of Alcohol Consumption				
3 – 4 times/wk	1.02	0.843	0.79	1.32
1-2 times/wk	0.95	0.694	0.72	1.23
1 -3 times per month	0.96	0.829	0.68	1.36
Special Occasions	1.18	0.327	0.85	1.65
Never	1.57	0.010	1.11	2.20
Moderate Exercise (at least 10 mins; number days/wk)				
1	0.66	0.040	0.44	0.98
2	0.71	0.045	0.52	0.99
3	0.65	0.011	0.46	0.90
4	0.81	0.250	0.57	1.15
5	0.70	0.031	0.51	0.97
6	0.74	0.173	0.48	1.14
7	0.72	0.037	0.54	0.98
Fruit (number of pieces/day)	0.86	<0.001	0.80	0.92
Lifetime number of sexual partners				
	1.00	0.536	0.999	1.001

The results confirm that increasing age is a risk factor for HNC, with each year conferring an additional 3% risk (OR 1.03). Males have a 75% higher risk of the disease, than women (OR 1.75). As smoking duration increases, risk of HNC also increases by 2% per year (OR 1.02).

Daily drinking was used as the baseline and 'never drinking' emerged as a risk factor for HNC (OR 1.57). The remaining categories for frequency of alcohol consumption were not significant. This will be discussed in section 6.9.

Increasing consumption of fruit offers a protective effect against HNC (OR 0.86); every additional piece of fruit consumed per day offers a 14% protective effect. Moderate exercise on at least 1 day per week is associated with a protective effect; only exercise on 1, 2, 3, 5 or 7 days per week was found to have a statistically significant association (at the 5% level) with a reduced risk of HNC. Increasing BMI also confers a protective effect (OR 0.94).

Smoking status, lifetime number of sexual partners and household income were not statistically significant in the multivariable model.

6.5. Individual Risk Prediction

To calculate the probability of disease for an individual, using the model(s) described, a linear predictor must be calculated. Let us consider a male, aged 65 years, who is a current smoker of 45 years, with an annual household income of <£18,000, who consumes alcohol 3-4 times per week, eats no fruit, never exercises and has 5 previous sexual partners.

$$Probability = \frac{1}{1 + \exp(linear\ predictor)}$$

where linear predictor (log odds) = $intercept + \ \beta_1 x_1 + \cdots + \beta_j x_j$, where β is the coefficient found in Table 6.2 and x is the value of the associated variable.

In our case:

$$\log odds = -6.094852 + (0.0254 \text{ x } 65) + (0.5554 \text{ x } 1) + (0.0025 \text{ x } 1) + (0.0170 \text{ x } 40) + (0.0001 \text{ x } 1) + (0.0257 \text{ x } 1) + (0.0002 \text{ x } 5) = -3.180152$$

Values for fruit and exercise are zero therefore are not seen in this equation.

$$Probability = \frac{1}{1 + \exp(-3.180152)} = 0.03992$$

This gives a percentage probability of head and neck cancer of 4%.

6.6 Assessing Model Performance: Internal Validation

Evaluating model performance is an important step in model development to predict how well the model will perform in external data (67). Analysis and reporting of model performance is required as part of the TRIPOD guidelines for developing a multivariable prediction model (134, 240). It is vital to know how well a model can discriminate between those who have the outcome of interest and those who do not, if the model is to be used in screening trials or in clinical decision making.

The results of the internal validation can reveal problems in the model development, such as over-fitting or optimism (section 6.6.3) (136). Correction of the model or recalculation of coefficients can then be undertaken prior to external validation (161). Obtaining external data in which to validate a model can be difficult and, if such data are available, it is important to maximise the opportunity by ensuring the model being tested is as robust as possible (161). Essentially, the purpose of internal validation is to examine optimism in apparent performance, produce optimism-adjusted performance and revise the developed model accordingly (136).

Firstly, the apparent performance (discrimination and calibration) should be calculated and this is discussed in 6.6.1. and 6.6.2. The problem of optimism is considered in 6.6.3, along with techniques to address this.

6.6.1 Discrimination

Performance of a model refers to its ability to accurately separate those with the outcome from those who do not have the outcome of interest (discrimination) within a population. For models with a binary outcome (as in this case), the Area Under the Receiver Operating Curve (AUROC) is used as a measure of discrimination (184). This is equivalent to the c-statistic for Cox-regression models (241). The AUROC plots the sensitivity (true positive rate) against '1-specificity' (false positive rate). A value of 0.5 indicates the model is no better than chance at predicting the outcome, whereas a value of 1 signifies perfect discrimination. Models are considered to show good discrimination if the AUROC is at least 0.7 and outstanding discrimination with an AUROC of at least 0.9 (242). However, the ROC should be interpreted in the context of the literature available in the subject area in which the model was developed and consideration must be given to the calibration performance (134).

6.6.2 Calibration

Another important aspect of model performance is calibration. This demonstrates how similar the predicted and observed risks are. With a well-calibrated model, x out of 100 patients with a predicted risk of $x\%$ should experience the event (67, 243). Calibration can be presented graphically as a calibration plot, with predicted and observed event rate plotted for defined risk groups, together with 95% confidence intervals (134, 135). The closer the plots lie to the 45-degree line, the better the calibration.

6.6.3 Optimism in Model Performance

The apparent performance of models developed in small datasets, with a low number of events-per-variable, can be over-optimistic. The model is built to fit the data in which it is developed, therefore it may not perform as well in external datasets (136). This is referred to as 'overfitting'. The best way to minimise optimism, or over-fitting, in risk models is to ensure one uses a dataset with enough events (i.e. patients with the outcome in question), in which to develop the model (175, 244). Models developed in datasets with at least 20 events per variable have been found to display minimal optimism (245). If large datasets are not available, there are techniques to

test and mediate for optimism, including cross validation and bootstrapping (181-183, 185, 244).

The UK Biobank development dataset contains 702 cases of head and neck cancer, and 23 variables have been considered in the final model. This gives an EPV of 30, which minimising the risk of over-fitting and makes Leave One Out Cross Validation (LOOCV) and bootstrapping unnecessary (244, 245). Furthermore, the model developed will be validated in external data, not used to develop the model; the results are presented in Chapter 7.

Measure of apparent discrimination and calibration are presented in section 6.7. For completion, cross-validation and bootstrapping will be discussed in sections 6.6.3.1 and 6.6.3.2.

6.6.3.1 Cross Validation

In situations where a relatively small dataset is available, it is considered wasteful to split the dataset into development and validation datasets (184). It is better to use the full data to develop the model and then use cross-validation or bootstrapping techniques to obtain measures of internal validation (246). Cross-validation involves splitting the data into N subgroups; the model is then developed in N-1 of the groups and tested in the remaining group. This is repeated N times and the average performance is calculated (181). Using 10 groups has been shown to produce the best results more efficiently, when compared to leave-one-out cross validation (LOOCV) (247). LOOCV involves the same procedure detailed above, where N is the total number of participants in the dataset.

6.6.3.2 Bootstrapping

An alternative to cross-validation is bootstrapping. This is another resampling procedure, in which samples of the same size as the original dataset are drawn with replacement from within, to create a new dataset (183, 185, 244). The model is then developed in the bootstrap sample and tested in the original data. The apparent performance is calculated in the bootstrap sample and tested in the original sample (test); optimism is calculated by subtracting the test performance from the apparent performance. This entire procedure is repeated between 200 and 1000 times,

following which the average optimism is calculated (248). Optimism-adjusted performance can then be calculated and if necessary, a shrinkage factor can be applied to the coefficients (249). Bootstrapping has been shown to provide accurate estimates of model performance and is generally preferred to cross-validation procedures as it is considered more efficient use of data (67).

6.7 Discrimination and Calibration of Multivariable Model using Standard Terms

Apparent discrimination, as measured by the AUROC is 0.67 (95% CI 0.64 – 0. 69), see Figure 6.1. This shows that the model is better than chance at predicting a case of HNC.

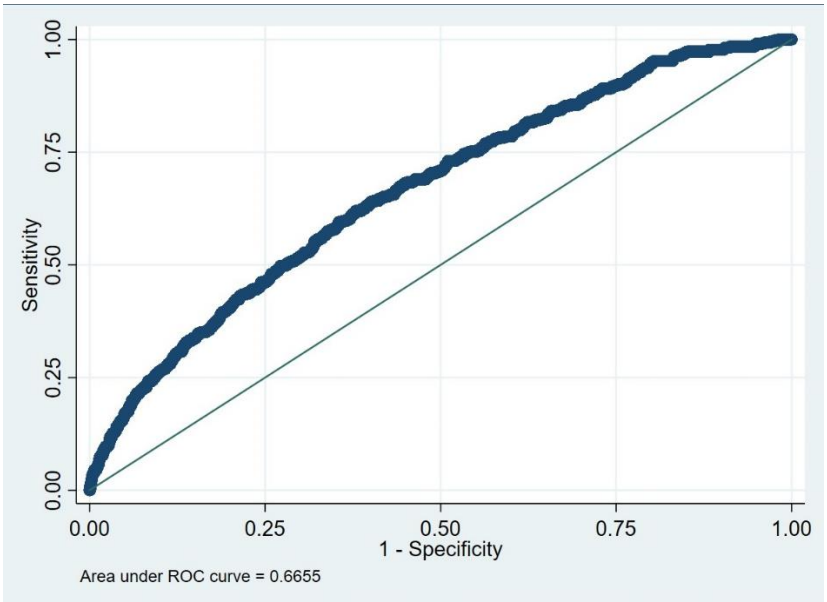


Figure 6.1. Area Under the Receiver Operating Curve for Multivariable Model of Head and Neck Cancer Risk Prediction.

Calibration was measured using expected:observed risk. The calibration slope has a value of 0.99 and is shown in Figure 6.2: The 'Expected' probability of a diagnosis of head and neck is calculated for each individual in the dataset. The 'Observed' risk is calculated as the mean of the outcome variable (HNC). The E:O ratio is simply the mean of the expected probabilities divided by the mean of the outcome variable. A value close to one indicates perfect calibration. A value less than one indicates that predictions are under-estimating risk and a value of greater than one indicates the predictions are over-estimating risk (67, 243). Figure 6.2 shows calibration of ten risk

groups, demonstrating that performance is good across risk groups, as displayed by close-proximity to the 45-degree line. Confidence intervals are shown and are narrow, indicating good calibration. Most of the deciles are clustered close to the left side of the graph, indicating the very low risk of head and neck cancer in the general population.

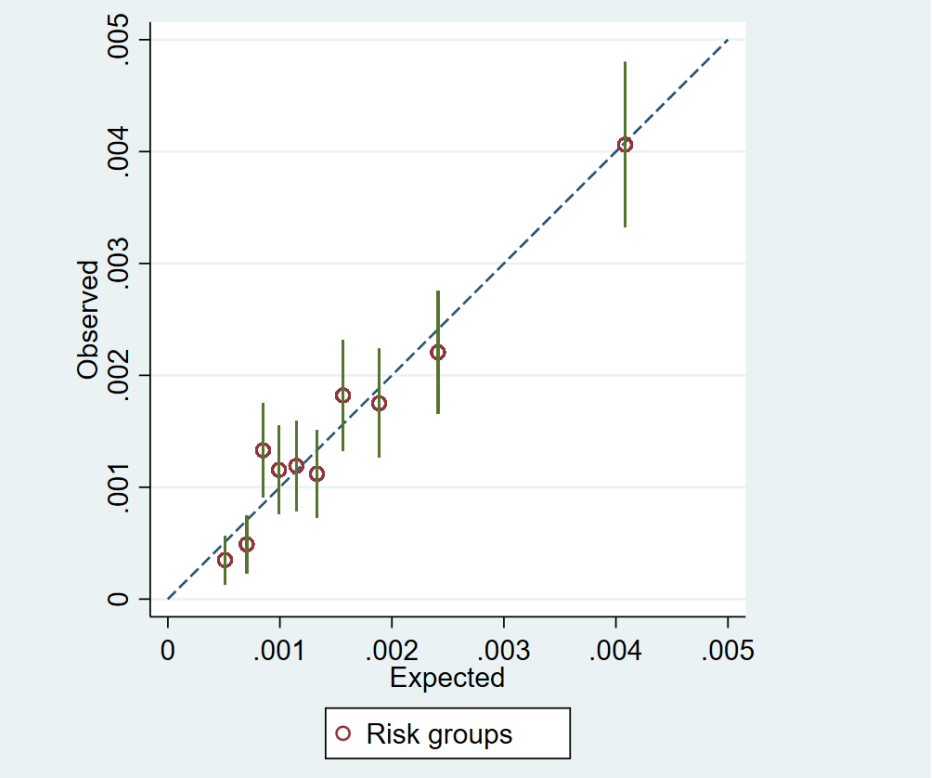


Figure 6.2. Calibration Slope for Multivariable Risk Model for Head and Neck Cancer

6.8 Discussion

This chapter has presented the first risk prediction model for absolute risk of head and neck cancer, developed using the UK Biobank dataset.

Logistic regression analysis has been used to develop the model. The binary outcome of "Head and Neck Cancer: yes or no" lends itself to logistic regression; this method of analysis is flexible and produces a clinically meaningful output (odds ratios) (151, 250).

In the univariable analysis, increasing age, male gender, past or current smoking, increasing smoking duration, being a previous alcohol drinker or a current alcohol

drinker, and living in an area categorised as deprived or very deprived (Townsend Groups 4 and 5) were significant risk factors for head and neck cancer. Increasing consumption of fruit, an annual household income of greater than or equal to £32,000 (compared to <£18,000) and increasing BMI were significantly protective against HNC.

The multivariable model included variables for age, gender, smoking status and smoking duration, BMI, frequency of alcohol intake, household income (as a measure of deprivation), number of sexual partners, fruit intake and exercise.

A multivariable model was built using untransformed continuous variables for ease of interpretation. Increasing age, male gender, increasing smoking duration, and never drinking alcohol were found to be risk factors for HNC. Moderate exercise, increasing BMI and increasing consumption of fruit were found to be protective. The increasing incidence of HPV-related oropharyngeal cancers justifies the inclusion number of sexual partners in the risk model (20, 228), as number of sexual partners has been established as a risk factor for this sub-type of HNC (30).

Increasing age, male gender and smoking are well established risk factors for HNC (194, 233, 251) and deprivation has also emerged as an important predictor of HNC (35, 227, 233), which justifies including household income in the model, as a proxy for individual-level deprivation (227, 252).

Alcohol is also a well-known risk factor for HNC and its effect is synergistic with smoking (192, 194). It is surprising that the risk prediction model reveals 'never drinking alcohol' as a risk factor for HNC. The dataset contains both prevalent and incident cases of HNC therefore it may be that changes in alcohol consumption following diagnosis of HNC has affected this result, i.e. it may be that cases have stopped drinking following their diagnosis of HNC. For the never drinkers, 77% (68/88) are former drinkers, compared to 44% (15,082/34,212) of controls (data not shown), which supports this suggestion. This reveals that current alcohol frequency may not be the most reliable predictor to use in a risk prediction model for HNC as it does not reflect lifetime use of alcohol. Use of alcohol is known to change throughout

life (253), therefore it may be more appropriate to seek information about drinking habits both past and current to improve the model's discriminative ability.

Exercise and diets rich in antioxidants are known to be beneficial in prevention of HNC (193, 194, 233) and this is supported by the present model, with significant protective effects demonstrate for increasing fruit consumption and exercise on at least one day per week.

BMI has been explored as a risk factor for HNC but no definite consensus has been reached as to its significance (201). Section 5.2.8.1 discussed the relevance of BMI to HNC. This model demonstrates that controls have a higher BMI than cases, implying that higher BMI is protective against HNC (OR 0.94). However, this dataset contains information on patients who were free from HNC at recruitment and those with a previous diagnosis of HNC. BMI may have been affected by the diagnosis itself, as HNC patients will frequently have periods of time where eating is difficult, which could result in weight loss (254). Unintentional weight loss is reported as a presenting symptom in 26% of patients who go on to receive a diagnosis of HNC (255). A prospective cohort with details of BMI in the years prior to diagnosis would be required to investigate this further.

6.8.1 Model Performance

The AUROC was 0.67, which is reasonable. The calibration was good with all risk groups lying close to the 45-degree line on the calibration curves.

Resampling techniques were not used for internal validation as the EPV is high in these data, which minimises optimism in model performance statistics. The true test of a model lies in its performance in external data, i.e. data in which the model was not developed, which is presented in Chapter 7.

This is the first risk prediction model to be developed with HNC as an outcome, for the general population; therefore, it is impossible to discuss this apparent performance in the context of the current literature.

One other risk model has been identified which predicts HNC in patients with current symptoms (256). This model is proposed for use in general practice as a tool for

guiding urgent referrals. This model was developed using a UK-based dataset with 397 cases and 4,318 controls. The model has an AUROC of 0.77. No calibration statistics are presented. This model was externally validated, by the same authors, in a Scottish dataset of 2000 individuals with 232 cases of HNC(255). The discrimination is good (C-statistic of 0.81); again, no measure of calibration is reported.

Speight *et al* published an extensive Health Technology Assessment report, in 2006, on the cost-effectiveness of oral cancer screening in the UK, using a simulated population of 100,000 (257). This incorporated some elements of risk modelling, although none that could be applied in general practice. No performance statistics are presented. The findings suggest that opportunistic screening of "high-risk" individuals could be cost-effective. They define high-risk as males over the age of 40 years, who smoke and consume alcohol.

6.8.2 Absolute Risk of HNC

Absolute risk is the risk of developing a disease within a given time period. Absolute risk can be calculated by linkage with regional incidence data as in Cassidy *et al* 2008 (188). In this paper, regional lung cancer incidence data was obtained from North West Cancer Intelligence Service, in 5-year age categories and the intercept (α) was calculated for each 5-year age group, using:

$$\alpha = \ln\left(\frac{p}{1-p}\right) - \sum \beta_i x_i, \text{ where } p = \frac{incidence\ rate\ per\ 100{,}000\ persons}{100{,}000}.$$

The intercept is a function of the ratio of number of cases to number of controls and does not pertain to absolute risk; hence, the number of person-years at risk must be reported or, as in this example, a more complex method of calculation, using regional cancer data can be employed. This will be discussed in Chapter 9 in relation to future aims.

6.9 Conclusions

The paucity of data on risk prediction in HNC highlights the need for the development of a validated risk prediction model. There is great potential for use of this model for defining selection of patients for screening trials and this is discussed in Chapter 9.

Incorporation of biomarkers could further refine the predictive ability of the model (136, 258), and such a model could be applied to a known high-risk group of patients with a diagnosis of oral pre-malignancy in order to predict malignant transformation and hence guide management decisions (see Chapter 8). Potential for clinical application and future work will be discussed in Chapter 9.

The model developed in this chapter shows reasonable discrimination and good calibration for prediction of head and neck cancer. The results of the external validation are presented in Chapter 7.

Chapter 7

External Validation of a Risk Prediction Model for Absolute Risk of Head and Neck Cancer, using the UK Biobank

7.1 Introduction

The previous chapter presented the development of the first risk prediction model for absolute risk of head and neck cancer, using the UK Biobank dataset. This chapter presents the validation of this model, using a subset of the UK Biobank dataset, containing persons living in the North West of England.

Validation of risk prediction models is of paramount importance to investigate their reliability in different populations, referred to as 'transportability'. Ideally models should be validated in external datasets to confirm their reliability and predictive accuracy, before they are used in impact studies to assess their clinical usefulness (161, 163, 240).

The North West of England is known to have a higher incidence of head and neck cancer than other parts of the UK (8, 149). For this reason, the original dataset was split geographically, into development and validation sets, to tests its performance in a cohort known to have a higher risk of HNC. It is not recommended to randomly split the data into development and validation sets (184), rather a geographical split

or time-dependent split is a better way of validating a model's transportability to different populations (67, 161) (see section 4.4.2.1.)

This chapter will present the methodology used for external validation (section 7.2), descriptive statistics for the validation cohort (section 7.3) and measures of model performance (section 7.4). Methods for improving model performance and the results of this will be presented in Section 7.5.

7.2 Methodology

The model for predicting risk of HNC, developed in section 6.4.1, contained variables for age, gender, smoking status and smoking duration, BMI, frequency of alcohol intake, household income (as a measure of deprivation), number of sexual partners, fruit intake and exercise.

Firstly, the differences between cases and controls in the validation dataset are explored using descriptive statistics (t-test for continuous and chi-squared for categorical predictors) and compared to the development cohort (section 7.3).

The linear predictor and predicted probability of head and neck cancer has been calculated for each individual in the validation dataset, using the log of the Odds Ratios found in Table 6.2 and the equation shown in section 6.5. The c-statistic (area under the receiver operating curve, AUROC) has been used as a measure of the model's ability to discriminate between cases and controls. The calibration slope and calibration plot are used as measures of calibration. Ten deciles of risk have been calculated to create risk groups, which are presented graphically as a calibration plot.

Given that the model will always perform better in the data in which it is developed, it is sometimes necessary to recalibrate the model for the data in which it is to be used (161). This can be achieved by updating the model intercept. This is discussed in section 7.5 and the effects of this updating on the discrimination and calibration are presented.

The model performance is assessed separately for males and females and separate calibration plots are presented. Risk of HNC is significantly higher for males than

females (OR 1.75; see table 6.2), therefore it is important to determine if the model performs equally well for both sexes.

7.3 The Validation Dataset

This section will describe differences between the HNC cases and controls in the validation dataset. These differences will be compared back to those found in the development dataset, which were presented in section 5.2.

The validation set contains 78,895 individuals, with 157 cases of head and neck cancer.

Table 7.1 presents the descriptive statistics detailing differences between cases and controls for all the variables used in the final model.

7.3.1 Similarities and Differences between the Validation and Development Cohorts

There are significantly more males than females with HNC. Males with HNC are significantly older than male controls but this was not seen for females, which is different to the development data (Chapter 5.2.1). There is a significant difference in the smoking status between cases and controls for males and females, which was also apparent in the development data (section 5.2.3). Smoking duration was not significantly different, neither was frequency of alcohol consumption. However, in the development dataset smoking duration was significantly different between cases and controls (section 5.2.3). Household income was significantly lower for cases compared to controls, which was also the case in the development data (section 5.2.2). Participation in moderate exercise was greater for female controls compared to cases but this difference was not seen in males. The opposite was seen in the development data: male cases reported less exercise than controls (section 5.2.6). Sexual history was not significantly different, however in the development data male cases reported statistically more sexual partners compared to controls (5.2.12). Fruit consumption was higher for male controls compared to cases, but no significant difference was clear for females. Fruit consumption was higher for both male and

female controls in the development dataset (5.2.5). This demonstrates some differences between the development and validation datasets, which has the potential to demonstrate the performance of the developed model in a broader population than initially considered. The prevalence of HNC in this population is 198 per 100,000 compared to 165 per 100,000 in the development dataset, indicating the higher risk of disease in this population.

Table 7.1 Descriptive Statistics for Risk Factors for Head and Neck Cancer in the Validation Cohort

Variable	Head and Neck Cancer Case		Control		*p*-value
	Males	**Females**	**Males**	**Females**	
Number (N (%))	94 (59.9)	63 (40.1)	36747 (46.7)	41991 (53.3)	0.001
Age at recruitment (years) (mean (std dev))	59.4 (6.5)	57.0 (7.0)	56.7 (8.2)	56.6 (8.0)	Males 0.003 Females 0.697
Never	33 (35.1)	21 (33.3)	17,435 (47.8)	24,163 (57.8)	
Previous	50 (53.2)	34 (54.0)	14,012 (38.4)	13,306 (31.8)	Males 0.012
Current	11 (11.7)	8 (12.7)	5,066 (13.8)	4,316 (10.4)	Females <0.001
N (%)	*94 (100)*	*63 (100)*	*36747 (100)*	*41991 (100)*	
Smoking Duration (ever smokers) Mean years (SD)	30.4 (14.5)	25.8 (13.2)	27.4 (12.9)	26.8 (12.7)	Males 0.105 Females 0.675
N Missing (%)	*10 (17)*	*n=11 (26)*	*4,680 (25)*	*5,335 (30)*	
Alcohol Frequency N(%)					
Daily	27 (28.7)	8 (12.7)	8,363 (22.8)	5,721 (13.7)	
3-4 times/wk	17 (18.0)	16 (25.4)	9,729 (26.6)	8,622 (20.6)	
1-2 times/wk	29 (30.9)	16 (25.4)	10,075 (27.5)	11,329 (27.0)	Males 0.126
1 – 3 times/month	5 (5.3)	7 (11.1)	3,293 (9.0)	5,583 (13.3)	Females 0.943
Special Occasions only	6 (6.4)	11 (17.5)	2,831 (7.7)	6,787 (16.2)	
Never	10 (10.6)	5 (7.9)	2,346 (6.4)	3,863 (9.2)	
N (%)	*94 (100)*	*63 (100)*	*36,637 (100)*	*41,991 (100)*	

Table 7.1 continued. Descriptive Statistics of Risk Factors for Head and Neck Cancer within the Validation Cohort					
Variable	**Head and Neck Cancer Case**		**Control**		***p*-value**
	Males	**Females**	**Males**	**Females**	
Household Income (£/year) N(%)					
<18,000	29 (40.3)	11 (24.4)	7,734 (25.3)	9,470 (29.2)	Males 0.039
18,000-31,999	12 (16.7)	19 (42.2)	8,076 (26.4)	9,011 (27.8)	Females 0.229
32,000 – 51,999	19 (26.4)	7 (15.6)	7,834 (25.6)	7,895 (24.3)	
52,000-99,999	10 (13.9)	6 (13.3)	5,770 (18.9)	5,090 (15.7)	
≥100,000	2 (2.8)	2 (4.4)	1,156 (3.8)	969 (3.0)	
N missing(%)	*22 (23)*	*18 (29)*	*6,177 (17)*	*9,556 (23)*	
Moderate Exercise (10 mins; no. days/wk) N(%)					
0	20 (22.0)	11 (18.6)	4,990 (14.3)	5,445 (13.9)	
1	5 (5.5)	8 (13.6)	2,839 (8.1)	2,935 (7.5)	
2	15 (16.5)	4 (6.8)	4,876 (14.0)	5,702 (14.6)	Males 0.325
3	13 (14.3)	15 (25.4)	4,814 (13.8)	6,251 (16.0)	Females 0.08
4	5 (5.5)	5 (8.5)	3,218 (9.2)	3,814 (9.8)	
5	10 (11.0)	8 (13.6)	5,694 (16.3)	5,366 (9.8)	
6	7 (7.7)	2 (3.4)	2,277 (6.52)	1,785 (4.6)	
7	16 (17.6)	6 (10.2)	6,208 (17.8)	7,825 (20.0)	
N missing (%)	*3 (3)*	*4 (6)*	*1,831 (5)*	*2,859 (7)*	
Fruit intake (no. pieces/day (sd))	1.6 (1.4)	2.1 (1.3)	2.1 (1.64)	2.4 (1.6)	Males 0.007
N Missing (%)	*9 (10)*	*0 (0)*	*1,921 (5)*	*1,198 (3)*	Females 0.133
Lifetime number of Sexual Partners (mean (sd))	14.5 (20.2)	4.2 (4.1)	11.0 (124.8)	4.3 (10.3)	Males 0.813 Females 0.9185
N Missing (%)	*24 (25%)*	*9 (14%)*	*7,949 (22%)*	*8,195 (19%)*	

7.4 Missing Data

Missing data was noted as shown in Table 7.1: missing data for number of sexual partners and household income and smoking duration was highest, whereas all other variables had ≤6% missing data.

Techniques for handing missing data were considered, including case-wise deletion or complete case analysis and multiple imputation. Multiple imputation was discussed in Chapter 4, section 4.4.3 and was used on the development dataset to handle missing data. Complete case analysis involves only using complete cases (i.e. with no missing data) in the analysis: individuals with any missing data are were removed for the purposes of the analysis.

In the validation dataset, complete case analysis was chosen due to the large size of the validation dataset and the fact that the variables with the highest amount of missing information were not statistically significant in the risk model (section 6.4.1). When the missing predictors do not have a significant effect on the outcome, complete case analysis is a simple and valid technique (259). However, it is recognised that multiple imputation is a robust method for handling missing data and preferred by some authors (162). 60,240 individuals were available for complete case analysis. Missing data is discussed in more detail in section 7.7.1.

7.4 Calculation of the Linear Predictor

The linear predictor (LP) was calculated for each patient in the validation dataset, using the coefficients obtained from the risk prediction model presented in 6.4.1 (Table 6.2). The coefficient is the log of the odds ratio. The LP is the log odds of each patient having the outcome of interest (151).

$$Linear\ Predictor = -6.094852\ (intercept) + (.0170573 * smoking\ duration) + (.0001917 * number\ of\ sexual\ partners) + (-.1552106 * fruit\ per\ day) + (-.322034 * (modex10 == 7)) + (-.299228 * (modex10 == 6)) + (-.3548187 * (modex10 == 5)) + (-.2049572 * (modex10 == 4)) + (-.4371079 * (modex10 == 3)) + (-.332567 * (modex10 == 2)) + (-.4220539 * (modex10 == 1)) + (.4487275 * (alcfreq == 6)) + (.1661107 * (alcfreq == 5)) + (-.0385644 * (aclfreq == 4)) + (-.0528734 * (alcfreq == 3)) + (.0257095 * (alcfreq == 2)) + (-.3233918 * (houseincome == 5)) + (-.2301338 * (houseincome == 4)) + (-.1571579 * (houseincome == 3)) + (.0001484 * (houseincome == 2)) + (.0024737 * (smoking\ status == 2)) + (.1402463 * (smoking\ status == 1)) + (.5554884 * gender) + (.0254182 * age) + (-0.026872 * \text{BMI}))$$

The mean of the LP for the validation dataset is -6.737 (sd 0.607), based on 60,240 observations. The linear predictor was -6.095 (sd 0.523) for the development dataset, which is similar. This allows us to compare the development and validation data and demonstrates that, on average, the risks are similar in the development and validation datasets.

7.4 Model Performance

7.4.1 Discrimination

The c-statistic (area under the receiver operating curve) for the model in the validation data is 0.64 (95% CI 0.59 - 0.70), which shows that the model is better than chance at predicting the outcome (see Figure 7.1). The performance is slightly worse than in the development data (AUROC 0.67 (95% CI 0.64 – 0. 69) – section 6.7). This may be due to slight overfitting of the model in the development dataset, however this is unlikely to be due to the large sample size (n=329,005).

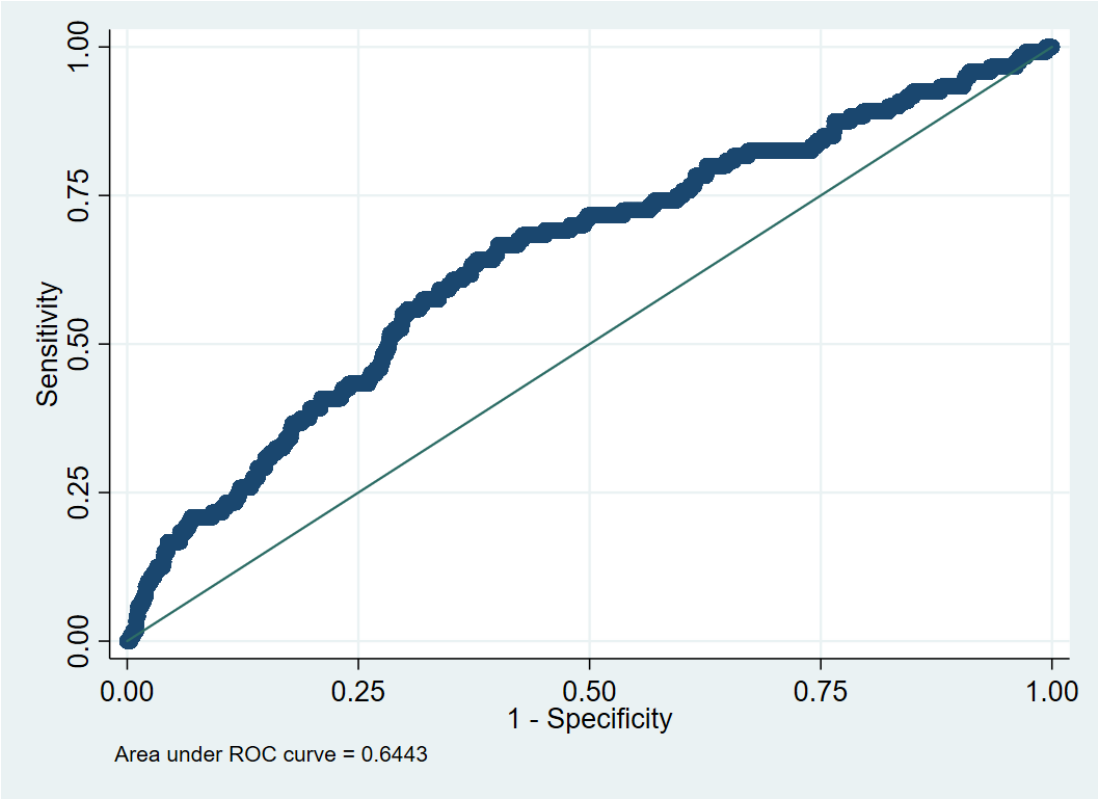


Figure 7.1. Area under the Receiver Operating Curve (AUROC) Graph demonstrating the Discrimination of the Risk Model in the Validation Dataset; C-statistic = 0.64

7.4.2 Calibration

The probability of head and neck cancer is very low, 0.00199 (n=78,895). The mean expected probability is 0.00143 (n=60,240).

Although this only equates to a difference of 0.00056, the expected:observed ratio is 0.72. Ideally the E:O would be 1, with no difference in the expected and observed probabilities. However, with such low incidence, even small differences can appear large when viewed as a relative measure, such as E/O.

The calibration slope is 0.83 (std error 0.14). This suggests the model is slightly overfitted, with predictions being slightly too high in all risk groups.

Ten risk groups were created, and a calibration plot generated (see Figure 7.2). The risk is very low (<0.01% for all ten groups) and the observed and expected probabilities are quite close to the reference line. The model generally overpredicts

risk of head and neck cancer, as seen by many of the points lying above the reference line and as shown by the calibration slope of 0.83.

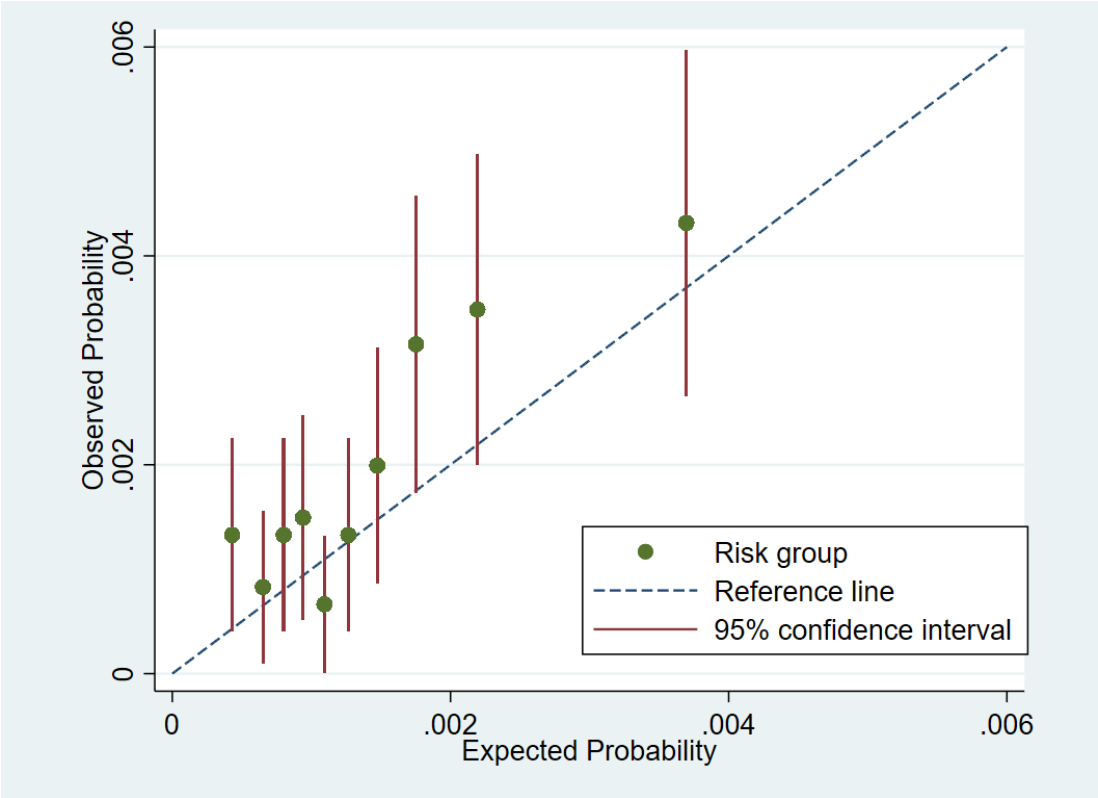


Figure 7.2. Calibration plot for Model Validation showing Expected and Observed Probabilities for Ten Risk Groups. The 45-degree line indicates perfect calibration. The points lie fairly close to this line indicating fairly good calibration of the model.

7.5 Improving Calibration

The problem of overfitting or optimism in model development was discussed in 6.6.3. In models developed in data with a low EPV or using data-driven techniques, such as automated selection of variables, one might expect significant overfitting (163). However, the present model was developed in data with an EPV of 30 and using clinical reasoning for variable selection to minimise this problem. However, the calibration in the external validation is worse than the apparent calibration in the development data, which had a calibration slope of 0.99. This is probably due to the fact that the prevalence of the outcome (HNC) is higher in the validation cohort

(section 7.3). There is one option available to improve the calibration in these circumstances, which involves updating the model intercept, i.e. updating the baseline risk to reflect the higher outcome frequency (161, 260). This has been shown to improve calibration when models were under- or over-predicting risk (261). Another option when faced with a model which performs worse than desired is to develop a completely new model and reject the first model. However, unless there have been significant concerns with the development of the initial model, it is recommended the model is simply updated, either by re-estimating the baseline risk (as in this case), or my re-estimating the effect estimates (161). This prevents loss of scientific information and prevents a large number of models being developed, which generates confusion about which model should be used (161).

The intercept is updated by fitting a logistic regression model with the original linear predictor (as an offset term) as the only covariate. The new coefficient generated is the updated intercept.

The updated intercept in this validation data is -5.762 (95% CI -5.943 - -5.583). The calibration slope is unchanged at 0.83 (sd 0.14) (see Figure 7.3) as is the discrimination as the ranking of the predictions is unchanged.

Looking at the calibration plot, we can see the points now lie closer to the line of agreement (the 45-degree line), showing better agreement.

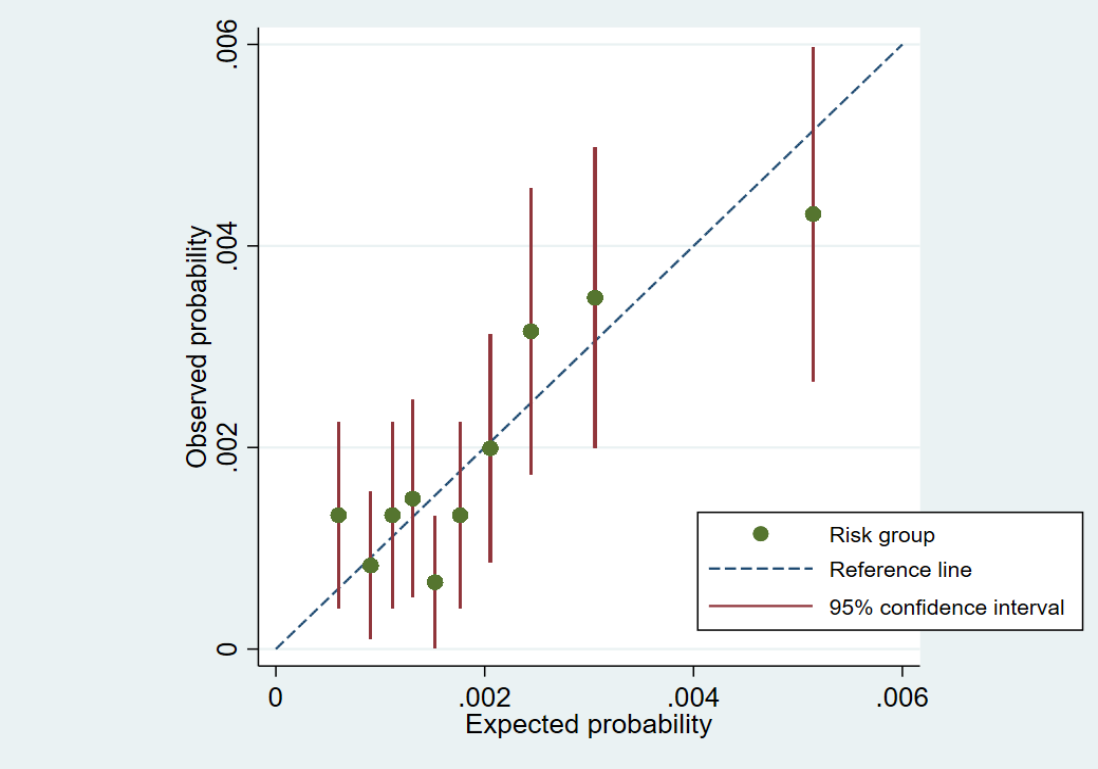


Figure 7.3. Calibration Plot showing Expected and Observed Probabilities for Ten Risk Groups, following updating of the Model Intercept.

Figure 7.4 shows the calibration plots for the original model and the updated model overlaid.

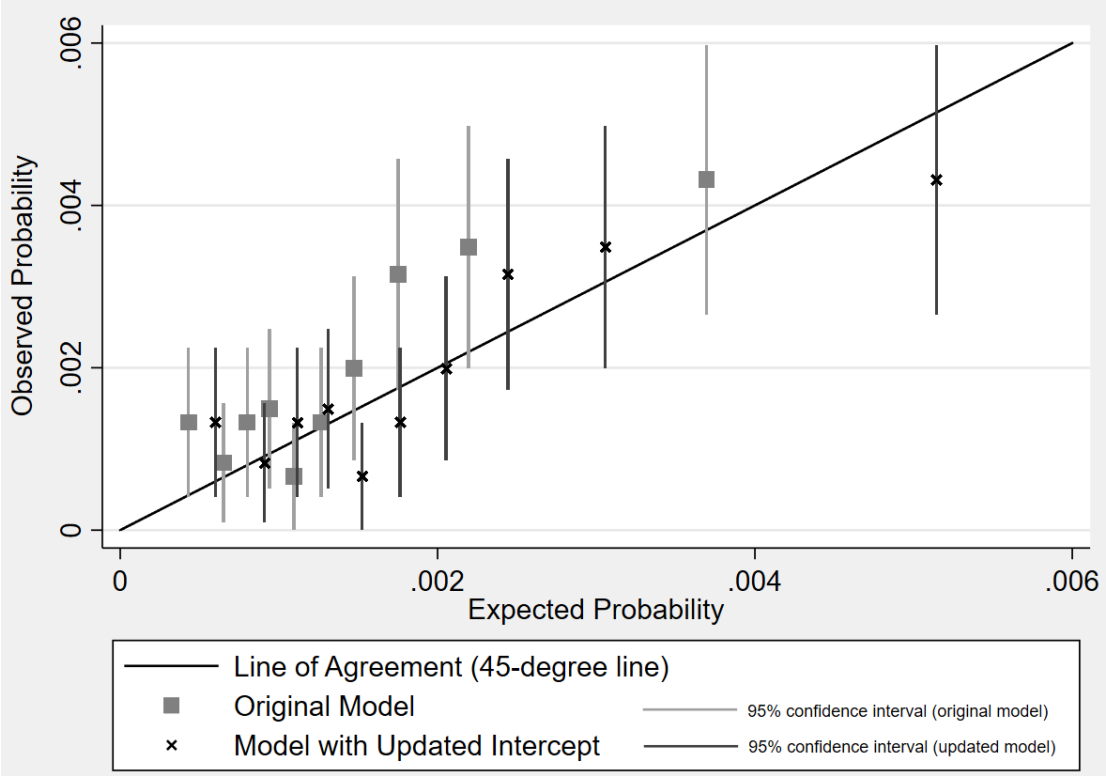


Figure 7.4. Graph showing calibration of original model overlaid with calibration of model with updated intercept. The expected:observed probabilities lie slightly closer to the 45-degree line for some of the risk groups, with the updated model

7.6 Calibration in Different Risk Groups

Risk is different in subgroups of the population and therefore one might expect a risk model would perform differently in these subgroups (161, 260). This model shows that male gender is a significant risk factor for HNC (6.4.1) and gender-specific risk factors for HNC have been explored in Chapter 3. For this reason, model calibration has been tested separately for males and females.

7.6.1 Model Performance: Males

The model performance was assessed in males within the validation cohort (n=27,364). The E:O was 1.02 indicating good calibration. The calibration slope was 0.90, which is better than in the overall validation cohort. The c-statistic is slightly improved but not significantly, at 0.65 (0.58 – 0.71). Figure 7.5 shows the calibration plot. All of the groups lie close to the 45-degree line.

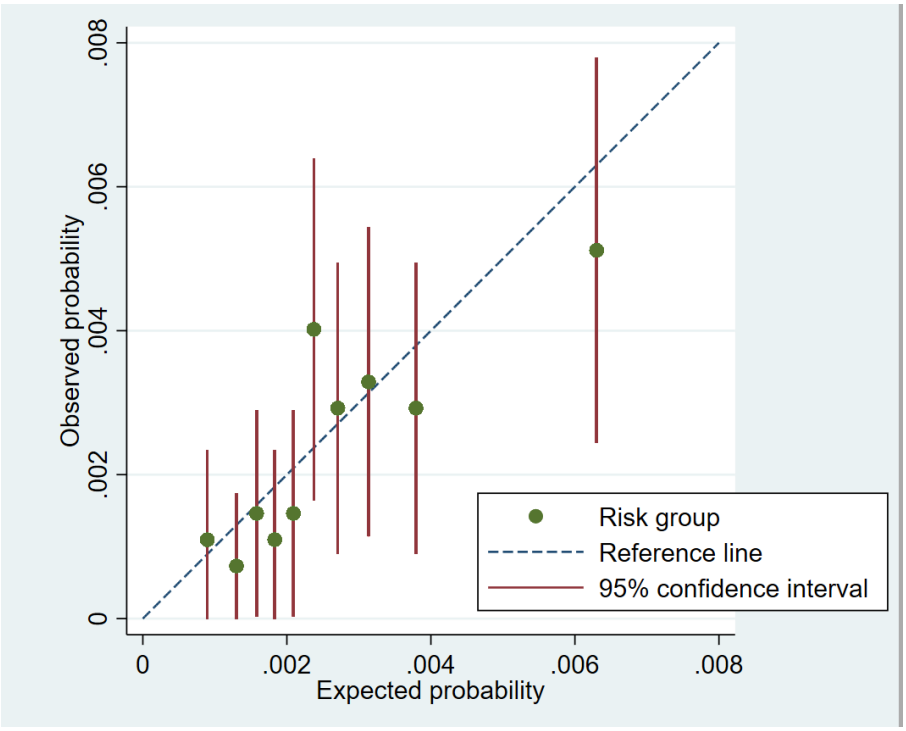


Figure 7.5. Calibration Plot of Risk Model for Head and Neck Cancer, with ten risk groups, for Males in the External Validation cohort.

7.6.2 Model Performance: Females

The model was validated in females only, n=32,876 using the same methodology described in section 7.2. The c-statistic is lower, at 0.61 (95% CI 0.52 – 0.69) and the calibration performance is also worse, with a calibration slope of 0.81, indicating that risk is under-predicted although, the E:O is 0.99, indicating good calibration overall. Figure 7.6. shows the calibration plot for ten risk groups of females in the validation dataset.

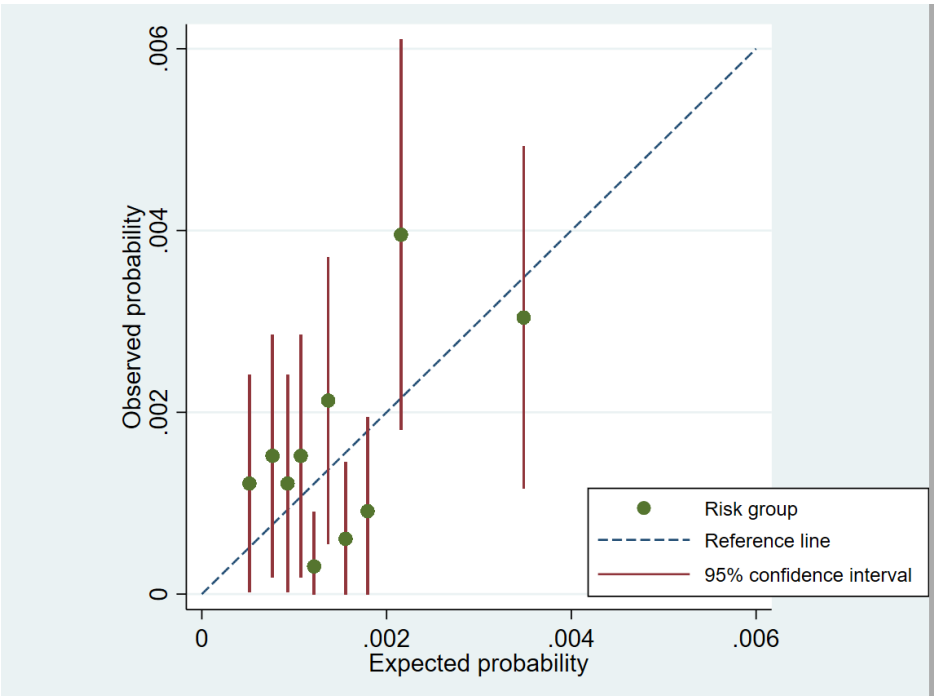


Figure 7.6. Calibration plot of risk model for Head and Neck Cancer, with ten risk groups, for females in the Validation dataset.

7.7 Discussion

The validation dataset contains 78,895 individuals with 157 cases of HNC and is drawn from a sub-group of the UK Biobank cohort. Individuals recruited at sites in the North West of England are included in the validation cohort; the model was developed in the remaining data containing 329,005 observations with 702 cases of HNC (Chapter 6).

The prevalence of HNC in the validation cohort is higher than that in the development cohort, which is consistent with reports of a higher incidence of HNC in the North West of England (8, 149). Other than this higher prevalence of the outcome, the case-mix is similar as demonstrated by comparisons between cases and controls in the development and validation cohorts (section 7.3).

The ability of the model to discriminate between cases and controls is reasonable but there is scope to refine the model, to improve performance. The c-statistic is 0.64 for the overall cohort, 0.65 for males only and 0.61 for females only. The calibration is good with the calibration plots showing points close to the 45-degree line, indicating the expected and observed probability of HNC is similar. The calibration was not significantly improved by updating the model intercept. It may be that the only way to improve overall performance would be to include extra, as yet unidentified, novel variables that are more accurate predictors of disease than those currently included (161). These risk factors may be molecular markers, which could preclude use of the model in general clinical practice. This will be discussed in Chapter 9.

7.7.1 Missing Data

Collins recommends external validation studies should contain a minimum of 100 events, and ideally 200 events, to ensure validity of the performance measures reported (164). This validation dataset contained 157 cases, so the results of this validation study should be an accurate reflection of model performance in this data.

Missing data was significant for three covariates (number of sexual partners, household income and smoking duration).

It has previously been reported that missing data for income is frequently high in responses to surveys, around 10-15% (262). One may assume that it is the personal nature of the questions surrounding income and sexual history that means patients are less likely to answer. The questions were answered as part of a Computer-

Assisted Self-Interview (CASI), as previously recommended when exploring sensitive information (263), in order to minimise the problem of missing data.

Patients from the Liverpool Oral Medicine Patient Research Forum (LOMPRF) were asked to complete a short questionnaire regarding questions they would be willing to answer, for the purposes of determining their risk of HNC. All patients (n=5) were willing to answer all questions posed (covering all variables included in the model), however questions were raised by two patients about the need for details of household income and sexual history. Once an explanation had been given regarding the relevance of these factors to HNC, the patients said they would be willing to provide this information. This informal, small, study does not provide the necessary evidence that patients would be willing to provide the details required for the risk model; a larger clinical utility study would be required. If patients are not willing to answer the necessary questions, these variables could be removed from the model. Alternatively, one could work with a Public and Patient Involvement (PPI) group such as LOMPRF to determine if there are better ways of asking these questions and collecting the data. Alternatively, real-time multiple imputation methods can be built in to computer software to overcome the problem of partial responses (264), assuming a web-based tool is being used.

The reason for missing information regarding smoking duration, which is up to 30%, is due to the missing data for age started smoking (and age stopped smoking for former smokers). Participants in the UK Biobank study were only asked for details of their age when they started (and stopped) smoking if they indicated they currently (or previously) smoke(d) "on all or most days of the week". Participants who reported to smoke 'occasionally' (n=14,455 for current smokers and n=71,472 for former smokers) or 'just once or twice' (n=80,991 for former smokers) were not asked for details of age at starting or stopping smoking. Of these, 66,224 (40%) report to be 'ever' smokers (i.e. have smoked at least 100 cigarettes in their lifetime). Given the importance of smoking duration in other smoking-related cancer risk prediction models (for example the LLP model (188)), it would be important to ensure these data are thoroughly collected in any future studies.

7.7.2 Performance compared to Published Risk Models

Whilst the performance of this model cannot be compared to similar models in the same field, due to the lack of such a model, the performance will be considered in relation to risk models in other smoking-related cancers (lung and oesophageal).

7.7.2.1 Lung Cancer

Risk prediction modelling in lung cancer has been established since the early-2000's when Bach *et al* published their risk model for lung cancer risk prediction amongst smokers (265). The c-statistic was 0.72. Many other lung cancer risk models have been produced, including the Liverpool Lung Project (LLP) model in 2008 with a c-statistic of 0.70 (188), which was updated in 2015 to the LLPi model which has a c-statistic of 0.85 (266). There is great variability in the apparent performance of the many lung models developed, with c-statistics ranging from 0.57 to 0.92 reported in the literature (267-272).

7.7.2.2 Oesophageal Cancer

A search of the literature revealed several risk prediction models for oesophageal cancer; the first were published in 2013 (43, 273) and several have been published between 2016 and 2018 with c-statistic ranging from 0.71 to 0.84 (70, 274-278). One of these models was developed within the UK Biobank data and included 220 incident cases and 355,034 controls (70). The model included variables for age, sex, smoking, body mass index, and history of oesophageal conditions or treatments. The c-statistic is 0.80 but the model has not yet been externally validated.

The models with better performance tended to have a disease-specific risk factor incorporated (275, 277), such as 'known oesophageal disease', as in this latter model (70) or genetic markers in the model of Dong et al (275).

7.8 Conclusion

The model developed provides a firm foundation on which to begin the discussion on risk modelling in HNC. The model demonstrates moderate discriminative ability and good calibration; its performance is consistent with models developed for predicting risk of other smoking-related cancers, but it is noted that several of these models out-perform the present model. This is likely to be because of the presence of disease-specific risk factors and genetic markers in the better models. The HNC model could be refined and updated to improve the performance, by including disease-specific risk factors or molecular biomarkers, if they can be identified. Chapter 9 will discuss the need for further validation studies in truly independent data and for clinical impact studies to determine the model's true potential in improving patient outcomes.

Chapter 8

The Link with Oral Epithelial Dysplasia

The work in this Chapter was published as an Editorial in *Oral Oncology* (Appendix 8).

Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ.

Editorial: The management of oral epithelial dysplasia. The Liverpool algorithm. *Oral Oncol*. 2015 Oct;51(10):883-7. doi: 10.1016/j.oraloncology.2015.06.015. Epub 2015 Jul 18.

8.1 Introduction

The work described in this thesis demonstrates the increasing incidence of HNC in the UK (chapter 2), explores novel gender-specific risk factors for HNC (chapter 3) and presents the first risk prediction model for HNC, developed and validated in a large UK dataset (chapters 4-7).

Risk prediction models have an important role to play in primary prevention efforts in many cancers, particularly HNC. If high-risk individuals can be accurately identified, targeted prevention efforts can be implemented. Patients with a diagnosis of Oral Dysplasia (oral pre-cancer) are known to be at high risk of developing oral cancer compared to the general population (279). Liverpool University Dental Hospital, manages a cohort of around 250 patients with histologically confirmed oral dysplasia; the malignant transformation rate has been reported as 25% over 5 years (280, 281).

There is potential for a risk prediction model to inform treatment and follow-up decisions (282). This chapter discusses the diagnosis of Oral Pre-malignancy (Oral Dysplasia) and reviews the current management strategies.

8.2 Oral Epithelial Dysplasia (OED)

8.2.1 Background and Current Management of Oral Epithelial Dysplasia

Oral epithelial dysplasia (OED) is a potentially malignant disorder of the oral mucosa, which may appear as a white patch, red patch or mixed red and white patch on any area of the oral mucosa (see Figure 8.1). The clinical appearance is described in section 8.2.3.1.

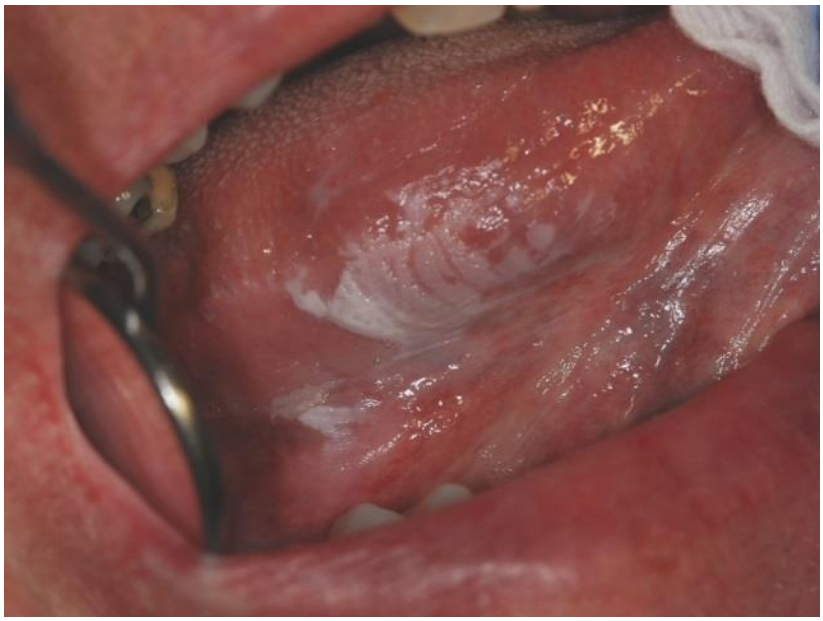


Figure 8.1. Clinical photograph of a homogenous, white dysplastic lesion on the lateral border (side) of the tongue, extending to the ventral (underside) surface.

These premalignant lesions undergo malignant transformation to oral cancer in 5.0-36.4% of cases (6, 279, 282-287).

A biopsy is required to confirm the diagnosis of OED. The lesion is graded histologically as mild, moderate or severe. Severe oral epithelial dysplasia has been found to transform to oral cancer in up to 50% of cases (288).

Ho M *et al* (2012) studied a cohort of 91 patients with histologically-confirmed OED from Liverpool University Dental Hospital. The authors reported a mean time to transformation (MTT) following diagnosis of 40 months, with 12% transforming within 2 years and 22% at five years (279). Ho PS (2009) reported malignant transformation of 24% (8 of 33) cases of OED over 38 months (6).

Prevention of malignant transformation is the primary aim of management. Failing this, detection of malignant transformation at the earliest possible opportunity, to allow minimally invasive treatment, is desirable.

OED may be managed by surgical excision (laser or scalpel), laser ablation or, less commonly, photodynamic therapy, cryotherapy or non-surgical treatments (discussed in 8.2.4.2). Close-monitoring with intervention in the event of a suspicious change in clinical appearance is offered in some cases and is discussed in 8.2.4.

The decision to proceed with treatment (as opposed to close monitoring) would ideally be based on a validated risk prediction model showing that the patient is at high risk of developing oral cancer. In clinical practice, because no such model is available, the decision is based on grade of dysplasia seen on histological examination and clinical risk factors for malignant transformation such as smoking status, site, size and appearance (279, 282). Feasibility of surgery, in terms of patient acceptance, anticipated quality of life following surgery, medical status of the patient and local factors such as requirements for reconstruction, are also major considerations.

Recurrence of lesions following surgery is reported in 4-17% of cases (289-292) (see section 8.2.4.1), therefore close follow-up is required. Length of follow-up and intervals between appointment are variable between clinicians and there is a need for consensus guidelines to inform clinicians how to manage these patients (279).

Management decisions are challenging, and at present the only guidelines in place regarding management of OED form part of the British Association of Head and Neck Oncologists (BAHNO) UK Head and Neck Cancer Multidisciplinary Management Guidelines (231). These guidelines advise on the "targeted use of biopsy and histopathological assessment, along with advice on reduction of environmental carcinogens (tobacco use and alcohol), followed by surgical excision of the lesion where the size of the lesion and subsequent function allows". Long term surveillance is recommended.

In the United Kingdom, primary care practitioners receive guidance from the National Institute for Health and Clinical Excellence (NICE) regarding referral of patients with suspected cancer (293), which have been summarised in the "Mouth Cancer Referral Guidelines for Dentists" by Cancer Research UK (294). These guidelines apply for patients with unexplained or persistent lesions of the oral mucosa; therefore, most patients with OED will be managed in secondary or tertiary care settings, following referral from primary care.

At Liverpool University Dental Hospital, a tertiary Regional OED clinic was created in recognition of the difficulties faced in managing patients with this condition. These clinics are intended to harness the combined expertise of both Oral and Maxillofacial

Surgery and Oral Medicine specialists to ensure patients receive the highest standard of care. This format also minimises delay to definitive treatment, which often includes surgery.

8.2.2 Current Methods for Diagnosis of OED

8.2.2.1 Histopathological Examination

Despite many studies into alternative methods, routine histopathological examination of a biopsy specimen remains the gold standard for diagnosis of OED. The 2005 WHO Classification of Tumours defined the features of OED in the hope of reducing intra- and inter-observer variability amongst histopathologists in reporting of OED (295-297). Presently, dysplasia is categorised as mild, moderate and severe, however studies have shown variability between specialist oral and maxillofacial pathologists in their interpretation of the architectural and cellular changes within the epithelium that lead them to their diagnosis (297, 298).

It has been suggested that a binary system, categorising lesions as 'low risk' and 'high risk', would be helpful in reducing inter-observer variability (298). It was also suggested that this may help in avoiding confusing messages to clinicians, such as reports stating "mild with focally moderate dysplasia", which can be difficult to interpret clinically (298). This binary system has been shown to correlate well with clinical outcomes, with only 15% of lesions categorised as 'low risk' undergoing malignant transformation, compared to 80% of 'high risk' lesions. Sensitivity and specificity of the binary system is reported as 84.9% and 85% respectively. Crucially, this method of reporting avoids the category of 'moderate dysplasia', for which treatment decisions can be particularly challenging.(298)

The use of toluidine blue, bio-optical imaging and cytological examination of brush-biopsy specimens are under intensive research (299-305), but as yet none of these methods are able to reliably replace routine histopathology. Toluidine blue is discussed below in view of the encouraging results indicating its ability to detect lesions more likely to progress to oral cancer.(282).

8.2.2.2 Toluidine Blue

Toluidine blue (Tolnium chloride) or TBlue is a dye with a high affinity for cells rich in nucleic acids (such as (pre)-malignant cells of the oral mucosa). It has been used in studies (301, 306, 307) to aid detection of dysplastic lesions and carcinoma of the oral mucosa. Sensitivity rates for detection of carcinoma are high (76 - 100%), however the figures are lower for detection of dysplasia (45-94%). Specificity is quite low, ranging from 39 to 45%(307). Detection rates improve with increasing severity of dysplasia (307). It has been proposed that Tblue detects 'molecularly-positive' lesions, as it stains nucleic acids, its retention being linked to loss of heterozygosity at various loci on tumour suppressor genes (300). That is, it is thought to stain high risk lesions that are likely to progress, even in the absence of histopathological features of dysplasia (282). Rock *et al* found that 22 out of 83 "TB-positive" lesions progressed to oral cancer against 34 out of 266 TB-negative lesions. This implies that lesions which stain positive for TB are more than twice as likely to progress to oral cancer (OR 2.65; 95%CI 1.45 – 4.83). This is attractive, as it may help to guide management and follow up of lesions but needs to be confirmed by a randomised control trial. The ease of application and immediate, chair-side result favours its use and results are easy to interpret, however further evidence is required regarding its use in detecting dysplasia. Its use is supported for detection of carcinomas and in biopsy site selection, as well as in mapping out a lesion prior to excision (308, 309).

8.2.3 Predictors of Malignant Transformation of OED

One of the main challenges in the management of OED is predicting which lesions will progress to invasive carcinoma. Factors including non-smoking status, lateral tongue site and non-homogenous appearance have been shown to be associated with higher rates of malignant transformation, along with female gender, larger size of lesion(>200mm^2) and non-homogenous appearance, as described previously (6, 279, 282).

8.2.3.1 Clinical Appearance

Dysplastic oral lesions may present as leukoplakia (white patches), erythroplakia (red patches), erythro-leukoplakia (mixed red and white patches), verrucous lesions

(usually thick, white lesion) or ulcers/erosions. Lesions may be homogenous (uniform in appearance) or non-homogenous (mixed appearance); it has been shown that speckled lesions (areas of erythro-leukoplakia) are more likely to be dysplastic and to undergo malignant transformation (286, 310).

Leukoplakia is a clinical diagnosis, defined as 'a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer' (295) and does not confirm the presence of dysplasia. Unfortunately, authors differ in their use of the term 'leukoplakia' which can make the results of studies ambiguous; some incorrectly use it to infer dysplasia. Studies reporting on malignant transformation of oral leukoplakia display a wide range of malignant transformation rates: 0.13-17.5% over a period of 6 months to 30 years (286, 310). There is variability between studies in the diagnosis of the disease, the population studied, the treatment modality and the follow-up arrangements, which is likely to account for the large range in malignant transformation rates. When comparing malignant transformation rates of OED between studies, one should be aware of the method used to diagnose oral dysplasia, so that similar studies can be compared.

Around 90% of red lesions (erythroplakia) show evidence of severe dysplasia or carcinoma on histology(311). Holmstrup *et al* (312) reported a 7-fold increase in malignant transformation in non-homogenous leukoplakia (i.e. mixed red and white lesions), therefore it is usual for these lesions to be treated more aggressively than their homogenous counterparts (312). Treatment almost always includes surgery and this is discussed below (section 8.2.4.1).

An annual malignant transformation rate of leukoplakia of 1.4-7% has been reported, with the highest rate of malignant transformation occurring in the first 2 years (6, 286, 310). Size of lesion has also been found to predict malignant transformation, with lesions over 200mm^2 found to transform more often than smaller lesions (279, 312).

The lateral tongue is the most common site for oral leukoplakia, followed by buccal mucosa. Ho *et al* found that 80% of lesions on the lateral tongue occurred in non-

smoking patients (279). These lesions transform more frequently than lesions elsewhere on the oral mucosa (279, 286, 289).

8.2.3.2. Grade of Dysplasia

Grade of dysplasia has been found to be strongly associated with malignant transformation, with lesions showing a higher grade of dysplasia more likely to transform to invasive carcinoma (285, 287, 289, 313). Lesions showing no evidence of dysplasia may also transform (285), which highlights the need for careful follow up of all patients with areas of change on the oral mucosa. Mild dysplasia shows less than 5% transformation, and moderate and severe dysplasias have transformation rates of 3-15% and 7-50% respectively (288). Amagasa *et al* (314) found that time to malignant transformation was reduced for lesions with higher grades of dysplasia.

Liu *et al* (289) showed an increased risk of malignant transformation for lesions histologically confirmed as dysplastic, with high grade lesions more likely to transform compared to low grade (OR 2.78). This finding is supported by Lee *et al* (313) who found a 2.30-fold increased risk of malignant transformation in lesions showing moderate/severe dysplasia compared to mild dysplasia.

The effect of field cancerization is well-known and it has been demonstrated that 58% of patients with a unilateral oral squamous cell carcinoma displayed evidence of histologically abnormal tissue on the contralateral side, which appeared clinically normal (315). This is consistent with a report by Lee *et al* (313) that for 41% of their patients who developed Oral Squamous Cell Carcinoma (OSCC), the cancer developed at a different site to the original leukoplakia for which they were being treated.

8.2.3.3 History of Oral Cancer

Previous history of oral cancer is a risk factor for malignant transformation of dysplastic lesions: Lee et al (313) showed that 63.6% of patients with previous cancer experienced malignant transformation of a dysplastic lesion compared to 25.4% of those with no previous history. Management of these patients is also likely to be more aggressive and include excision or laser ablation of new lesions as they develop.

8.2.3.4 Smoking Status

Non-smoking patients have been found to be at higher risk of malignant transformation compared to ever-smokers. Ho *et al* (279) reported that non-smokers were 7.1 times more likely to undergo malignant transformation than heavy smokers (>20 pack years). Rock *et al* published results in 2018 of their study of 444 patients with OED in Canada (282) and reported an increased risk of malignant transformation for dysplastic tongue lesions; 44 of the 85 tongue lesions in non-smokers progressed to oral cancer (OR 7.3; 95% CI 1.7-31.1). The wide confidence intervals cast some doubt on the validity of the overall result.

That non-smokers appear to be at higher risk of malignant transformation contrasts with the commonly accepted fact that smoking is a risk factor for oral cancer. The increased risk of malignant transformation in non-smokers may be due to underlying (epi-)genetic differences. Oral dysplasia that has developed in the absence of classic carcinogens suggests an alternative aetiology such as unique genetic mutations or replicative errors, which may confer increased risk (282).

8.2.3.5 Molecular Markers of Malignant Transformation

Various molecular markers of malignant transformation have also been explored (316-318). Loss of Heterozygosity (LOH) and methylation of p16 will be discussed briefly. Rock *et al* have previously developed a prediction model for progression of OED based on LOH-status alone (319). Their cohort contained 44 cases of oral dysplasia which progressed to oral cancer out of 296 total cases. They have shown that LOH in a dysplastic lesion in a non-smoker confers a greatly increased risk of malignant transformation (HR 60.7 (95% CI 7.1 – 514.5)) and conclude that LOH "should be an important consideration in the management of OED". The addition of methyl groups to tumour suppressor genes (methylation) reduces their activity: 27.1% of lesions showing evidence of p16 methylation underwent malignant transformation compared to 8.1% of un-methylated p16 cases (OR 4.6) (320). Molecular markers should be considered in any future risk prediction model for oral epithelial dysplasia.

8.2.4 Management Decisions in OED

Section 8.2.1 discussed the current management of OED and the brief guidelines provided within the UK National Multidisciplinary Guidelines for Head and Neck Cancer (231). The value of clinical photographs for surveillance is recognised, with 72% of Consultant Oral and Maxillofacial Surgeons photographing lesions at the patient review appointments. However, only 26% of these specialists would always biopsy a potentially premalignant oral lesion, although 99% would biopsy a speckled patch (321). Clinicians must decide whether to monitor a lesion for signs of progression, prior to definitive surgical intervention vs proceeding directly to surgical excision. Patients with multiple lesions, larger lesions and lesions present at high risk sites (lateral border of tongue/floor of mouth), are considered to be at high risk of malignant transformation and may therefore be offered intervention, rather than active surveillance (279). These decisions are made based on best-available evidence and potentially would benefit from the use of a risk prediction model, together with clinical acumen. For lesions thought to be at low risk of progression, e.g. a mildly dysplastic lesion in a low-risk site, active monitoring is a realistic management plan (322). Active monitoring may include clinical examination, photographic recording and surveillance biopsies.

Management of moderate dysplasia varies between clinicians and may include a period of monitoring followed by resection if changes are noticed. Other clinicians recommend excision of all areas of leukoplakia, due to reports of malignant transformation of non-dysplastic areas of leukoplakia many years after initial diagnosis (322). Without conclusive evidence to support or reject the use of surgical excision of dysplastic lesions, it remains common practice to excise lesions showing histopathological evidence of severe dysplasia or carcinoma *in-situ*, as they would be considered at high risk of malignant transformation (323).

8.2.4.1 Surgical Management of Oral Epithelial Dysplasia

Some authors recommend excision of all areas of leukoplakia (322), with the aim of preventing malignant transformation. In complete contrast, it has been suggested that surgical excision of hamster tongue mucosa treated with carcinogen promotes

malignant transformation (324), although this has not be shown in humans. In the absence of good quality evidence that surgical intervention helps to prevent malignant transformation, it is necessary to consider the need for multicentre, randomised control trials with long follow-up periods, to accurately determine the outcome of surgical intervention.

Despite the current lack of RCTs into surgical intervention, it remains the most commonly used intervention in treating oral epithelial dysplasia. When treatment is advised, this may include laser ablation, laser resection or conventional scalpel excision(285).

8.2.4.1.1 Scalpel Excision

Scalpel excision remains a common treatment for dysplastic oral mucosal lesions. Studies over the last 10-15 years show a mean recurrence rate of 11.9% and malignant transformation rate of 4.6% for lesions that are excised (see Table 8.1) (325-329).

Laser resection offers the advantages over scalpel excision of: haemorrhage control, improved visibility, shortening of operative time, decreased post-operative pain and swelling, minimal scarring and good post-operative tissue mobility (330). Recurrence rates from studies into laser treatment of OED range from 7.7 to 38.1%. (331-333).

Table 8.1. Studies of Surgical interventions in Oral Epithelial Dysplasia. The results for recurrence rate and malignant transformation rate, following surgery, are shown for each study

Author and Year	Type of Treatment	% Recurrence	% Malignant Transformation amongst treated cases
Jaber 2010 (325)	"Surgery" or "drug therapy" or "other"	16.7	4.7
Holmstrup 2006 (312)	Scalpel Excision	13.5	12.4
Kuribayashi 2012 (327)	Scalpel Excision following application of Lugols Iodine	15.1	1.9
Thomas 2012 (328)	Scalpel excision	4.2	4.1
Pandey 2001 (329)	Surgical Excision	10.1	0
Jerjes 2012 (334)	Laser excision and/or ablation	19.5	10.4
Van der Hem 2005 (335)	Prophylactic laser treatment	9.9	1.1
Ishii 2003 (330)	Laser treatment	29.3	1.2

8.2.4.2 Other Methods of Treatment

8.2.4.2.1 Photodynamic Therapy

Photodynamic therapy (PDT) has also produced positive results in the treatment of oral leukoplakia in short-term studies, although recurrence within 6 months was reported in one case (290). Jerjes reported a complete response with PDT in 81% of treated lesions, malignant transformation in 7.5% of cases and progressive disease in a further 7.5% (336).

8.2.4.2.2 Chemoprevention

Several authors have investigated the use of chemoprevention in the management of oral dysplasia. Vitamin A and beta carotene were explored as part of a double-blind, placebo-controlled, randomised control trial (291) and it was demonstrated that 52% of lesions regressed with a regime of oral vitamin A, whilst 33% of lesions regressed with beta carotene. Only 10% regressed in patients taking placebo. This response was not maintained following cessation of the therapy, with up to 66% of responders relapsing.

Epstein *et al* (292) used topical bleomycin in the management of oral dysplasia and demonstrated a decrease in clinical size and in grade of dysplasia compared to placebo. Whether or not this translated to a decreased rate of malignant transformation is not clear.

13-cis-retinoic acid and oral lycopene have also shown promising short-term results (337, 338), however reports of adverse reactions and early relapse limit their clinical usefulness.

The most recent Cochrane review regarding management of oral leukoplakia concluded that there is insufficient high-quality evidence to support the use of non-surgical interventions for treatment of oral epithelial dysplasia (339). Only 2% of Oral and Maxillofacial (OMFS) consultants reported ever using chemopreventive agents for patients with oral premalignant lesions (321).

A UK-based multicentre, double-blind, placebo-controlled, randomised control trial of Sodium Valproate for high-risk oral epithelial dysplasia, has been funded by the

Medical Research Council (ISRCTN12448611) (340) . This trial is due to open in 2019 and will recruit 110 patients with high risk oral dysplasia. Patients will receive either 4 months of Sodium Valproate or placebo, following which the histological and molecular changes will be assessed. Interest in Sodium Valproate as a chemopreventive agent in HNC was raised following publication of the Kang study (341): over 400,000 US Veterans, of which 27,000 were taking sodium valproate, were recruited. Results showed a significant protective effect against HNC for those veterans taking sodium valproate for greater than 3 years (HR 0.66 (95%CI 0.48-0.92)).

8.2.4.3 Follow-up

Currently there is no international / national consensus for exact duration of follow-up or follow-up intervals for monitoring of dysplastic lesions (342). Some suggest lifelong follow-up at intervals of no more than 6 months (322), due to the potential for malignant transformation many years following the initial diagnosis of dysplasia. However, this has to be considered in terms of clinical resources; a risk assessment model would be extremely useful to select high risk individuals for follow up in secondary care, with low risk individuals discharged back to the Dentist for lifelong follow up. Evidence from Taiwan, of 2229 male patients with Oral Leukoplakia showed a five year and ten year malignant transformation rate of 5% and 9.56% respectively, demonstrating the need for vigilance, even after the first five years (343).

One survey of 189 UK OMFS Consultants (321) reports that 96% would follow up a patient with severe dysplasia but that only 70% would follow up moderate dysplasia. Thus, in the UK we already have an agreement to focus on the highest risk patients, but this could be improved with a validated risk model. This indicates that clinicians regard grade of dysplasia as an important predictor for malignant transformation and plan their follow up of patients on that basis.

8.2.5 Risk Prediction for Oral Epithelial Dysplasia

There are no current risk prediction models in clinical use for Oral Epithelial Dysplasia. Decisions on management are based on clinical and histological predictors. Attempts have been made to develop a risk model of malignant transformation: Lee *et al* (313) used a dataset containing 70 patients with OED with median 7.2 years follow up, with 22 cases of malignant transformation. They considered a total of 12 variables in their Cox regression model, of which three were significant at the 5% level. Age >60, positive cancer history and moderate/severe dysplasia (vs mild dysplasia) were found to be risk factors for transformation. Unfortunately, no discrimination or calibration statistics were presented, and the model has not been internally or externally validated. This model is underpowered to detect variables significantly associated with the outcome, given the small number of cases that progressed to cancer (n=22). Using the rule of ten events per variable, only 2 variables should have been considered, which demonstrates the need for a larger dataset in which to develop this model.

8.3 Discussion

Patients with Oral Epithelial Dysplasia have a significantly increased risk of developing oral cancer compared to the general population (25% vs 0.2%) (281, 341). There is a need for consensus guidelines, based on the available evidence, for the management of OED. Ideally, management decisions should be based on a robust and properly-validated risk prediction model. No such risk model exists at present and a large dataset is required to achieve this aim. OED is diagnosed by clinical examination and histopathology, which remain the gold standard for diagnosis considering current evidence. With further development of the technologies discussed in this chapter, this may change in the future.

The forum in which patients are managed may be significant for patient outcome: Liverpool University Dental Hospital has a specialist oral pre-malignancy clinic, which involves clinicians from the specialities of Oral Medicine, Oral and Maxillofacial Surgery and Oral Pathology. This group has shown that patients managed within this multidisciplinary dysplasia clinic, whose lesions undergo malignant transformation,

present with lower stage tumours (T1) in comparison to patients presenting with oral cancer from general practice or elsewhere (281). This permits more limited surgical intervention (wide local excision), when compared to higher stage tumours, which may be treated with more invasive surgery plus adjuvant radiotherapy with or without concurrent chemotherapy. There is also a survival advantage, with 100% 5 year survival reported, in the group of patients (n=23) who developed oral cancer, from dysplasia, having first been managed within the tertiary care clinic (281).

The fourth World Workshop on Oral Medicine (WWOM IV) review of the management of oral epithelial dysplasia (344) concluded that there is a lack of RCTs assessing the effectiveness of surgical intervention in preventing malignant transformation. However, surgery (laser or scalpel) remains the most appropriate treatment option for many patients. Laser ablation can also be considered for larger areas where surgical removal may not be compatible with function. The use of toluidine blue in identification of high risk lesions, selecting biopsy sites and helping to ensure clear margins is increasing and good results are emerging (282, 299, 301, 307) as discussed in 8.2.2.2.

Alternative modes of management such as chemoprevention have been explored and clinical trials are currently been undertaken, however high quality evidence is required before chemopreventive options can be considered in the management of OED (344). Regular and long-term follow up is required for all patients with OED; at least 5 years follow up by specialists is suggested. The location of this follow up may include tertiary dysplasia clinics, oral medicine clinics, and OMFS departments at district general hospitals. Patients will need to be individually assessed to determine the most appropriate location for follow-up. Due to the potential for late malignant transformation, all patients discharged from specialist care will require lifelong surveillance in General Dental Practice; patients should be re-referred in the event of a change in the clinical appearance of the lesion.

It is questionable whether more aggressive management is justified for patients with particular risk factors (e.g. non-smoking patients). In the absence of RCTs the evidence does point to a high risk of malignant transformation for dysplastic lesions

on the lateral tongue of non-smoking patients (279, 282). An ambition for the future will be to create a risk model for malignant transformation of dysplastic lesions, which will then need to be utilised in a RCT, with the aim of eventually offering a personalised treatment plan for patients with OED. Development of a dysplasia risk model will require a dataset with sufficient numbers of cases of OED, progressing to oral cancer, requiring a multicentre study. Ideally the model will include molecular markers, necessitating a prospective study.

8.4 Conclusion

The evidence presented here has highlighted the need for a risk prediction model to aid decision making, with the aim of improving outcomes for patients with this potentially malignant disease. Chapter 9 provides conclusions and proposals for future work following the development and validation of the risk model for head and neck cancer in chapters 6 and 7.

Chapter 9

Conclusions and Further Work

9.1 Introduction

Head and Neck Cancer is a debilitating disease affecting 12,000 people in the UK every year and over 500,000 individuals globally (345). The incidence is rising, particularly in subgroups of HNC related to HPV infection (31). Risk prediction models offer an exciting opportunity to enhance patient care in HNC. There is potential to reduce morbidity and mortality associated with HNC through targeted screening of high-risk individuals, hopefully leading to earlier detection of disease and the possibility of less invasive treatments (257). There is potential for a risk calculator to be used in clinical trial design to enable recruitment of sub-groups of patients with the highest risk of disease. Using a risk prediction tool in general dental practice could offer an exciting opportunity to educate patients regarding their risk habits, based on a personalised risk score.

This thesis has discussed the increasing incidence of HNC in the UK, explored novel risk factors for HNC in females and described the development and validation of the first risk prediction model for absolute risk of HNC in a UK population, using the UK Biobank dataset. Oral pre-malignancy has also been discussed, as this condition affects a group of individuals with a particularly high risk of developing HNC. This chapter draw conclusions from the work presented in chapters 2 and 3 (sections 9.2 and 9.3) and will discuss the potential for further external validation (section 9.5) and testing of the risk prediction model for HNC (presented in Chapter 6) in feasibility and impact studies (section 9.6). Options for implementation of the risk model in HNC clinical trials and as a tool for the dental team to guide patient counselling on risk

behaviours are discussed in 9.7 and 9.8, including the potential to translate this work into Oral Pre-malignancy.

9.2 Incidence of Head and Neck Cancer

The incidence of HNC increased from 12.2 to 15.9 per 100,000 between 2002 and 2011, in the UK (149). However, at sites strongly associated with HPV-infection (the oropharynx, tonsil and base of tongue), the incidence of cancers doubled. This trend has been reported by others (31, 346) and in July 2018 the UK Government announced that the HPV vaccination programme would be extended to include boys (216) to address the issue of HPV-related oropharyngeal cancers. The HPV vaccination should significantly reduce the incidence of HPV-related HNC, however, this effect will not be demonstrated for several decades due to the lag time between initial infection and presentation with HPV-related oropharyngeal cancer (216).

9.3 Novel Risk Factors

Smoking, alcohol and particularly the combination of the two are well-established risk factors for HNC (22). Increasing age and male gender are also known to increase the risk of disease. However, there is increasing acceptance that lack of fresh fruit and vegetables and lack of exercise are risk factors for HNC. Closely related to this is the problem of social deprivation; areas of significant deprivation in the UK have rates of HNC three-times the national average (8). However, not all patients conform to the stereotype of a HNC patient by being an older male with a long history of smoking and drinking alcohol. Work in this thesis has demonstrated an increasing incidence of oral cancer in older females (Chapter 2). There is also a known cohort of non-smoking female patients with oral pre-malignancy, who suffer a higher rate of malignant transformation compared to their smoking counterparts (279, 282). This raised the question as to whether hormone-related risk factors were specific to females. The systematic review presented in Chapter 3 demonstrated a lack of studies addressing this issue but confirmed an increased risk of oesophageal cancer for women entering menopause before the age of 45 years; similar but less significant results were noted for HNC. Hormone related risk factors (early menopause and hormone replacement therapy) were not found to be significantly different between

cases and controls when assessed in the UK Biobank data (Chapter 5). However, in a pooled analysis of 11 HNC studies, with 1572 cases of HNC, HRT offered a significant protective effect (OR 0.58 (95% CI 0.34-0.77)), which justifies further exploration of hormone-related risk factors in female HNC (347).

9.4 Improving Model Performance

Chapter 6 presented the development and performance of a risk prediction model for HNC using the UK Biobank dataset. The final model included variables for age, gender, smoking duration and smoking status, frequency of alcohol consumption, lifetime number of sexual partners, daily consumption of fruit, moderate exercise and annual household income. This model was developed using a nested case-control study within the UK Biobank, which contains 702 cases of HNC and 423,752 controls. The model performance was moderate in terms of its ability to discriminate between cases and controls (c-statistic 0.67) but displayed good calibration. The model was validated in a sub-group of individuals from the North West of England, known to have a higher incidence of HNC (8). The performance of the model in this external validation was reasonable, with a c-statistic of 0.64.

9.4.1 Limitations of the Model and the Data

The addition of further HNC-specific risk factors could potentially improve the discriminative ability of the current model. Certainly, the addition of molecular biomarkers has been shown to improve performance of other cancer risk prediction models (275, 348). There is increasing evidence of a role for biomarkers, present in saliva, which are associated with increased risk of HNC, specifically lactate dehydrogenase (349), sialic acid (350) and presence of HPV in oral rinses (351). As technology develops and chairside analysis of saliva for relevant biomarkers becomes possible, the model could be updated.

It was surprising to note that those currently 'never' drinking alcohol were at higher risk of HNC than daily drinkers (Table 6.2). This may be explained by looking at the univariable analysis of alcohol status (Table 6.1), which revealed that 'previous drinkers' were at higher risk of HNC than current drinkers and never drinkers. It is possible that those currently not drinking have stopped consuming alcohol for health-

related reasons, for example alcoholic liver disease. It is not possible to capture a picture of lifetime consumption of alcohol from the UK Biobank data and this is a limitation of the study. However, we did note that a statistically significantly greater number of male and female cases report drinking "less alcohol now than 10 years previously", compared to controls (see Table 5.3). This could be due to the diagnosis of HNC, as discussed in 5.3.6.

The Biobank data contains both prevalent and incident cases of HNC (see section 5.2.1). Both were included in the model development and validation data. It would be possible to include only incident cases to remove any bias introduced from including prevalent cases. Patients may have changed their alcohol or smoking habits due to the diagnosis of HNC which could result in artificially lower effect estimates for these variables. Data on lifetime smoking and alcohol can help to overcome this, however, lifetime alcohol consumption was not captured within the Biobank data. Smoking duration was used within the model to reflect lifetime exposure to cigarette smoke.

Household income is lower in the HNC cases than controls and this may be explained due to the fact a greater percentage of cases are retired compared to controls (section 5.2.2); therefore, a different measure of socio-economic deprivation could be considered for future models, such as Index of Multiple Deprivation (IMD). IMD data was not available in the Biobank. Townsend deprivation index was available, but this was not selected for the final model as it cannot be simply calculated from a postcode. Lifetime number of sexual partners could be removed from future iterations of the model as this is only relevant to oropharyngeal cancers (see sections 1.2.4 and 5.2.12) due to the association with Human papillomavirus.

Due to the heterogeneous nature of HNC and differences in risk profiles between patients with the difference sub-types of HNC, it would be sensible to consider individual risk models for the different sub-types. However, many of the subtypes are extremely rare and it would require a dataset much larger than the UK Biobank in order to develop a robust model.

This study calculated absolute risk of head and neck cancer, with an average person-time at risk of 63.5 years (see section 5.2.1). A model for 5-year or 10-year risk could be considered, and regional cancer incidence data could be used to facilitate absolute risk calculation over this period, as described in section 6.8.2.

9.5 External Validation Studies

Many risk prediction models have been developed but few are validated in external data and even fewer have been assessed for their clinical impact on patient outcomes (264, 352). It is recognised that the model developed in this thesis will require further validation in data external to the UK Biobank. INHANCE (International Head and Neck Cancer Epidemiology Consortium) is a collaborative group of HNC researchers that contains over 30 member studies with greater than 30,000 cases of HNC and over 40,000 controls (353). We will seek to collaborate with individuals within this consortium to validate this HNC risk prediction model. Discussions regarding data sharing are underway.

Head and Neck Cancer 5000 is a UK based cohort study of 5000 patients with a diagnosis of HNC (354), who were asked to provide details on lifestyle, including sexual history, at baseline. Researchers are encouraged to apply for access to this data, therefore this could provide a valuable UK-based dataset for validation of the model, assuming comparable controls are available.

9.6 Impact Studies

Many risk prediction models are developed with the ultimate aim of having a positive impact on patients, whether through guiding decision-making (264) or reducing the burden of disease through screening (355). Section 9.6.1 will briefly discuss models which have been successfully developed and implemented to demonstrate this is a realistic possibility for a HNC risk model. Section 9.6.2 and 9.6.3 discuss a framework for moving forward following the model development phase.

9.6.1 Successful Development and Implementation of Risk Prediction Models in Lung Cancer

Lung cancer risk prediction models have been developed, validated and tested in screening trials; the use of such models has been found to be beneficial in selecting high-risk patients for screening (356). Selecting high-risk individuals, using risk algorithms, improves cost-effectiveness of screening for lung cancer and reduces the risk of false positive diagnoses (357, 358). The PLCOm2012 model (Prostate, Lung, Colorectal and Ovarian modified risk prediction model) has been developed (359) and externally validated (360-363) and has now been adopted for use in selection of high-risk individuals for the Cancer Care Ontario pilot study of lung cancer screening (356, 364). Individuals with a greater than 2% risk as defined by the PLCOm2012 model are invited for low-dose CT screening (356).

The Liverpool Lung Project modified risk prediction model (LLPv2) (365) has also been externally validated (360-362) and used in the UKLS trial (United Kingdom Lung Cancer Screening Trial) (366). UKLS is a randomised controlled trial of low dose CT screening for lung cancer against usual care (no screening). 4055 patients were recruited to the pilot study; patients were classified as high-risk (and therefore eligible for inclusion) if they had a >5% chance of lung cancer as determined by the LLPv2 model (52). 46 (2.1%) participants were diagnosed with lung cancer and over 85% were detected at an early stage (Stage I or II). The LLPv2 is also used in the Liverpool Healthy Lung Project, funded by Liverpool Clinical Commissioning Group (367) through which patients with a greater than 5% risk of lung cancer are invited for LDCT scan via their GP.

This demonstrates that with proper development, validation and impact studies, risk prediction models can be a valuable tool in clinical trials and screening programmes.

9.6.2 The Process following Model Development

Developing and validating this HNC risk prediction model is only the first step towards achieving the aim of reducing the incidence of head and neck cancer.

A model that performs well in validation studies could be expected to perform well in clinical practice. However, just because a model exists does not mean that a clinician will choose to use it or that it will improve decision-making, or indeed health-

outcomes (264). These potential pitfalls can be addressed systematically through feasibility studies, clinical utility studies and ultimately impact studies. This involves significant time and monetary costs so one must be confident that the model in question is ready for implementation in clinical practice (264, 352, 368, 369).

The model should be externally validated in at least one external dataset and ideally within the population that the impact study will be performed. This allows coefficients to be recalculated to fit the population in which it is to be used if necessary. One should also be confident that the aim of the model is realistic; for example, if the aim is to reduce the incidence of HNC through targeted screening of high-risk individuals, one should be sure that there is evidence to support this. Appropriate software would also need to be developed to allow the risk model to be combined with existing programmes in clinical practice (369).

The way in which the model is introduced to clinical practice is of paramount importance and should be done in consultation with the clinicians involved. The model can be presented to clinicians in a directive or assistive format (264). In the directive format, the clinician is given a direct recommendation from the model output, e.g. to order a diagnostic test. In the assistive format, the clinician is presented with a probability of the outcome for that individual and can make their own decision about how that should be interpreted. The directive format is preferred by clinicians and has been shown to improve patient outcomes, compared to the assistive format (264). When applying this to screening programmes, patient choice will also be a factor, as any screening programme carries the risk of uncertain diagnoses and inaccurate results. Patients should be fully appraised of the role of the risk model in selecting them for screening, and the potential risks and benefits of the screening offered (370, 371).

9.6.3 Study Design

To test the effect of a risk model on decision making or outcome, a clinical trial is required. This may take the form of a cluster cross-over RCT, in which certain clusters use the model and others do not, following which the group initially using the model becomes the control group and vice versa. Closely related to this is the 'parallel

group' design, where parallel groups either use the model or act as controls. In this case, it is very important to study the decision making of clinicians in each group prior to the trial, so that one can account for any differences at baseline. Alternatively, a before-after study design can be used, where the effects of the risk model on decision making (or other outcome) are compared before and after model implementation (352, 368).

Studying the effect of a model on the health-outcome in question can require very long studies, especially if the outcome is rare, as is the case with HNC. In this situation, it is reasonable to study the effect on decision-making initially. This can be achieved through clinical trials as described above, however, decision analytic studies can be used prior to committing to expensive RCTs (368, 372). These studies model the effects of the risk prediction model on decision making and outcome, based on the model's predictive accuracy and the effectiveness of the intervention proposed, within pre-existing datasets. If there is no effect on decision-making in the decision analysis, it would be hard to justify a trial to study change in outcome. Decision analytic modelling also forms an important part of Health Economic Evaluations (HEE), which considers the cost of an intervention (for example, screening) in relation to improvement in quality of life. HEE for prediction models are rare and there is a need for guidance in this area (368).

Wallace *et al* proposed a framework for the implementation of a clinical prediction model, as follows (369):

1. Exploratory phase: explore how well the model performs in external validation.
2. Preparation for impact analysis: Conduct a feasibility study to investigate clinician-acceptance of the model and consider potential barriers to implementation.
3. Experimental phase: Monitor the use of the model in clinical practice (through a trial).
4. Long-term implementation phase: examine if a model is used long-term and the methods used to achieve this.

The model developed here in this thesis could be externally validated in large, existing datasets to confirm its predictive accuracy. Software could be developed to integrate the model into existing software programmes in general dental and medical practice. A decision-analysis study could be completed to model the effect of the risk model on clinicians' decisions to screen high-risk individuals for oral cancer. Pending the results of such analysis, a cluster RCT could be designed to test the use of the model in general practice.

9.7 Implementation: Counselling on Risk Behaviours

General Dental Practitioners are required to screen all patients for oral cancer (373). However, only 51% of the adult population of the UK visit a Dentist each year (374). Whilst it may not be necessary to use a clinical risk calculator in General Dental Practice to guide screening of high-risk individuals, as all patients will undergo an oral examination, using a personalised risk score could support discussions between dental professionals and patients regarding risk behaviours, such as smoking and alcohol consumption. It could also provide an opportunity for the dental team to discuss health promoting behaviours, such as eating fresh fruit and vegetables and taking regular exercise. There is evidence from an RCT that use of a risk score when providing smoking cessation advice results in longer term success with smoking cessation (375). The effects of this would hopefully be more wide-reaching than the effect on incidence of HNC alone, due to the damaging effects of smoking and alcohol on general health. This provides an exciting opportunity to implement what is already being done in relation to lung cancer (375) into General Dental Practice. Feasibility and impact studies would be required to test whether the HNC risk model is well-received by clinicians and patients, and the impact on smoking cessation rates and other risk behaviours.

9.8 Translation to Oral Pre-Malignancy

Finally, risk prediction modelling could offer huge benefits in guiding the management of oral pre-malignancy and in the design of clinical trials.

The management of oral pre-malignancy is currently based on clinical and histological diagnosis, with no use of risk prediction scores to guide the clinician. Although many molecular markers, which may predict malignant transformation, are under investigation, none are currently being used to guide patient management. Nikitakis *et al* reviewed the current literature on molecular markers associated with progression of oral dysplasia to oral cancer, in 2018 (376). They concluded that "a combined panel embracing all of these parameters (molecular markers) and an algorithm to provide quantitative scoring should be developed" (376).

A large prospective dataset would be required to develop such a model and external data would be required to validate the model. This is likely to require a multicentre, national or international study, of significant duration. The model should then be tested for its clinical usefulness and ultimately for its effect on the incidence of HNC.

9.8.1 Risk modelling in Clinical Trials

In addition to the potential for guiding management decisions and improving outcomes for patients with Oral Epithelial Dysplasia, there is potential for a risk prediction model to be used in clinical trials. Phase II trials are feasibility trials, usually involved in testing novel drugs or other interventions. Rather than comparing outcome between index and control groups, one can predict survival in both groups based on usual standard of care (using the risk model) and compare this to the observed survival (or other outcome measure). This helps to control for the differences between trial patients in each group (372).

Phase III trials are expensive, and it is desirable to recruit patients at highest risk of poor outcome, to increase the expected event rate and hence minimise sample size requirements. Exposing low-risk patients to potentially toxic drugs or the inconvenience of screening and risk of false positive results would not be ethical, which further supports the need for recruitment of high-risk patients. These high-risk patients can be identified through use of a risk model, which helps to provide a definitive cut off point for inclusion criteria (372).

9.9 Concluding Remarks

Risk prediction modelling is currently under-utilised in HNC research. There is great potential to build, validate and implement risk calculators in many areas of HNC clinical practice. The work presented in this thesis should stimulate discussion between clinicians and academics about future work in this area. The model developed could be refined, validated and implemented to inform recruitment of high-risk individuals to clinical trials, guide the dental team when counselling patients on risk behaviours and be explored as a tool for screening of high-risk individuals. There is potential to translate this work to Oral Pre-malignancy, to allow the development of personalised treatment plans, based on the individual's' risk of developing oral cancer, calculated using a properly developed and validated risk prediction model.

References

1. Doobaree IU, Landis SH, Linklater KM, El-Hariry I, Moller H, Tyczynski J. Head and neck cancer in South East England between 1995-1999 and 2000-2004: An estimation of incidence and distribution by site, stage and histological type. Oral Oncol. 2009;45(9):809-14.
2. Library of Recommendations on Coding and Classification Policy and Practice agreed by the UKACR Executive Committee [Internet]. 2002. Available from: http://www.ukacr.org/content/practise.
3. Csikar J, Aravani A, Godson J, Day M, Wilkinson J. Incidence of oral cancer among South Asians and those of other ethnic groups by sex in West Yorkshire and England, 2001-2006. The British journal of oral & maxillofacial surgery. 2013;51(1):25-9.
4. Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006;135(3):451-7.
5. Cancer Research UK. Head and Neck Cancer Incidence Statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers.
6. Ho PS, Chen P-L, Warnakulasuriya S, Sheih T-Y, Chen Y-K, Huang IY. Malignant transformation of oral potentially malignant disorders in males: a retrospective cohort. BMC Cancer. 2009;9.
7. Purkayastha M, McMahon AD, Gibson J, Conway DI. Trends of oral cavity, oropharyngeal and laryngeal cancer incidence in Scotland (1975-2012) - A socioeconomic perspective. Oral Oncol. 2016;61:70-5.
8. Taib BG, Oakley J, Dailey Y, Hodge I, Wright P, du Plessis R, et al. Socioeconomic deprivation and the burden of head and neck cancer-Regional variations of incidence and mortality in Merseyside and Cheshire, North West, England. Clin Otolaryngol. 2018;43(3):846-53.
9. Attar E, Dey S, Hablas A, Seifeldin IA, Ramadan M, Rozek LS, et al. Head and neck cancer in a developing country: a population-based perspective across 8 years. Oral Oncol. 2010;46(8):591-6.
10. Blomberg M, Nielsen A, Munk C, Kjaer SK. Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites. Int J Cancer. 2011;129(3):733-41.
11. Forte T, Niu J, Lockwood GA, Bryant HE. Incidence trends in head and neck cancers and human papillomavirus (HPV)-associated oropharyngeal cancer in Canada, 1992-2009. Cancer Causes Control. 2012;23(8):1343-8.
12. Monteiro LS, Antunes L, Bento MJ, Warnakulasuriya S. Incidence rates and trends of lip, oral and oro-pharyngeal cancers in Portugal. J Oral Pathol Med. 2013;42(4):345-51.
13. Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, et al. National Cancer Database report on cancer of the head and neck: 10-year update. Head Neck. 2009;31(6):748-58.
14. de Souza DL, Perez MM, Curado MP. Predicted incidence of oral cavity, oropharyngeal, laryngeal, and hypopharyngeal cancer in Spain and implications for cancer control. Cancer Epidemiol. 2011;35(6):510-4.
15. Hertrampf K, Wiltfang J, Katalinic A, Timm O, Wenz HJ. Trends in incidence, tumour sites and tumour stages of oral and pharyngeal cancer in Northern Germany. J Cancer Res Clin Oncol. 2012;138(3):431-7.
16. Sharpe KH, McMahon AD, McClements P, Watling C, Brewster DH, Conway DI. Socioeconomic inequalities in incidence of lung and upper aero-digestive tract cancer by age,

tumour subtype and sex: a population-based study in Scotland (2000-2007). Cancer Epidemiol. 2012;36(3):e164-70.
17. Braakhuis BJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol. 2009;45(9):e85-9.
18. Znaor T, Vucemilo L, Kulis T, Znaor A. Incidence and mortality trends of head and neck cancer in Croatia in the period 1988-2008. Acta Otolaryngol. 2013;133(3):305-12.
19. Oxford Cancer Intelligence Unit. Profiles of Head and Neck Cancer in England: Incidence, Mortality and Survival. 2010.
20. Hocking JS, Stein A, Conway EL, Regan D, Grulich A, Law M, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Cancer. 2011;104(5):886-91.
21. Sivasithamparam J, Visk CA, Cohen EE, King AC. Modifiable risk behaviors in patients with head and neck cancer. Cancer. 2013;119(13):2419-26.
22. Dal Maso L, Torelli N, Biancotto E, Di Maso M, Gini A, Franchin G, et al. Combined effect of tobacco smoking and alcohol drinking in the risk of head and neck cancers: a re-analysis of case-control studies using bi-dimensional spline models. Eur J Epidemiol. 2016;31(4):385-93.
23. Radoi L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community Dent Oral Epidemiol. 2013;41(2):97-109, e78-91.
24. Galbiatti AL, Padovani-Junior JA, Maniglia JV, Rodrigues CD, Pavarino EC, Goloni-Bertollo EM. Head and neck cancer: causes, prevention and treatment. Braz J Otorhinolaryngol. 2013;79(2):239-47.
25. Muwonge R, Ramadas K, Sankila R, Thara S, Thomas G, Vinoda J, et al. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. Oral Oncol. 2008;44(5):446-54.
26. Castellsague X, Quintana MJ, Martinez MC, Nieto A, Sanchez MJ, Juan A, et al. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. Int J Cancer. 2004;108(5):741-9.
27. Shah G, Chaturvedi P, Vaishampayan S. Arecanut as an emerging etiology of oral cancers in India. Indian J Med Paediatr Oncol. 2012;33(2):71-9.
28. Donaldson CD, Jack RH, Moller H, Luchtenborg M. Oral cavity, pharyngeal and salivary gland cancer: disparities in ethnicity-specific incidence among the London population. Oral Oncol. 2012;48(9):799-802.
29. Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, et al. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer. 2008;122(10):2330-6.
30. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. PLoS One. 2014;9(1):e86023.
31. Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, et al. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. Cancer Res. 2016;76(22):6598-606.
32. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-75.
33. Eliot MN, Michaud DS, Langevin SM, McClean MD, Kelsey KT. Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma. Cancer Causes Control. 2013;24(7):1315-22.
34. Tezal M, Sullivan MA, Hyland A, Marshall JR, Stoler D, Reid ME, et al. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2009;18(9):2406-12.

35. Conway DI, Brenner DR, McMahon AD, Macpherson LM, Agudo A, Ahrens W, et al. Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. Int J Cancer. 2015;136(5):1125-39.
36. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122(12):2811-9.
37. Cancer IAfRo. A Review of Human Carcinogens: arsenic, metals, fibres, and dusts. Lyon, France: IARC; 2012.
38. Awan KH, Hegde R, Cheever VJ, Carroll W, Khan S, Patil S, et al. Oral and pharyngeal cancer risk associated with occupational carcinogenic substances: Systematic review. Head Neck. 2018;40(12):2724-32.
39. Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL, et al. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. Occup Environ Med. 2000;57(6):376-84.
40. Laforest L, Luce D, Goldberg P, Begin D, Gerin M, Demers PA, et al. Laryngeal and hypopharyngeal cancers and occupational exposure to formaldehyde and various dusts: a case-control study in France. Occup Environ Med. 2000;57(11):767-73.
41. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Int J Epidemiol. 2000;29(6):991-8.
42. Langevin SM, McClean MD, Michaud DS, Eliot M, Nelson HH, Kelsey KT. Occupational dust exposure and head and neck squamous cell carcinoma risk in a population-based case-control study conducted in the greater Boston area. Cancer Med. 2013;2(6):978-86.
43. Thrift AP, Kendall BJ, Pandeya N, Whiteman DC. A model to determine absolute risk for esophageal adenocarcinoma. Clin Gastroenterol Hepatol. 2013;11(2):138-44 e2.
44. SEER stat Database. SEER 13 (1992-2010) [Internet].
45. Olsen MH, Boje CR, Kjaer TK, Steding-Jessen M, Johansen C, Overgaard J, et al. Socioeconomic position and stage at diagnosis of head and neck cancer - a nationwide study from DAHANCA. Acta Oncol. 2015;54(5):759-66.
46. Jerjes W, Upile T, Hamdoon Z, Mosse CA, Akram S, Hopper C. Prospective evaluation of outcome after transoral CO(2) laser resection of T1/T2 oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(2):180-7.
47. Landy R, Pesola F, Castañón A, Sasieni P. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case-control study. British journal of cancer. 2016;115(9):1140-6.
48. Smith RA, Brooks D, Cokkinides V, Saslow D, Brawley OW. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin. 2013;63(2):88-105.
49. Massat NJ, Dibden A, Parmar D, Cuzick J, Sasieni PD, Duffy SW. Impact of Screening on Breast Cancer Mortality: The UK Program 20 Years On. Cancer Epidemiol Biomarkers Prev. 2016;25(3):455-62.
50. Logan RFA, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. 2012;61(10):1439-46.
51. Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut. 2002;50(6):840-4.
52. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016;71(2):161-70.

53. Walter JE, Heuvelmans MA, de Jong PA, Vliegenthart R, van Ooijen PMA, Peters RB, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol. 2016;17(7):907-16.
54. Yousaf-Khan U, van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Lammers JW, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax. 2017;72(1):48-56.
55. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. Lancet Oncol. 2017;18(12):e754-e66.
56. Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev. 2003(4):CD004150.
57. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. Oral Oncol. 2013;49(4):314-21.
58. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879-86.
59. EP OCBBBTW. Screening for Oral Cancer: A Targeted Evidence Update for the U.S Preventive Services Task Force. AHRQ Publication No 13-05186-EF-1.Evidence Synthesis No. 102.
60. UK National Screening Comittee. UK National Screening Committee Recommendation on Bowel Cancer Screening. In: England PH, editor. 2018.
61. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007;335(7611):136.
62. Marcus MW, Chen Y, Raji OY, Duffy SW, Field JK. LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence. Cancer prevention research (Philadelphia, Pa). 2015;8(6):570-5.
63. Meads C, Ahmed I, Riley RD. A systematic review of breast cancer incidence risk prediction models with meta-analysis of their performance. Breast Cancer Res Treat. 2012;132(2):365-77.
64. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-30.
65. Selvachandran SN, Hodder RJ, Ballal MS, Jones P, Cade D. Prediction of colorectal cancer by a patient consultation questionnaire and scoring system: a prospective study. Lancet. 2002;360(9329):278-83.
66. Stegeman I, Bossuyt PM. Cancer risk models and preselection for screening. Cancer Epidemiol. 2012;36(5):461-9.
67. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology. 2010;21(1):128-38.
68. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-87.
69. Thrift AP, Kendall BJ, Pandeya N, Vaughan TL, Whiteman DC, Study of Digestive H. A clinical risk prediction model for Barrett esophagus. Cancer Prev Res (Phila). 2012;5(9):1115-23.
70. Kunzmann AT, Thrift AP, Cardwell CR, Lagergren J, Xie S, Johnston BT, et al. Model for Identifying Individuals at Risk for Esophageal Adenocarcinoma. Clin Gastroenterol Hepatol. 2018;16(8):1229-36 e4.

71. Ferlay J SH, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010 Available from: http://globocaniarcfr, accessed on 03/11/2013
72. Gupta B, Johnson NW, Kumar N. Global Epidemiology of Head and Neck Cancers: A Continuing Challenge. Oncology. 2016;91(1):13-23.
73. Price G RM, Crowther R, Wright R Profiles of Head and Neck Cancers in England: Incidence, Mortality and Survival. 2010.
74. Quinn M BP, Brock A, Kirby L, Jones J. Office for National Statistics: Cancer Trends in England and Wales , 1950-1999, SMPS No. 66 2005. Available from: http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-trends-in-england-and-wales/smps-no--66/index.html.
75. Office for National Statistics. National Population Projections: 2016-based statistical bulletin. 2017.
76. Klop C, van Staa TP, Cooper C, Harvey NC, de Vries F. The epidemiology of mortality after fracture in England: variation by age, sex, time, geographic location, and ethnicity. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(1):161-8.
77. Tazhibi M, Dehkordi ZF, Babazadeh S. Trends in breast cancer incidence rates by age and tumor characteristics of women in the city of Isfahan for the period 2001-2010: An application of joinpoint analysis. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2014;19(4):319-25.
78. Yeole BB. Trends in incidence of head and neck cancers in India. Asian Pacific journal of cancer prevention : APJCP. 2007;8(4):607-12.
79. Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, Macpherson LM. Incidence of oral and oropharyngeal cancer in United Kingdom (1990-1999) -- recent trends and regional variation. Oral oncology. 2006;42(6):586-92.
80. Coupland VH, Chapman P, Linklater KM, Sehgal A, Moller H, Davies EA. Trends in the epidemiology of larynx and lung cancer in south-east England, 1985-2004. British journal of cancer. 2009;100(1):167-9.
81. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-16.
82. Hübbers CU, Akgül B. HPV and cancer of the oral cavity. Virulence. 2015;6(3):244-8.
83. Bunnell A, Pettit N, Reddout N, Sharma K, O'Malley S, Chino M, et al. Analysis of primary risk factors for oral cancer from select US states with increasing rates. Tobacco induced diseases. 2010;8(1):5-.
84. Evans M, Newcombe R, Fiander A, Powell J, Rolles M, Thavaraj S, et al. Human Papillomavirus-associated oropharyngeal cancer: an observational study of diagnosis, prevalence and prognosis in a UK population. BMC cancer. 2013;13:220.
85. Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. Journal of the National Cancer Institute. 2003;95(23):1772-83.
86. Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. Eur J Cancer. 2015;51(9):1144-63.
87. Diz P, Meleti M, Diniz-Freitas M, A.R V, Warnakulasuriya KA, Johnson NW, et al. Oral and pharyngeal cancer in Europe: Incidence, mortality and trends as presented to the Global Oral Cancer Forum. Translational Research in Oral Oncology. 2017;2:1-13.
88. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in

the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541-50.
89. Office for National Statistics. General Lifestyle Survey , 2011.
90. Shohaimi S, Luben R, Wareham N, Day N, Bingham S, Welch A, et al. Residential area deprivation predicts smoking habit independently of individual educational level and occupational social class. A cross sectional study in the Norfolk cohort of the European Investigation into Cancer (EPIC-Norfolk). Journal of epidemiology and community health. 2003;57(4):270-6.
91. Communities and Local Government. English Indices of Deprivation 2010 2011.
92. Health and Social Care Information Centre. Smoking, drinking and drug use among young people in England in 2009: NHS Information Centre for Health and Social Care.; 2010. Available from: http://www.ic.nhs.uk/pubs/sdd09fullreport.
93. Moles DR, Fedele S, Speight PM, Porter SR, dos Santos Silva I. Oral and pharyngeal cancer in South Asians and non-South Asians in relation to socioeconomic deprivation in South East England. Br J Cancer. 2008;98(3):633-5.
94. Office for National Statistics. Cancer Registration Statistics, England, 2013. 2015.
95. Eliassen AM, Hauff SJ, Tang AL, Thomas DH, McHugh JB, Walline HM, et al. Head and neck squamous cell carcinoma in pregnant women. Head & neck. 2013;35(3):335-42.
96. Grimm M, Biegner T, Teriete P, Hoefert S, Krimmel M, Munz A, et al. Estrogen and Progesterone hormone receptor expression in oral cavity cancer. Med Oral Patol Oral Cir Bucal. 2016;21(5):e554-8.
97. Toporcov TN, Znaor A, Zhang ZF, Yu GP, Winn DM, Wei Q, et al. Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium. Int J Epidemiol. 2015;44(1):169-85.
98. Bae JM. Modifiable risk factors of lung cancer in "never-smoker" women. Epidemiology and health. 2015;37:e2015047.
99. Wang BJ, Zhang B, Yan SS, Li ZC, Jiang T, Hua CJ, et al. Hormonal and reproductive factors and risk of esophageal cancer in women: a meta-analysis. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2015.
100. Green J, Roddam A, Pirie K, Kirichek O, Reeves G, Beral V, et al. Reproductive factors and risk of oesophageal and gastric cancer in the Million Women Study cohort. British journal of cancer. 2012;106(1):210-6.
101. Yao Y, Gu X, Zhu J, Yuan D, Song Y. Hormone replacement therapy in females can decrease the risk of lung cancer: a meta-analysis. PLoS One. 2013;8(8):e71236.
102. Lee KD, Wang TY, Lu CH, Huang CE, Chen MC. The bidirectional association between oral cancer and esophageal cancer: A population-based study in Taiwan over a 28-year period. Oncotarget. 2017;8(27):44567-78.
103. Franceschi S, Talamini R, Barra S, Baron AE, Negri E, Bidoli E, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res. 1990;50(20):6502-7.
104. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol. 2014;6(5):112-20.
105. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol. 2015;8(9):11884-94.
106. Freedman ND, Lacey JV, Jr., Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. The Association of Menstrual and Reproductive Factors With Upper Gastrointestinal Tract Cancers in the NIH-AARP Cohort. Cancer. 2010;116(6):1572-81.
107. Langevin SM, Grandis JR, Taioli E. Female hormonal and reproductive factors and head and neck squamous cell carcinoma risk. Cancer Letters. 2011;310(2):216-21.
108. Bosetti C, Negri E, Franceschi S, Conti E, Levi F, Tomei F, et al. Risk factors for oral and pharyngeal cancer in women: a study from Italy and Switzerland. British journal of cancer. 2000;82(1):204-7.

109. Gallus S, Bosetti C, Franceschi S, Levi F, Simonato L, Negri E, et al. Oesophageal cancer in women: tobacco, alcohol, nutritional and hormonal factors. British journal of cancer. 2001;85(3):341-5.
110. Yu H, Liu G, Zhao P, Zhu L. Hormonal and reproductive factors and risk of esophageal cancer in Chinese postmenopausal women: a case-control study. Asian Pacific journal of cancer prevention : APJCP. 2011;12(8):1953-6.
111. Chen ZH, Shao JL, Lin JR, Zhang X, Chen Q. Reproductive factors and oesophageal cancer in Chinese women: a case-control study. BMC gastroenterology. 2011;11:49.
112. Lindblad M, Garcia Rodriguez LA, Chandanos E, Lagergren J. Hormone replacement therapy and risks of oesophageal and gastric adenocarcinomas. British journal of cancer. 2006;94(1):136-41.
113. Gallus S, Bosetti C, Franceschi S, Levi F, Negri E, La Vecchia C. Laryngeal cancer in women: tobacco, alcohol, nutritional, and hormonal factors. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2003;12(6):514-7.
114. Pokoradi AJ, Iversen L, Hannaford PC. Factors associated with age of onset and type of menopause in a cohort of UK women. American journal of obstetrics and gynecology. 2011;205(1):34 e1-13.
115. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015;18(4):483-91.
116. A. Monterrosa-Castro JEB, K. Portela-Buelvas, E. Mezones-Holguín, G. Barón, A. Bencosme, Z. Benítez, L. M. Bravo, A. Calle, P. Chedraui, D. Flores, M. T. Espinoza, G. Gómez, J. A. Hernández-Bueno, F. Laribezcoa, S. Lima, M. Martino, D. Mostajo, E. Ojeda, W. Onatra, H. Sánchez, D. Navarro, K. Tserotas, M. S. Vallejo, S. Witis, M. C. Zuñiga & for the Collaborative Group for Research of the Climacteric in Latin America (REDLINC). Type II diabetes mellitus and menopause: a multinational study. Climacteric. 2013;16(6):663-72.
117. Stott-Miller M, Chen C, Chuang SC, Lee YC, Boccia S, Brenner H, et al. History of diabetes and risk of head and neck cancer: a pooled analysis from the international head and neck cancer epidemiology consortium. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012;21(2):294-304.
118. Zhu Y, Yue D, Yuan B, Zhu L, Lu M. Reproductive factors are associated with oesophageal cancer risk: results from a meta-analysis of observational studies. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation. 2016.
119. Hashim D, Sartori S, La Vecchia C, Serraino D, Maso LD, Negri E, et al. Hormone factors play a favorable role in female head and neck cancer risk. Cancer Med. 2017;6(8):1998-2007.
120. Menon U, Burnell M, Sharma A, Gentry-Maharaj A, Fraser L, Ryan A, et al. Decline in use of hormone therapy among postmenopausal women in the United Kingdom. Menopause. 2007;14(3 Pt 1):462-7.
121. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Jama. 2002;288(3):321-33.
122. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9382):419-27.
123. Studd J. 'PROFOX'--the post HRT nightmare. Climacteric. 2011;14(2):217-9.
124. Ayres J. Premature menopause: management challenges after the Women's Health Initiative. The journal of the British Menopause Society. 2005;11(4):157.
125. NICE. Menopause: diagnosis and management (NG23)2015.

126. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012;21(1):20-38.
127. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer. 2009;45(6):1017-27.
128. Utsumi Y, Nakamura T, Nagasue N, Kubota H, Morikawa S. Role of estrogen receptors in the growth of human esophageal carcinoma. Cancer. 1989;64(1):88-93.
129. Kalayarasan R, Ananthakrishnan N, Kate V, Basu D. Estrogen and progesterone receptors in esophageal carcinoma. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2008;21(4):298-303.
130. Lukits J, Remenar E, Raso E, Ladanyi A, Kasler M, Timar J. Molecular identification, expression and prognostic role of estrogen- and progesterone receptors in head and neck cancer. International journal of oncology. 2007;30(1):155-60.
131. Chandanos E, Lagergren J. The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen. Eur J Cancer. 2009;45(18):3149-55.
132. Egloff AM, Rothstein ME, Seethala R, Siegfried JM, Grandis JR, Stabile LP. Cross-talk between estrogen receptor and epidermal growth factor receptor in head and neck squamous cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(21):6529-40.
133. Chang YL, Hsu YK, Wu TF, Huang CM, Liou LY, Chiu YW, et al. Regulation of estrogen receptor alpha function in oral squamous cell carcinoma cells by FAK signaling. Endocrine-related cancer. 2014;21(4):555-65.
134. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Br J Cancer. 2015;112(2):251-9.
135. Moons KG, Altman DG, Reitsma JB, Collins GS, Transparent Reporting of a Multivariate Prediction Model for Individual Prognosis or Development I. New Guideline for the Reporting of Studies Developing, Validating, or Updating a Multivariable Clinical Prediction Model: The TRIPOD Statement. Adv Anat Pathol. 2015;22(5):303-5.
136. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):683-90.
137. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plastic and reconstructive surgery. 2010;126(6):2234-42.
138. Sedgwick P. Bias in observational study designs: prospective cohort studies. BMJ. 2014;349:g7731.
139. Howe LD, Tilling K, Galobardes B, Lawlor DA. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. Epidemiology. 2013;24(1):1-9.
140. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ, Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. Epidemiology. 2016;27(1):91-7.
141. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60.
142. Elwood M. Critical Appraisal of Epidemiological Studies and Clinical Trials. 3rd Edition ed. Oxford: Oxford University Press; 2007. p. 1–570.
143. Biesheuvel CJ, Vergouwe Y, Oudega R, Hoes AW, Grobbee DE, Moons KG. Advantages of the nested case-control design in diagnostic research. BMC Med Res Methodol. 2008;8:48.
144. Sedgwick P. Case-control studies: measures of risk. BMJ. 2013;346:f1185.
145. Sedgwick P. Nested case-control studies. BMJ. 2010;340:c2582.
146. UK Biobank. UK Biobank Protocol for a large-scale prospective epidemiological resource 2007 26/09/2017. Available from: http://www.ukbiobank.ac.uk/wp-

content/uploads/2011/11/UK-Biobank-Protocol.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6.
147. Team RC. R: A language and environment for statistical computing. In: Computing RFfS, editor. 3.4.1 ed. Vienna, Austria2013.
148. Organisation WH. International Statistical Classification of Diseases and related Health Problems (ICD-10); 10th Revision. 2016 [Available from: http://apps.who.int/classifications/icd10/browse/2016/en.
149. McCarthy CE, Field JK, Rajlawat BP, Field AE, Marcus MW. Trends and regional variation in the incidence of head and neck cancers in England: 2002 to 2011. Int J Oncol. 2015;47(1):204-10.
150. Shiga K, Ogawa T, Katagiri K, Yoshida F, Tateda M, Matsuura K, et al. Differences between oral cancer and cancers of the pharynx and larynx on a molecular level. Oncology letters. 2012;3(1):238-43.
151. Hosmer D, Lemeshow S. Applied Logistic Regression. New York: John Wiley & Sons; 1989.
152. Zhang Z. Multivariable fractional polynomial method for regression model. Ann Transl Med. 2016;4(9):174.
153. Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. AJNR Am J Neuroradiol. 2011;32(3):437-40.
154. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
155. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25(1):127-41.
156. Irwin JR, McClelland GH. Negative Consequences of Dichotomizing Continuous Predictor Variables. Journal of Marketing Research. 2003;40(3):366-71.
157. Collins GS, Ogundimu EO, Cook JA, Manach YL, Altman DG. Quantifying the impact of different approaches for handling continuous predictors on the performance of a prognostic model. Stat Med. 2016;35(23):4124-35.
158. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling (with discussion). Applied Statistics. 1994;43(3):429 - 67.
159. Royston P, Altman DG. Approximating statistical functions by using fractional polynomial regression. Statistician. 1997;46:411 - 22.
160. Townsend P. Deprivation. J Soc Policy. 1987;16(2):125-46.
161. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012;98(9):691-8.
162. Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. BMC Med Res Methodol. 2014;14:40.
163. Riley RD, Ensor J, Snell KI, Debray TP, Altman DG, Moons KG, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ. 2016;353:i3140.
164. Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med. 2016;35(2):214-26.
165. Little RJB, Rubin DB. Statistical Analysis with Missing Data: John Wiley & Sons, Inc.; 2014.
166. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.

167. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 2004.
168. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC medical research methodology. 2009;9:57-.
169. Heinze G, Dunkler D. Five myths about variable selection. Transpl Int. 2017;30(1):6-10.
170. Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practicing statistician. Biom J. 2018;60(3):431-49.
171. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol. 1996;49(8):907-16.
172. Nemes S, Jonasson JM, Genell A, Steineck G. Bias in odds ratios by logistic regression modelling and sample size. BMC Med Res Methodol. 2009;9:56.
173. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
174. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med. 2000;19(8):1059-79.
175. Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. J Clin Epidemiol. 2011;64(9):993-1000.
176. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-8.
177. van Smeden M, de Groot JAH, Moons KGM, Collins GS, Altman DG, Eijkemans MJC, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. BMC medical research methodology. 2016;16(1):163-.
178. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine. 2008;3(1):17.
179. Royston PS, W. Multivariable model-building: A Pragmatic approach to regression analysis Based on Fractional Polynomials for Continuous Variables. New York: Wiley; 2008.
180. Austin PC, Tu JV. Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. J Clin Epidemiol. 2004;57(11):1138-46.
181. Jung Y, Hu J. A K-fold Averaging Cross-validation Procedure. J Nonparametr Stat. 2015;27(2):167-79.
182. Efron B, Tibshirani R. An introduction to the bootstrap. New York: Chapman & Hall; 1993. xvi, 436 p. p.
183. Efron B, Tibshirani R. Improvements on cross-validation: the 632 + bootstrap method. JASA. 1997;92:548-60.
184. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54(8):774-81.
185. Marcus MW, Field JK. Is Bootstrapping Sufficient for Validating a Risk Model for Selection of Participants for a Lung Cancer Screening Program? J Clin Oncol. 2017;35(8):818-9.
186. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. J Public Health (Oxf). 2005;27(1):101-6.
187. Bhatt SP, Kim YI, Harrington KF, Hokanson JE, Lutz SM, Cho MH, et al. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. Thorax. 2018;73(5):414-21.

188. Cassidy A, Myles JP, van Tongeren M, Page RD, Liloglou T, Duffy SW, et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer. 2008;98(2):270-6.
189. Peto J. That the effects of smoking should be measured in pack-years: misconceptions 4. British Journal of Cancer. 2012;107(3):406-7.
190. Troy JD, Grandis JR, Youk AO, Diergaarde B, Romkes M, Weissfeld JL. Childhood passive smoke exposure is associated with adult head and neck cancer. Cancer Epidemiol. 2013;37(4):417-23.
191. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007;99(10):777-89.
192. Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Maso LD, Herrero R, et al. Type of Alcoholic Beverage and Risk of Head and Neck Cancer—A Pooled Analysis Within the INHANCE Consortium. American Journal of Epidemiology. 2009;169(2):132-42.
193. Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 2012;23(1):69-88.
194. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort. Head & neck. 2013;35(7):914-22.
195. Nicolotti N, Chuang SC, Cadoni G, Arzani D, Petrelli L, Bosetti C, et al. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) Consortium. Eur J Epidemiol. 2011;26(8):619-28.
196. World Health Organisation. What is Moderate-intensity and Vigorous-intensity Physical Activity? 2018 [Available from: https://www.who.int/dietphysicalactivity/physical_activity_intensity/en/.
197. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ open. 2016;6(1):e010210.
198. Yen YC, Lin C, Lin SW, Lin YS, Weng SF. Effect of metformin on the incidence of head and neck cancer in diabetics. Head & neck. 2015;37(9):1268-73.
199. Rego DF, Pavan LM, Elias ST, De Luca Canto G, Guerra EN. Effects of metformin on head and neck cancer: a systematic review. Oral Oncol. 2015;51(5):416-22.
200. Okoye CC, Bucher J, Tatsuoka C, Parikh SA, Oliveira GH, Gibson MK, et al. Cardiovascular risk and prevention in patients with head and neck cancer treated with radiotherapy. Head & neck. 2017;39(3):527-32.
201. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, et al. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol. 2010;39(4):1091-102.
202. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014;384(9945):755-65.
203. Public Health England. Supporting the health system to reduce inequalities in screening PHE Screening inequalities strategy. 2018.
204. Bar S, Milanaik R, Adesman A. Long-term neurodevelopmental benefits of breastfeeding. Curr Opin Pediatr. 2016;28(4):559-66.
205. Victora CG, Bahl R, Barros AJ, Franca GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475-90.

206. Martin RM, Gunnell D, Owen CG, Smith GD. Breast-feeding and childhood cancer: A systematic review with metaanalysis. Int J Cancer. 2005;117(6):1020-31.
207. Martin RM, Middleton N, Gunnell D, Owen CG, Smith GD. Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst. 2005;97(19):1446-57.
208. Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. Cancer. 2017;123(12):2219-29.
209. Schmeler KM, Sturgis EM. Expanding the benefits of HPV vaccination to boys and men. Lancet. 2016;387(10030):1798-9.
210. Villa A, Hanna GJ. Human papillomavirus and oropharyngeal cancer. Current problems in cancer. 2018.
211. Schnelle C, Whiteman DC, Porceddu SV, Panizza BJ, Antonsson A. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. Int J Cancer. 2017;140(5):1027-34.
212. Castellsague X, Paavonen J, Jaisamrarn U, Wheeler CM, Skinner SR, Lehtinen M, et al. Risk of first cervical HPV infection and pre-cancerous lesions after onset of sexual activity: analysis of women in the control arm of the randomized, controlled PATRICIA trial. BMC infectious diseases. 2014;14:551.
213. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307(7):693-703.
214. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis. 2009;199(9):1263-9.
215. Department of Health and Social Care. HPV vaccine to be given to boys in England 2018 [Available from: https://www.gov.uk/government/news/hpv-vaccine-to-be-given-to-boys-in-england.
216. Joint Committee for Vaccination and Immunisation. Statement on HPV Vaccination. In: Dept of Health, editor. www.gov.uk/dh2018.
217. Fatusi AO, Blum RW. Predictors of early sexual initiation among a nationally representative sample of Nigerian adolescents. BMC Public Health. 2008;8:136.
218. Santelli JS, Lowry R, Brener ND, Robin L. The association of sexual behaviors with socioeconomic status, family structure, and race/ethnicity among US adolescents. Am J Public Health. 2000;90(10):1582-8.
219. Singh S, Darroch JE, Frost JJ. Socioeconomic disadvantage and adolescent women's sexual and reproductive behavior: the case of five developed countries. Fam Plann Perspect. 2001;33(6):251-8, 89.
220. Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet. 2013;382(9907):1781-94.
221. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farre R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 2012;186(2):190-4.
222. Weinmayr G, Pedersen M, Stafoggia M, Andersen ZJ, Galassi C, Munkenast J, et al. Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE). Environ Int. 2018;120:163-71.
223. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013;14(13):1262-3.
224. Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect. 2014;122(9):906-11.

225. Office of Disease Prevention. Introducing Healthy People 2020 [Available from: https://www.healthypeople.gov/2020/About-Healthy-People.
226. von Ruesten A, Weikert C, Fietze I, Boeing H. Association of sleep duration with chronic diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. PLoS One. 2012;7(1):e30972.
227. Auluck A, Walker BB, Hislop G, Lear SA, Schuurman N, Rosin M. Population-based incidence trends of oropharyngeal and oral cavity cancers by sex among the poorest and underprivileged populations. BMC Cancer. 2014;14:316.
228. Rettig EM, Zaidi M, Faraji F, Eisele DW, El Asmar M, Fung N, et al. Oropharyngeal cancer is no longer a disease of younger patients and the prognostic advantage of Human Papillomavirus is attenuated among older patients: Analysis of the National Cancer Database. Oral Oncol. 2018;83:147-53.
229. Chancellor JA, Ioannides SJ, Elwood JM. Oral and oropharyngeal cancer and the role of sexual behaviour: a systematic review. Community dentistry and oral epidemiology. 2016.
230. Pezzuto F, Buonaguro L, Caponigro F, Ionna F, Starita N, Annunziata C, et al. Update on Head and Neck Cancer: Current Knowledge on Epidemiology, Risk Factors, Molecular Features and Novel Therapies. Oncology. 2015;89(3):125-36.
231. Shaw R, Beasley N. Aetiology and risk factors for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S9-S12.
232. D'Souza G, Wentz A, Kluz N, Zhang Y, Sugar E, Youngfellow RM, et al. Sex Differences in Risk Factors and Natural History of Oral Human Papillomavirus Infection. The Journal of infectious diseases. 2016;213(12):1893-6.
233. Winn DM, Lee YC, Hashibe M, Boffetta P. The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer. Oral diseases. 2015;21(6):685-93.
234. Kunzmann AT, Mallon KP, Hunter RF, Cardwell CR, McMenamin UC, Spence AD, et al. Physical activity, sedentary behaviour and risk of oesophago-gastric cancer: A prospective cohort study within UK Biobank. United European Gastroenterol J. 2018;6(8):1144-54.
235. Biobank U. UK BiobankL Protocol for a large-scale prospective epidemiological resource2007 26/09/2017. Available from: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6.
236. Morris TP, White IR, Carpenter JR, Stanworth SJ, Royston P. Combining fractional polynomial model building with multiple imputation. Stat Med. 2015;34(25):3298-317.
237. Austin PC, Park-Wyllie LY, Juurlink DN. Using fractional polynomials to model the effect of cumulative duration of exposure on outcomes: applications to cohort and nested case-control designs. Pharmacoepidemiol Drug Saf. 2014;23(8):819-29.
238. McKenna H, Treanor C, O'Reilly D, Donnelly M. Evaluation of the psychometric properties of self-reported measures of alcohol consumption: a COSMIN systematic review. Subst Abuse Treat Prev Policy. 2018;13(1):6.
239. Stockwell T, Zhao J, Greenfield T, Li J, Livingston M, Meng Y. Estimating under- and over-reporting of drinking in national surveys of alcohol consumption: identification of consistent biases across four English-speaking countries. Addiction. 2016;111(7):1203-13.
240. Heus P, Damen J, Pajouheshnia R, Scholten R, Reitsma JB, Collins GS, et al. Poor reporting of multivariable prediction model studies: towards a targeted implementation strategy of the TRIPOD statement. BMC Med. 2018;16(1):120.
241. Pencina MJ, D'Agostino RB, Sr. Evaluating Discrimination of Risk Prediction Models: The C Statistic. JAMA. 2015;314(10):1063-4.
242. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315-6.

243. Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW. A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol. 2016;74:167-76.
244. Smith GC, Seaman SR, Wood AM, Royston P, White IR. Correcting for optimistic prediction in small data sets. Am J Epidemiol. 2014;180(3):318-24.
245. van der Ploeg T, Austin PC, Steyerberg EW. Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. BMC Medical Research Methodology. 2014;14:137.
246. Collins GS. When data are scarce, model validation should be efficient: Letter Re: Dolera-Moreno C, Palazon-Bru A, Colomina-Climent F, Gil-Guillen VF. Construction and internal validation of a new mortality risk score for patients admitted to the intensive care unit. Int J Clin Pract 2016; 10.1111/ijcp.12851. Int J Clin Pract. 2016;70(11):960.
247. James G, Witten D, Hastie T, Tibshirani R. An Introduction to Statistical Learning: Springer; 2013.
248. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Stat Med. 2007;26(30):5512-28.
249. Qian SS, Stow CA, Cha Y. Implications of Stein's Paradox for Environmental Standard Compliance Assessment. Environ Sci Technol. 2015;49(10):5913-20.
250. Tu JV. Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes. J Clin Epidemiol. 1996;49(11):1225-31.
251. Beynon RA, Lang S, Schimansky S, Penfold CM, Waylen A, Thomas SJ, et al. Tobacco smoking and alcohol drinking at diagnosis of head and neck cancer and all-cause mortality: Results from head and neck 5000, a prospective observational cohort of people with head and neck cancer. Int J Cancer. 2018.
252. Chaparro MP, Benzeval M, Richardson E, Mitchell R. Neighborhood deprivation and biomarkers of health in Britain: the mediating role of the physical environment. BMC Public Health. 2018;18(1):801.
253. Britton A, Ben-Shlomo Y, Benzeval M, Kuh D, Bell SJBM. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. 2015;13(1):47.
254. Bressan V, Stevanin S, Bianchi M, Aleo G, Bagnasco A, Sasso L. The effects of swallowing disorders, dysgeusia, oral mucositis and xerostomia on nutritional status, oral intake and weight loss in head and neck cancer patients: A systematic review. Cancer Treat Rev. 2016;45:105-19.
255. Tikka T, Paleri V, MacKenzie K. External validation of a cancer risk prediction model for suspected head and neck cancer referrals. Clin Otolaryngol. 2018;43(2):714-7.
256. Tikka T, Pracy P, Paleri V. Refining the head and neck cancer referral guidelines: a two centre analysis of 4715 referrals. Br J Oral Maxillofac Surg. 2016;54(2):141-50.
257. Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, et al. The cost-effectiveness of screening for oral cancer in primary care. Health Technol Assess. 2006;10(14):1-144, iii-iv.
258. Marcus MW, Raji OY, Duffy SW, Young RP, Hopkins RJ, Field JK. Incorporating epistasis interaction of genetic susceptibility single nucleotide polymorphisms in a lung cancer risk prediction model. Int J Oncol. 2016;49(1):361-70.
259. Vach M, Blettner M. Missing Data in Epidemiological Studies: Encyclopedia of Biostatistics. Armitage P, Colton T, editors: Wiley and Sons, New York; 1998.
260. Janssen KJ, Vergouwe Y, Kalkman CJ, Grobbee DE, Moons KG. A simple method to adjust clinical prediction models to local circumstances. Can J Anaesth. 2009;56(3):194-201.
261. Rauh SP, Heymans MW, Mehr DR, Kruse RL, Lane P, Kowall NW, et al. Predicting mortality in patients treated differently: updating and external validation of a prediction

model for nursing home residents with dementia and lower respiratory infections. BMJ Open. 2016;6(8):e011380.
262. Davern M, Rodin H, Beebe TJ, Call KT. The effect of income question design in health surveys on family income, poverty and eligibility estimates. Health Serv Res. 2005;40(5 Pt 1):1534-52.
263. Harling G, Gumede D, Mutevedzi T, McGrath N, Seeley J, Pillay D, et al. The impact of self-interviews on response patterns for sensitive topics: a randomized trial of electronic delivery methods for a sexual behaviour questionnaire in rural South Africa. BMC Med Res Methodol. 2017;17(1):125.
264. Kappen TH, van Klei WA, van Wolfswinkel L, Kalkman CJ, Vergouwe Y, Moons KG. Evaluating the impact of prediction models: lessons learned, challenges, and recommendations. Diagnostic and Prognostic Research. 2018;2:11.
265. Bach PB, Kattan MW, Thornguist MD, Kris MG, Tate RC, Barnett MJ, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst. 2003;96(6):8.
266. Marcus MW, Chen Y, Raji OY, Duffy SW, Field JK. LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence. Cancer Prev Res (Phila). 2015;8(6):570-5.
267. Spitz MR, Hong WK, Amos CI, Wu X, Schabath MB, Dong Q, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst. 2007;99(9):715-26.
268. Spitz MR, Etzel CJ, Dong Q, Amos CI, Wei Q, Wu X, et al. An expanded risk prediction model for lung cancer. Cancer Prev Res (Phila). 2008;1(4):250-4.
269. Weissfeld JL, Lin Y, Lin HM, Kurland BF, Wilson DO, Fuhrman CR, et al. Lung Cancer Risk Prediction Using Common SNPs Located in GWAS-Identified Susceptibility Regions. J Thorac Oncol. 2015;10(11):1538-45.
270. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst. 2011;103(13):1058-68.
271. El-Zein RA, Lopez MS, D'Amelio AM, Jr., Liu M, Munden RF, Christiani D, et al. The cytokinesis-blocked micronucleus assay as a strong predictor of lung cancer: extension of a lung cancer risk prediction model. Cancer Epidemiol Biomarkers Prev. 2014;23(11):2462-70.
272. Markaki M, Tsamardinos I, Langhammer A, Lagani V, Hveem K, Roe OD. A Validated Clinical Risk Prediction Model for Lung Cancer in Smokers of All Ages and Exposure Types: A HUNT Study. EBioMedicine. 2018;31:36-46.
273. Chang J, Huang Y, Wei L, Ma B, Miao X, Li Y, et al. Risk prediction of esophageal squamous-cell carcinoma with common genetic variants and lifestyle factors in Chinese population. Carcinogenesis. 2013;34(8):1782-6.
274. Xie SH, Ness-Jensen E, Medefelt N, Lagergren J. Assessing the feasibility of targeted screening for esophageal adenocarcinoma based on individual risk assessment in a population-based cohort study in Norway (The HUNT Study). The American journal of gastroenterology. 2018;113(6):829-35.
275. Dong J, Buas MF, Gharahkhani P, Kendall BJ, Onstad L, Zhao S, et al. Determining Risk of Barrett's Esophagus and Esophageal Adenocarcinoma Based on Epidemiologic Factors and Genetic Variants. Gastroenterology. 2018;154(5):1273-81.e3.
276. Liu M, Liu Z, Cai H, Guo C, Li X, Zhang C, et al. A Model To Identify Individuals at High Risk for Esophageal Squamous Cell Carcinoma and Precancerous Lesions in Regions of High Prevalence in China. Clin Gastroenterol Hepatol. 2017;15(10):1538-46 e7.
277. Koyanagi YN, Ito H, Oze I, Hosono S, Tanaka H, Abe T, et al. Development of a prediction model and estimation of cumulative risk for upper aerodigestive tract cancer on the basis of the aldehyde dehydrogenase 2 genotype and alcohol consumption in a Japanese population. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2017;26(1):38-47.

278. Xie SH, Lagergren J. A model for predicting individuals' absolute risk of esophageal adenocarcinoma: Moving toward tailored screening and prevention. Int J Cancer. 2016;138(12):2813-9.
279. Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, et al. The clinical determinants of malignant transformation in oral epithelial dysplasia. Oral Oncol. 2012;48(10):969-76.
280. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, et al. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. Br J Oral Maxillofac Surg. 2013;51(7):594-9.
281. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, et al. Outcomes of oral squamous cell carcinoma arising from oral dysplasia: the rationale for monitoring of oral premalignant lesions in a multidisciplinary clinic. BJOMS.
282. Rock LD, Rosin MP, Zhang L, Chan B, Shariati B, Laronde DM. Characterization of epithelial oral dysplasia in non-smokers: First steps towards precision medicine. Oral Oncol. 2018;78:119-25.
283. Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, et al. Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. JOral PatholMed. 2009;38(6):540-4.
284. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. Oral SurgOral MedOral PatholOral RadiolEndod. 1995;79(3):321-9.
285. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck. 2009;31(12).
286. Silverman S, Jr., Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer. 1984;53(3):563-8.
287. Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, et al. Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. JOral PatholMed. 2011.
288. Speight PM. Update on Oral Epithelial Dysplasia and Progress to Cancer. Head and Neck Pathol. 2007;1:61-6.
289. Liu W, Bao ZX, Shi LJ, Tang GY, Zhou ZT. Malignant transformation of oral epithelial dysplasia: clinicopathological risk factors and outcome analysis in a retrospective cohort of 138 cases. Histopathology. 2011;59(4):733-40.
290. Sieron A, Adamek M, Kawczyk-Krupka A, Mazur S, Ilewicz L. Photodynamic therapy (PDT) using topically applied d-aminolevulinic acid (ALA) for the treatment of oral leukoplakia. Oral Pathol and Med. 2003;32(6).
291. Sankaranarayanan R. Systemic and topical treatment of oral leukoplakia. BrJ Oral MaxillofacSurg. 1989;27(3):260-1.
292. Epstein JB, Wong FL, Millner A, Le ND. Topical bleomycin treatment of oral leukoplakia: a randomized double-blind clinical trial. Head Neck. 1994;16(6):539-44.
293. NICE. Referral Guidelines for suspected cancer. 2005.
294. Cancer Research UK. Oral Cancer Recognition Toolkit. 2015.
295. Barnes L, Eveson J, Reichart P, Sidransky D, editors. World Health Organisation classification of tumours. Pathology and genetics of tumours of the head and neck. Lyon: IARC Press; 2005.
296. Abbey LM, Kaugars GE, Gunsolley JC, Burns JC, Page DG, Svirsky JA, et al. Intraexaminer and interexaminer reliability in the diagnosis of oral epithelial dyplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;80.
297. Kujan O, Khattab A, Oliver RJ, Roberts SA, Thakker N, Sloan P. Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: An attempt to understand the sources of variation. Oral Oncol. 2007;43:224-31.

298. Kujan O, Oliver R, Khattab A, Roberts SA, Thakker N, Sloan P. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncology. 2005;42:987-93.
299. Awan K, Yang Y, Morgan P, Warnakulasuriya S. Utility of toluidine blue as a diagnostic adjunct iin the detection of potentially malignant disorders of the oral cavity - a clinical and histological assessment. Oral diseases. 2012;18(8):728-33.
300. Guneri P, Epstein JB, Kaya A, Veral A, Kazandi A, Boyacioglu H. The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions. Int J Oral Maxillofac Surg. 2011;40:155-61.
301. Epstein JB, Silverman Jr S, Epstein JD, Lonky SA, Bride MA. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. Oral Oncol. 2008;44:538-44.
302. Tan N, Mellor T, Brennan PA, Puxeddu R. Use of narrow band imagine in the management of oral erythroplakia. Br J Oral Maxillofac Surg. 2011;49:488-90.
303. Fedele S. Diagnostic aids in the screening of oral cancer. Head Neck Oncol. 2009;1:5.
304. Pierce MC, Schwarz RA, Bhattar VS, et al. Accuracy of In Vivo Multimodal Optical Imaging for Detection of Oral Neoplasia. Cancer Prev Res. 2012;5:801-9.
305. Poate TWJ, Buchanan JAG, Hodgson TA, Speight PM, Barrett AW, Moles DR, et al. An audit of the efficacy of the oral brush biopsy technique in a specialist Oral Medicine unit. Oral Oncology. 2004;40:829-34.
306. Rahman F, Tippu SR, Khandelwal S, Girish KL, Manjunath BC, Bhargava A. A study to evaluate the efficacy of toluidine blue and cytology in detecting oral cancer and dysplastic lesions. QuintessenceInt. 2012;43(1):51-9.
307. Chainani-Wu N, Madden E, Cox D, Sroussi H, Epstein J, Silverman S, Jr. Toluidine blue aids in detection of dysplasia and carcinoma in suspicious oral lesions. Oral Dis. 2015;21(7):879-85.
308. Pallagatti S, Sheikh S, Aggarwal A, Gupta D, Singh R, Handa R, et al. Toluidine blue staining as an adjunctive tool for early diagnosis of dysplastic changes in the oral mucosa. J Clin Exp Dent. 2013;5(4):e187-91.
309. Singh D, Shukla RK. Utility of toluidine blue test in accessing and detecting intra-oral malignancies. Indian J Otolaryngol Head Neck Surg. 2015;67(Suppl 1):47-50.
310. Schepman KP, van der Meij EH, Smeele LE, van dWI. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. Oral Oncol. 1998;34(4):270-5.
311. Pereira JS, Carvalho MV, Henriques AC, de Queiroz Camara TH, Miguel MC, Freitas RA. Epidemiology and correlation of the clinicopathological features in oral epithelial dysplasia: analysis of 173 cases. AnnDiagnPathol. 2011;15(2):98-102.
312. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. Oral Oncol. 2006;42(5):461-74.
313. Lee JJ, Hong WK, Hittelman WN, Mao L, Lotan R, Shin DM, et al. Predicting cancer development in oral leukoplakia: ten years of translational research. ClinCancer Res. 2000;6(5):1702-10.
314. Amagasa T, Yamashiro M, Uzawa N. Oral premalignant lesions: from a clinical perspective. IntJClinOncol. 2011;16(1):5-14.
315. Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis? IntJ Oral MaxillofacSurg. 2002;31(3):262-6.
316. Torres-Rendon A, Stewart R, Craig GT, Wells M, Speight PM. DNA ploidy analysis by image cytometry helps to identify oral epithelil dysplasias with a high risk of malignant progression. Oral Oncol. 2009;45:468-73.
317. Bradley G, Odell EW, Raphael S, Ho J, Le LW, Benchimol S, et al. Abnormal DNA content in oral epithelial dysplasia is associated with increased risk of progression to carcinoma. Br J Cancer. 2010;103:1432-42.

318. Humayun S, Ram Prasad V. Expression of p53 protein and ki-67 antigen in oral premalignant lesions and oral squamous cell carcinomas: An immunohistochemical study. Nat J Maxillofacial Surg. 2011;2(1).
319. Zhang L, Poh CF, Williams M, Laronde DM, Berean K, Gardner PJ, et al. Loss of heterozygosity (LOH) profiles--validated risk predictors for progression to oral cancer. Cancer prevention research. 2012;5(9):1081-9.
320. Liu H, Liu XW, Dong G, Zhou J, Liu Y, Gao Y, et al. P16 Methylation as an Early Predictor for Cancer Development From Oral Epithelial Dysplasia: A Double-blind Multicentre Prospective Study. EBioMedicine. 2015;2(5):432-7.
321. Kanatas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN. The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association of Oral and Maxillofacial Surgeons. BrJ Oral MaxillofacSurg. 2011;49(2):99-105.
322. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. Oral Oncology. 2010;46.
323. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, et al. The management of oral epithelial dysplasia: The Liverpool algorithm. Oral Oncol. 2015;51(10):883-7.
324. Maeda H, Kameyama Y. Effect of excisional wounding on DMBA-induced hamster tongue carcinogenesis. J Oral Pathol. 1986;15(1):21-7.
325. Jaber MA. Oral epithelial dysplasia in non-users of tobacco and alcohol: an analysis of clinicopathologic characteristics and treatment outcome. JOral Sci. 2010;52(1):13-21.
326. Holmstrup P. Can we prevent malignancy by treating premalignant lesions? Oral Oncol. 2009;45(7):549-50.
327. Kuribayashi Y, Tsushima F, Sato M, Morita K, Omura K. Recurrence patterns of oral leukoplakia after curative surgical resection: important factors that predict the risk of recurrence and malignancy. J Oral Pathol Med. 2012;41:682-8.
328. Thomas G, Kunnambath R, Somanathan T, Mathew B, Pandey M, Rangaswamy S. Long-term Outcome of Surgical Excision of Leukoplakia in a Screening Intervention Trial, Kerala, India. p. 126-9.
329. Pandey M, Thomas G, Somanathan T, Sankaranarayanan R, Abraham EK, Jacob BJ, et al. Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. Oral Oncol. 2001;37(1):103-9.
330. Ishii J, Fujita K, Komori T. Laser surgery as a treatment for oral leukoplakia. Oral Oncol. 2003;39(8):759-69.
331. Roodenburg JL, Panders AK, Vermey A. Carbon dioxide laser surgery of oral leukoplakia. Oral SurgOral MedOral Pathol. 1991;71(6):670-4.
332. Chiesa F, Tradati N, Sala L, Costa L, Podrecca S, Boracchi P, et al. Follow-up of oral leukoplakia after carbon dioxide laser surgery. ArchOtolaryngolHead Neck Surg. 1990;116(2):177-80.
333. Schoelch ML, Sekandari N, Regezi JA, Silverman S, Jr. Laser management of oral leukoplakias: a follow-up study of 70 patients. Laryngoscope. 1999;109(6):949-53.
334. Jerjes W, Upile T, Hamdoon Z, Al-Khawalde M, Morcos M, Mosse CA, et al. CO2 laser of oral dysplasia: clinicopathological features of recurrence and malignant transformation. Lasers MedSci. 2012;27(1):169-79.
335. van der Hem PS, Nauta JM, van der Wal JE, Roodenburg JL. The results of CO2 laser surgery in patients with oral leukoplakia: a 25 year follow up. Oral Oncol. 2005;41(1):31-7.
336. Jerjes W, Upile T, Hamdoon Z, Alexander Mosse C, Morcos M, Hopper C. Photodynamic therapy outcome for T1/T2 N0 oral squamous cell carcinoma. Lasers in surgery and medicine. 2011;43(6):463-9.
337. Hong WK, Endicott J, Itri LM, Doos W, Batsakis JG, Bell R, et al. 13-cis-retinoic acid in the treatment of oral leukoplakia. NEnglJ Med. 1986;315(24):1501-5.

338. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. Oral Oncol. 2004;40(6):591-6.
339. Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia. CochraneDatabaseSystRev. 2006(4):CD001829.
340. SAVER Trial Website [Available from: https://www.lctu.org.uk/LCTU_NET/Frontend/Core/Features/TrialInfo.aspx?Data=W1tkSEpwWVd4bmNtOTFjQT09XV1bTWc9PV1bW2RISnBZV3hwWkE9PV1dW016QTRdW1tiRzlqWVd4bF1dW01RPT1d.]
341. Kang H, Gillespie TW, Goodman M, Brodie SA, Brandes M, Ribeiro M, et al. Long-term use of valproic acid in US veterans is associated with a reduced risk of smoking-related cases of head and neck cancer. Cancer. 2014;120(9):1394-400.
342. Kantas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN. The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association of Oral and Maxillofacial Surgeons. BJOMS. 2011;49:99-105.
343. Lian Ie B, Tseng YT, Su CC, Tsai KY. Progression of precancerous lesions to oral cancer: results based on the Taiwan National Health Insurance Database. Oral Oncol. 2013;49(5):427-30.
344. Brennan M, Migliorati CA, Lockhart PB, Wray D, Al-Hashimi I, Axell T. Management of oral epithelial dysplasia: a review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103 (suppl 1):s19.e1-s.e2.
345. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer Journal international du cancer. 2015;136(5):E359-86.
346. Shaw R, Robinson M. The increasing clinical relevance of human papillomavirus type 16 (HPV-16) infection in oropharyngeal cancer. Br J Oral Maxillofac Surg. 2011;49(6):423-9.
347. Hashim D, Sartori S, La Vecchia C, Serraino D, Dal Maso L, Negri E, et al. Hormone factors play a favourable role in female head and neck cancer risk. Cancer Medicine. 2017;6:1998-2007.
348. Raji OY, Agbaje OF, Duffy SW, Cassidy A, Field JK. Incorporation of a genetic factor into an epidemiologic model for prediction of individual risk of lung cancer: the Liverpool Lung Project. Cancer Prev Res (Phila). 2010;3(5):664-9.
349. Kallalli BN, Rawson K, Muzammil, Singh A, Awati MA, Shivhare P. Lactate dehydrogenase as a biomarker in oral cancer and oral submucous fibrosis. J Oral Pathol Med. 2016;45(9):687-90.
350. Achalli S, Madi M, Babu SG, Shetty SR, Kumari S, Bhat S. Sialic acid as a biomarker of oral potentially malignant disorders and oral cancer. Indian J Dent Res. 2017;28(4):395-9.
351. Yoshida H, Murono S, Ueno T, Nakanishi Y, Tsuji A, Hatano M, et al. Usefulness of human papillomavirus detection in oral rinse as a biomarker of oropharyngeal cancer. Acta Otolaryngol. 2017;137(7):773-7.
352. Wallace E, Uijen MJ, Clyne B, Zarabzadeh A, Keogh C, Galvin R, et al. Impact analysis studies of clinical prediction rules relevant to primary care: a systematic review. BMJ Open. 2016;6(3):e009957.
353. University of Utah. International Head and Neck Cancer Epidemiology Consortiuum (INHANCE) [Available from: https://www.inhance.utah.edu/.
354. University Hospital Bristol NHS Foundation Trust. Head and Neck Cancer 5000 [Available from: http://www.headandneck5000.org.uk/home/.
355. Brain K, Carter B, Lifford KJ, Burke O, Devaraj A, Baldwin DR, et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. Thorax. 2017;72(10):912-8.
356. Tammemägi MC. Selecting lung cancer screenees using risk prediction models-where do we go from here. Translational lung cancer research. 2018;7(3):243-53.

357. Ten Haaf K, Tammemagi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. PLoS medicine. 2017;14(2):e1002225.
358. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. Lancet Oncol. 2017;18(11):1523-31.
359. Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. The New England journal of medicine. 2013;368(8):728-36.
360. Katki HA, Kovalchik SA, Petito LC, Cheung LC, Jacobs E, Jemal A, et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Annals of internal medicine. 2018;169(1):10-9.
361. Li K, Husing A, Sookthai D, Bergmann M, Boeing H, Becker N, et al. Selecting High-Risk Individuals for Lung Cancer Screening: A Prospective Evaluation of Existing Risk Models and Eligibility Criteria in the German EPIC Cohort. Cancer Prev Res (Phila). 2015;8(9):777-85.
362. Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS medicine. 2017;14(4):e1002277.
363. Weber M, Yap S, Goldsbury D, Manners D, Tammemagi M, Marshall H, et al. Identifying high risk individuals for targeted lung cancer screening: Independent validation of the PLCOm2012 risk prediction tool. International journal of cancer Journal international du cancer. 2017;141(2):242-53.
364. Ontario Cancer Care. Lung Cancer Screening Pilot for People at High Risk 2017 [Available from: https://www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/lung-cancer-screening-pilot-people-at-high-risk?redirect=true.
365. Raji OY, Duffy SW, Agbaje OF, Baker SG, Christiani DC, Cassidy A, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med. 2012;157(4):242-50.
366. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016;20(40):1-146.
367. Liverpool Clinical Commissioning Group. Healthy Lungs 2018 [Available from: https://www.liverpoolccg.nhs.uk/health-and-services/healthy-lungs/.]
368. van Giessen A, Peters J, Wilcher B, Hyde C, Moons C, de Wit A, et al. Systematic Review of Health Economic Impact Evaluations of Risk Prediction Models: Stop Developing, Start Evaluating. Value Health. 2017;20(4):718-26.
369. Wallace E, Smith SM, Perera-Salazar R, Vaucher P, McCowan C, Collins G, et al. Framework for the impact analysis and implementation of Clinical Prediction Rules (CPRs). BMC Med Inform Decis Mak. 2011;11:62.
370. Goodson JD. POINT: Should Only Primary Care Physicians Provide Shared Decision-making Services to Discuss the Risks/Benefits of a Low-Dose Chest CT Scan for Lung Cancer Screening? Yes. Chest. 2017;151(6):1213-5.
371. Powell CA. COUNTERPOINT: Should Only Primary Care Physicians Provide Shared Decision-making Services to Discuss the Risks/Benefits of a Low-Dose Chest CT Scan for Lung Cancer Screening? No. Chest. 2017;151(6):1215-7.
372. Kaur S, Choy CY. Ethical considerations in clinical trials: a critique of the ICH-GCP guideline. Dev World Bioeth. 2014;14(1):20-8.
373. Faculty of General Dental Practice (UK). Standards in Dentistry. 2018.
374. NHS Digital. NHS Dental Statistics for England 2016-17. 2017.

375. Sherratt FC, Marcus MW, Robinson J, Field JK. Utilizing Lung Cancer Risk Prediction Models to Promote Smoking Cessation: Two Randomized Controlled Trials. Am J Health Promot. 2018;32(5):1196-205.
376. Nikitakis NG, Pentenero M, Georgaki M, Poh CF, Peterson DE, Edwards P, et al. Molecular markers associated with development and progression of potentially premalignant oral epithelial lesions: Current knowledge and future implications. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):650-69.

Appendix 1. Chapter 2: Incidence of Head and Neck Cancers in England, by Sex: 2002-2011

Table A1.1 Incidence of Head and Neck Cancer and sub-types, per 100,000 persons, for males and females from 2002-2011, in England

Year	Value	Cancer Type											
		Head and Neck Cancer			OPSCC			Oral Cancer			Laryngeal Cancer		
		Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
2002	Incidence	**12.2**	**17.4**	**7.4**	**1.8**	**2.7**	**1.0**	**5.2**	**6.6**	**3.8**	**3.4**	**5.7**	**1.2**
	N	6,082	4,215	1,867	899	654	245	2,582	1,611	971	1,674	1,374	300
2003	Incidence	**13.1**	**18.4**	**7.9**	**2.0**	**3.1**	**1.0**	**5.6**	**7.2**	**4.1**	**3.4**	**5.7**	**1.2**
	N	6,532	4,505	2,027	1,004	756	248	2,809	1,756	1,053	1,698	1,380	318
2004	Incidence	**13.1**	**18.6**	**7.8**	**2.1**	**3.1**	**1.1**	**5.5**	**7.0**	**4.1**	**3.4**	**5.8**	**1.1**
	N	6,554	4,563	1,991	1,040	761	279	2,771	1,730	1,041	1,693	1,424	269
2005	Incidence	**13.2**	**18.6**	**8.1**	**2.2**	**3.4**	**1.1**	**5.6**	**7.0**	**4.3**	**3.4**	**5.8**	**1.2**
	N	6,700	4,617	2,083	1,119	835	284	2,831	1,733	1,098	1,729	1,432	297
2006	Incidence	**14.3**	**20.1**	**8.6**	**2.5**	**3.9**	**1.2**	**6.0**	**7.7**	**4.5**	**3.3**	**5.6**	**1.2**
	N	7,272	5,033	2,239	1,284	969	315	3,083	1,920	1,163	1,708	1,405	303

Table A1.1 continued. Incidence of Head and Neck Cancer and Sub-types (per 100,000 persons) for Males and Females 2002-2011, in England

Year	Value	Cancer Type											
		Head and Neck Cancer			OPSCC			Oral Cancer			Laryngeal Cancer		
		Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
2007	Incidence	**14.1**	**19.9**	**8.5**	**2.5**	**3.9**	**1.3**	**6.0**	**7.7**	**4.4**	**3.3**	**5.7**	**1.1**
	N	7229	5012	2217	1304	974	330	3098	1942	1156	1714	1436	278
2008	Incidence	**15.1**	**21.1**	**9.2**	**2.7**	**4.3**	**1.2**	**6.6**	**8.1**	**5.0**	**3.5**	**5.9**	**1.2**
	N	7799	5364	2435	1415	1089	326	3394	2066	1328	1798	1492	306
2009	Incidence	**15.4**	**21.7**	**9.4**	**3.0**	**4.5**	**1.5**	**6.6**	**8.4**	**4.9**	**3.4**	**5.9**	**1.1**
	N	8034	5550	2484	1549	1156	393	3469	2161	1308	1797	1496	301
2010	Incidence	**15.9**	**22.1**	**9.9**	**3.4**	**5.2**	**1.7**	**6.7**	**8.4**	**5.1**	**3.5**	**5.9**	**1.2**
	N	8355	5711	2644	1794	1339	455	3524	2167	1357	1837	1529	308
2011	Incidence	**15.9**	**22.1**	**9.8**	**3.3**	**5.1**	**1.6**	**6.9**	**8.7**	**5.1**	**3.5**	**5.8**	**1.3**
	N	8424	5788	2636	1772	1338	434	3647	2271	1376	1848	1506	342
	p-value	**<0.001**	**0.003**	**0.004**	**<0.001**	**0.003**	**0.003**	**<0.001**	**0.005**	**0.004**	**0.32**	**0.40**	**0.40**

Appendix 2. Further Results from Chapter 2.

Table A2.1. Incidence per 100,000 persons of HNC in England, in each 5-year age category, from 2002-2011.

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Age Cat	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
40-44	2.1	0.5	2.2	0.6	1.9	0.8	2.8	0.5	2.9	0.7	2.9	1.2	2.7	0.9	3.0	0.9	3.2	0.9	2.8	0.9
45-49	5.2	1.2	5.4	1.4	5.5	1.4	5.3	1.6	6.2	1.6	6.5	1.9	7.2	2.0	6.2	2.1	7.6	2.2	7.3	2.0
50-54	6.6	2.2	7.6	2.1	7.5	2.3	10.2	2.5	8.7	2.9	11.3	2.2	10.7	2.9	12.8	3.6	12.0	3.7	12.5	3.5
55-59	8.3	2.9	10.0	2.9	9.2	2.7	9.8	2.7	11.1	3.4	10.0	3.5	14.1	3.3	15.1	4.5	17.2	5.0	17.6	5.2
60-64	7.7	2.6	9.7	2.5	9.7	3.7	10.1	2.4	11.9	3.3	11.2	3.5	10.5	3.3	12.2	4.4	16.9	5.9	16.2	4.8
65-69	6.2	2.0	6.4	2.0	7.6	2.7	9.2	2.3	8.8	2.6	10.0	2.5	13.1	2.6	11.3	3.6	13.3	3.9	13.6	3.9
70-74	6.0	3.1	6.8	2.7	6.0	2.0	6.6	2.7	6.7	1.9	7.1	3.2	10.0	2.8	9.6	3.1	10.8	3.7	12.5	3.5
75-79	5.4	1.3	4.5	1.9	6.5	2.1	5.4	2.5	8.0	2.3	5.9	1.8	7.4	2.5	7.4	3.0	7.7	2.4	7.9	2.6
80-84	4.5	1.9	4.1	1.4	5.3	2.7	5.7	2.8	6.3	1.5	5.2	1.6	4.3	1.5	6.2	1.6	8.2	2.7	5.9	2.3
85+	5.6	2.2	3.8	1.2	5.9	1.5	2.4	1.6	5.4	1.7	3.5	2.4	4.2	1.7	3.2	1.1	4.3	1.6	4.8	1.8

Table A2.2. Incidence per 100,000 persons, of OPSCC in England, in 5 - year age categories, from 2002-2011

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Age Cat	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
40-44	2.1	0.5	2.2	0.6	1.9	0.8	2.8	0.5	2.9	0.7	2.9	1.2	2.7	0.9	3.0	0.9	3.2	0.9	2.8	0.9
45-49	5.2	1.2	5.4	1.4	5.5	1.4	5.3	1.6	6.2	1.6	6.5	1.9	7.2	2.0	6.2	2.1	7.6	2.2	7.3	2.0
50-54	6.6	2.2	7.6	2.1	7.5	2.3	10.2	2.5	8.7	2.9	11.3	2.2	10.7	2.9	12.8	3.6	12.0	3.7	12.5	3.5
55-59	8.3	2.9	10.0	2.9	9.2	2.7	9.8	2.7	11.1	3.4	10.0	3.5	14.1	3.3	15.1	4.5	17.2	5.0	17.6	5.2
60-64	7.7	2.6	9.7	2.5	9.7	3.7	10.1	2.4	11.9	3.3	11.2	3.5	10.5	3.3	12.2	4.4	16.9	5.9	16.2	4.8
65-69	6.2	2.0	6.4	2.0	7.6	2.7	9.2	2.3	8.8	2.6	10.0	2.5	13.1	2.6	11.3	3.6	13.3	3.9	13.6	3.9
70-74	6.0	3.1	6.8	2.7	6.0	2.0	6.6	2.7	6.7	1.9	7.1	3.2	10.0	2.8	9.6	3.1	10.8	3.7	12.5	3.5
75-79	5.4	1.3	4.5	1.9	6.5	2.1	5.4	2.5	8.0	2.3	5.9	1.8	7.4	2.5	7.4	3.0	7.7	2.4	7.9	2.6
80-84	4.5	1.9	4.1	1.4	5.3	2.7	5.7	2.8	6.3	1.5	5.2	1.6	4.3	1.5	6.2	1.6	8.2	2.7	5.9	2.3
85+	5.6	2.2	3.8	1.2	5.9	1.5	2.4	1.6	5.4	1.7	3.5	2.4	4.2	1.7	3.2	1.1	4.3	1.6	4.8	1.8

Appendix 2 continued. Further Results from Chapter 2.

Table A2.3. Incidence per 100,000 of Oral Cancer in England, in five-year age categories, from 2002-2011

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Age Cat	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
40-44	3.5	1.2	3.5	1.5	2.8	1.3	3.5	1.5	3.4	2.0	3.1	1.1	4.1	2.0	3.6	2.8	3.7	2.4	3.4	1.4
45-49	7.6	2.6	6.6	4.0	6.5	3.1	6.5	3.3	7.4	3.2	6.7	3.6	6.8	4.0	7.1	3.1	7.4	3.2	8.5	3.1
50-54	12.4	4.5	12.4	5.0	12.3	6.8	12.6	5.7	12.6	5.8	15.2	6.2	13.9	6.7	13.0	6.2	13.6	6.7	13.1	7.1
55-59	16.2	6.1	17.1	7.5	16.6	7.1	15.3	6.1	18.4	7.6	20.0	7.9	19.2	7.8	21.3	8.4	20.7	9.7	22.3	8.8
60-64	18.1	8.4	21.9	8.0	20.6	8.4	20.2	10.2	21.7	8.4	23.4	8.8	22.6	9.8	22.8	10.3	26.4	9.5	26.5	10.2
65-69	19.5	8.3	22.2	9.7	17.8	9.9	21.6	11.2	24.4	10.3	23.1	10.5	25.1	11.8	26.8	13.5	26.5	12.9	24.0	13.6
70-74	18.9	11.6	21.1	12.2	23.3	11.0	20.8	12.1	21.0	13.4	22.2	11.1	22.7	15.5	26.6	12.3	25.1	15.3	26.9	15.9
75-79	19.8	12.8	24.7	11.0	23.8	12.9	22.8	12.3	23.6	12.5	21.1	15.4	26.3	14.1	29.1	15.5	23.6	16.8	24.7	17.1
80-84	25.7	14.8	21.2	14.4	24.4	15.9	23.0	16.7	26.8	17.8	20.3	16.7	29.6	19.6	23.4	16.4	25.1	18.9	25.8	20.9
85+	28.7	15.7	24.5	20.5	27.2	17.6	25.9	19.0	25.7	22.6	25.5	18.2	25.2	23.1	23.7	22.6	25.2	21.9	30.0	19.7

Table A2.4. Incidence, per 100,000 persons, of Laryngeal Cancer in England, in five-year age categories, from 2002-2011

Year	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011	
Age Cat	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
40-44	1.2	0.4	1.2	0.4	1.3	0.2	1.0	0.3	1.3	0.3	0.8	0.2	0.8	0.5	1.4	0.4	1.4	0.3	1.0	0.2
45-49	3.2	0.5	3.9	0.7	2.6	0.5	3.1	0.9	3.6	0.9	3.0	0.3	4.0	0.4	2.9	0.6	3.0	0.6	3.3	0.8
50-54	7.5	1.2	6.9	1.6	6.9	1.6	7.1	1.6	7.2	2.3	7.7	1.7	7.2	1.8	6.6	1.4	7.5	1.4	5.2	1.7
55-59	13.5	2.8	13.7	2.0	13.0	1.5	13.1	2.1	11.4	1.9	12.4	2.0	10.9	1.9	12.7	1.9	12.7	2.6	12.6	1.8
60-64	18.1	2.6	16.0	3.8	19.2	3.4	18.6	3.3	19.4	3.9	15.2	3.0	18.4	3.6	17.8	2.5	16.9	2.9	15.6	3.2
65-69	20.8	4.1	20.0	4.3	19.8	3.3	20.1	3.2	21.8	3.6	22.9	3.1	20.6	3.2	20.3	3.9	22.5	4.4	20.9	4.1
70-74	24.8	4.2	22.8	4.3	22.9	3.5	21.9	3.1	20.3	2.4	24.4	3.6	23.9	4.0	26.0	4.7	23.3	3.8	22.7	4.6
75-79	22.9	3.7	26.2	4.1	28.3	4.6	24.2	5.3	22.5	3.6	21.8	3.1	24.2	3.0	23.5	3.3	24.6	3.5	24.7	4.6
80-84	23.4	5.0	25.3	4.3	26.1	3.1	27.9	4.1	22.6	4.4	22.4	4.5	23.9	4.6	24.2	4.5	21.2	3.5	24.0	4.7
85+	18.6	3.2	23.0	3.3	22.8	3.2	25.9	2.7	22.9	3.2	28.2	2.9	27.1	3.2	18.1	2.7	21.6	3.1	26.2	3.3

Appendix 3. Chapter 3 – Data Collection Sheet for Systematic Review

Table A3.1. Data Collection Sheet for Systematic Review in Chapter 3

Study Number		1	2	3	4	5	6	7	8
Year									
First Author									
Country									
Study Type									
Aim of Study									
Inclusion criteria									
Exclusion Criteria									
Number in cohort									
Follow up time for Cohort studies									
Number	Cases								
	Controls								
Loss to follow up									
Age (mean)	Cases								
	Controls								

Table A3.1 continued. Data Collection Sheet for Systematic Review in Chapter 3

	Study Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Male:Female Ratio	Cases								
	Controls								
Age at Menopause	Cases								
	Controls								
Use of HRT	Cases								
	Controls								
Duration of HRT	Cases								
	Controls								
Type of HRT	Cases								
	Controls								
Smoking	Cases								
	Controls								

Table A3.1 continued. Data Collection Sheet for Systematic Review in Chapter 3

Study Number		1	2	3	4	5	6	7	8
Alcohol	Cases								
	Controls								
SES measure used									
SES results	Cases								
	Controls								
Newcastle Ottawa Score									
Comments									

Appendix 4.

Material Transfer Agreement for UK Biobank Data

The Material Transfer Agreement received from the UK Biobank can be found inserted here.

Appendix 5. Full list of Variables Considered Contained in the Development Dataset

General

Encoded anonymised participant ID

Sex

Year of birth

Month of birth

Date of attending assessment centre

UK Biobank assessment centre

Age at death

Date of death

Underlying (primary) cause of death: ICD10

Contributory (secondary) causes of death: ICD10

Ethnic background

Weight

Age when attended assessment centre

Age at recruitment

Country of Birth (non-UK origin)

Home location at assessment - east co-ordinate (rounded)

Home location at assessment - north co-ordinate (rounded)

Pulse rate

Number of children fathered

Handedness (chirality/laterality)

Skin colour

Hair colour (natural, before greying)

Facial ageing

Country of birth (UK/elsewhere)

Length of mobile phone use

Weekly usage of mobile phone in last 3 months

Usual side of head for mobile phone use

Sleep duration

Snoring

Medical History

Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor

Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones

Medical History continued

Diastolic blood pressure, automated reading

Exercise

Number of days/week of moderate physical activity 10+ minutes

Number of days/week of vigorous physical activity 10+ minutes

Place of Birth

Place of birth in UK - north co-ordinate

Place of birth in UK - east co-ordinate

Screening-related Variables

Ever had bowel cancer screening

Ever had prostate specific antigen (PSA) test

Ever had breast cancer screening / mammogram

Ever had cervical smear test

Early-life and Family History

Adopted as a child

Part of a multiple birth

Maternal smoking around birth

Father still alive

Fathers age at death

Mother still alive

Number of full brothers

Number of full sisters

Mothers age at death

Number of older siblings

Birth weight

Illnesses of father

Illnesses of mother

Illnesses of siblings

Non-accidental death in close genetic family

Socio-Economic Variables

Age completed full time education

Qualifications

Current employment status

Job code – deduced

Current employment status - corrected

Socio-Economic Variables

Townsend deprivation index at recruitment

Appendix 5 continued. Full list of Variables in the Model Development Dataset

Systolic blood pressure, automated reading
Body mass index (BMI)
Body fat percentage
Number of self-reported non-cancer illnesses
Number of operations, self-reported
Number of treatments/medications taken
Overall health rating
Long-standing illness, disability or infirmity
Had major operations
Diabetes diagnosed by doctor
Fractured/broken bones in last 5 years
Other serious medical condition/disability diagnosed by doctor
Taking other prescription medications
Had other major operations
Age high blood pressure diagnosed
Age diabetes diagnosed
Age angina diagnosed
Stomach/abdominal pain for 3+ months
Age hay fever, rhinitis or eczema diagnosed
Age asthma diagnosed
Operative procedures - main OPCS
Diagnoses - main ICD10
Interpolated Year when non-cancer illness first diagnosed
Interpolated Age of participant when non-cancer illness first diagnosed
Non-cancer illness code, self-reported
Medication for cholesterol, blood pressure or diabetes
Mouth/teeth dental problems
Vascular/heart problems diagnosed by doctor
Medication for pain relief, constipation, heartburn
Heel bone mineral density (BMD) T-score, automated (left)
Age heart attack diagnosed
Age emphysema/chronic bronchitis diagnosed
Age deep-vein thrombosis (DVT, blood clot in leg) diagnosed
Age pulmonary embolism (blood clot in lung) diagnosed
Gestational diabetes only
Facial pains for 3+ months
Spells in hospital
Illness, injury, bereavement, stress in last 2 years

Female-Hormone Related Variables

Age when periods started (menarche)

Female Hormone continued

Average total household income before tax
Home area population density - urban or rural
Particulate matter air pollution (pm10); 2010
Particulate matter air pollution (pm2.5); 2010
Nitrogen dioxide air pollution; 2010
Nitrogen oxides air pollution; 2010

Smoking-related Variables

Current tobacco smoking
Past tobacco smoking
Smoking/smokers in household
Exposure to tobacco smoke at home
Exposure to tobacco smoke outside home
Light smokers, at least 100 smokes in lifetime
Age started smoking in former smokers
Type of tobacco previously smoked
Number of cigarettes previously smoked daily
Age stopped smoking
Ever stopped smoking for 6+ months
Number of unsuccessful stop-smoking attempts
Likelihood of resuming smoking
Age started smoking in current smokers
Type of tobacco currently smoked
Number of cigarettes currently smoked daily (current cigarette smokers)
Time from waking to first cigarette
Difficulty not smoking for 1 day
Ever tried to stop smoking
Wants to stop smoking
Smoking compared to 10 years previous
Previously smoked cigarettes on most/all days
Why stopped smoking
Why reduced smoking
Number of cigarettes previously smoked daily (current cigar/pipe smokers)
Age stopped smoking cigarettes (current cigar/pipe or previous cigarette smoker)
Smoking status
Ever smoked
Pack years of smoking
Pack years adult smoking as proportion of life span exposed to smoking

Alcohol-related Variables

Alcohol intake frequency
Average weekly red wine intake

Alcohol continued

Appendix 5. continued. Full List of Variables in the Development Dataset

Had menopause

Number of live births
Birth weight of first child
Age at first live birth
Age at last live birth
Ever had stillbirth, spontaneous miscarriage or termination
Ever taken oral contraceptive pill
Age started oral contraceptive pill
Age when last used oral contraceptive pill
Ever used hormone-replacement therapy (HRT)
Age at hysterectomy
Bilateral oophorectomy (both ovaries removed)
Pregnant
Age started hormone-replacement therapy (HRT)
Age last used hormone-replacement therapy (HRT)
Age at menopause (last menstrual period)
Ever had hysterectomy (womb removed)
Time since last menstrual period
Length of menstrual cycle
Number of stillbirths
Number of spontaneous miscarriages
Number of pregnancy terminations
Age of primiparous women at birth of child
Age at bilateral oophorectomy (both ovaries removed)

Cancer-related Variables

Number of self-reported cancers
Cancer diagnosed by doctor
Cancer code, self-reported
Interpolated Year when cancer first diagnosed
Interpolated Age of participant when cancer first diagnosed
Date of cancer diagnosis
Type of cancer: ICD10
Age at cancer diagnosis
Reported occurrences of cancer
Histology of cancer tumour
Behaviour of cancer tumour
Type of cancer: ICD9

Sexual History

Age first had sexual intercourse
Lifetime number of sexual partners
Ever had same-sex intercourse
Lifetime number of same-sex sexual partners

Average weekly champagne plus white wine intake
Average weekly beer plus cider intake
Average weekly spirits intake
Average weekly fortified wine intake
Alcohol usually taken with meals
Alcohol intake versus 10 years previously
Reason for reducing amount of alcohol drunk
Former alcohol drinker
Alcohol consumed
Red wine intake
Rose wine intake
White wine intake
Beer/cider intake
Fortified wine intake
Spirits intake
Other alcohol intake
Alcohol drinker status

Diet-related Variables

Cooked vegetable intake
Salad / raw vegetable intake
Fresh fruit intake
Dried fruit intake
Oily fish intake
Non-oily fish intake
Processed meat intake
Poultry intake
Beef intake
Lamb/mutton intake
Pork intake
Cheese intake
Milk type used
Spread type
Bread intake
Bread type
Cereal intake
Cereal type
Salt added to food
Tea intake
Coffee intake
Coffee type
Water intake
Major dietary changes in the last 5 years
Variation in diet
Breastfed as a baby
Never eat eggs, dairy, wheat, sugar

Appendix 6. Rules applied for Managing Variables

Category	Criteria for removal of variable/data point
Missing Data	>40% missing data
Duplicate Cancer Diagnosis	Same histological type of cancer recorded at same sub-type within 1 week of original diagnosis
Repeated Measures	All variables representing repeated measures (i.e. data not collected at first visit)
Irrelevant Variables	Remove all variables not listed in Appendix 5.

Appendix 7. TRIPOD Checklist

Topic	Checklist Item	Section in Thesis	Page Number
Title and Abstract			
Title	Identify the study as developing and/or validating a multivariable model, the target population and the outcome to be predicted	Title Page – Chapter 6 Title Page- Chapter 7	127 147
Abstract	Summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results and conclusions	6.1	127
Introduction			
Background and Objectives	Explain medical context and rationale for development/validation of the model	1.4	12-13
	Specify the objectives, including whether the study describes development, validation or both	1.4	12-13
Methods			
Source of data	Describe the source of the data Specify the key study dates (start and end of accrual)	4.3.2	62-3

Appendix 7. TRIPOD Checklist

Topic	Checklist Item	Section in Thesis	Page Number
Participants	Specify key elements of the study setting, including number and location of centres. Describe eligibility criteria Details of treatment received, if relevant	4.3.2.2	63
Outcome	Clearly define the outcome that is predicted by the prediction model, including how and when assessed Report any actions to blind assessment of the outcome	4.3.4	66-7
Predictors	Clearly define all predictors used including how and when they were measured Report any measures to blind assessment of predictors	4.3.2.3	64-5
Sample Size	Explain how the study size was arrived at	4.3.2.2	64
Missing Data	Describe how missing data were handled with details of any imputation method	4.4.3	69

Appendix 7. TRIPOD Checklist

Topic	Checklist Item	Section in Thesis	Page Number
Statistical Analysis Methods	Describe how predictors were handled	4.3.5	67
	Specify the type of model, any predictor selection and method for internal validation	4.4.5.3 and 4.5.1	72 & 73-4
	For validation, describe how the predictors were calculated	4.3.2.3	64-5
	Specify all measures used to assess model performance and, if relevant, to compare multiple models	7.2	148
Risk Groups	Provide details on how risk groups were created, if done	N/A	N/A
Development vs Validation	For validation, identify any difference from the development data in setting, eligibility criteria, outcome and predictors	7.1	147

Appendix 7. TRIPOD Checklist

Topic	Checklist Item	Section in Thesis	Page Number
Results: Participants	Describe the flow of participants through the study, including the number of participants with and without the outcome Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 5.19 Table 7.1	124-26 151-52
Results: Model Development	Specify the number of participants and outcome events in each analysis. If done, report the unadjusted association between each candidate predictor and outcome	6.1 Table 6.1	127 130
Results: Model Specification	Present the full prediction model to allow predictions for individuals (i.e. all regression coefficients, and model intercept)	Table 6.2	135
Results: Model Performance	Report performance measures with CI's for the prediction model	7.4.1	154

Appendix 7. TRIPOD Checklist

Topic	Checklist Item	Section in Thesis	Page Number
Results: Model updating	If done, report the results from any model updating	7.5	156
Discussion			
Limitations	Discuss any limitations of the study	6.8.1	144-46
Interpretation	For validation, discuss the results with reference to performance in the development data and any other validation data Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence	7.7.1 7.8	161 164
Implications	Discuss the potential clinical use of the model and implications for future research	9.7 and 9.8	190-91
Other information			
Supplementary information	Provide information about the availability of supplementary resources, such as web calculator and datasets	n/a	n/a
Funding	Give the source of funding and the role of funders for the present study.	n/a	n/a

Appendix 8. Published Papers

This text box is where this unabridged thesis contains the following copyrighted material;

McCarthy CE, Field JK, Rajlawat BP, Field EA, Marcus MW. "Trends and Regional Variation in the Incidence of head and neck cancers in England: 2002-2011". *Int J Oncol*. 2015 Jul;47(1):204-10.

***doi*: http://dx.doi.org/10.3892/ijo.2015.2990.**

This text box is where this unabridged thesis contains the following copyrighted material;

McCarthy CE, Field JK, Marcus MW. "Age at Menopause and Hormone Replacement Therapy as risk factors for Head and Neck and Oesophageal Cancer. A systematic review". *Oncol Rep*. 2017 Oct;38(4):1915-1922.

***doi*: http://dx.doi.org/10.3892/or.2017.5867.**

This text box is where this unabridged thesis contains the following copyrighted material;

Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ. "Editorial: The management of oral epithelial dysplasia. The Liverpool algorithm".*Oral Oncol*. 2015 Oct;51(10):883-7.

doi: http://dx.doi.org/10.1016/j.oraloncology.2015.06.015.