

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/117162/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Conway, D I, Purkayastha, M and Chestnutt, Ivor 2018. The changing epidemiology of oral cancer: definitions, trends, and risk factors. *British Dental Journal* 225 , pp. 867-873. 10.1038/sj.bdj.2018.922

Publishers page: <https://doi.org/10.1038/sj.bdj.2018.922>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Title:

The changing epidemiology of oral cancer: definitions, trends, and risk factors

Authors

David I Conway, School of Medicine, Dentistry, and Nursing, University of Glasgow

Mitana Purkayastha, School of Medicine, Dentistry, and Nursing, University of Glasgow

Ivor G Chestnutt, Cardiff University School of Dentistry

Corresponding author:

Professor David Conway

Professor in Dental Public Health

School of Medicine, Dentistry, and Nursing

University of Glasgow

Glasgow Dental Hospital & School

378 Sauchiehall Street

Glasgow G2 3JZ

david.conway@glasgow.ac.uk

Key words: oral cancer, epidemiology, aetiology, trends

Abstract

This review has three objectives, namely: (i) to discuss how oral cancer is and ought to be defined and recorded; (ii) to present up to date data on the incidence burden of the disease in the four countries of the UK, and review recent analyses of trends in the disease; and (iii) to summarise recent evidence on risk factors of the disease. Emerging evidence of the role played by risk factors in different anatomical sites means that oral cavity cancer and oropharynx cancer should be considered distinct disease entities – and a standardised attribution of anatomical subsites will be helpful in ensuring consistency in how data are presented. In 2016, over 3,700 people were diagnosed with oral cavity cancer and over 3,500 people were diagnosed with oropharyngeal cancer in the UK. Incidence of oropharyngeal cancer is rapidly rising across the UK. Rates of oral cavity cancer are higher in N.Ireland and higher still (and relatively stable) in Scotland, but rising in England and Wales. The International Head and Neck Cancer Epidemiology (INHANCE) consortium have pooled data from multiple case-control studies providing the best estimates of risk factors. They show that while the consumption of alcohol and tobacco are the prime risk factors for oral cavity and oropharyngeal cancers, they provide greater certainty in the preventive benefits of reducing these risk factors. The role played by other factors such as low socioeconomic status, genetics, oral health, and Human Papillomavirus (only for oropharyngeal cancer) have become clearer.

Key points:

- This paper discusses issues affecting the definition of oral cancer and makes the case that emerging differences in the aetiology of the disease at different sites requires oral cavity cancer and oropharyngeal cancer to be clearly defined, recorded, and reported separately.
- In 2016, over 3700 people were diagnosed with oral cavity cancer and over 3500 people were diagnosed with oropharyngeal cancer in the UK. Incidence of oropharyngeal cancer is rapidly rising across the UK. Rates of oral cavity cancer are higher in N.Ireland and higher still (and relatively stable) in Scotland, but rising in England and Wales.
- Pooled international case-controlled study data are shedding increasing light not only on the causes of oral cavity and oropharyngeal cancers, but on the impact of avoiding risk factors.

Introduction

Epidemiology

The term “epidemiology” is derived from the Greek word “epidemion”, a verb meaning “to visit” used in connection with human illnesses in the writings of Hippocrates, who in addition referred to the term in the distribution of disease in the population as per its Greek language origins “epi” about and “demos” people [1]. According to Buck and colleagues (1988), the first published use of the word was the Spanish “epidemiologia” in a study of the bubonic plague and it became the term employed for the study of communicable disease epidemics [1]. Since then epidemiology has continually evolved as a scientific discipline, investigating a wide range of non-communicable as well as communicable diseases and health outcomes – including cancer. The focus is always on populations rather than individuals – although the findings of epidemiological studies can have implications and applications for individuals as well as populations.

The main cancer epidemiology approaches involve:

- describing the burden and natural history of disease in populations (descriptive epidemiology) – which is the mainstay of cancer surveillance. This provides insights and the development of hypotheses around potential causes which can be tested using analytical study designs
- analysing the aetiological determinants or risk factors for cancer (analytical epidemiology) [2].

Understanding the burden and causes of cancer is essential for developing and evaluating healthcare services and prevention programmes.

Oral Cancer

There is a lack of consensus on the definitions of oral cancer in the literature and multiple terms are used. This is further complicated with “head and neck cancer” terminology [3,4]. Quantitative analysis of disease relies on clear and uniform definitions and this is fundamental to cancer epidemiology, including definitions of topography (site), morphology (histopathology), and tumour behaviour (invasion – malignant, benign, *in-situ*).

However, in relation to oral cancer, there are also variations in the anatomical subsites included in oral cavity and oropharynx groupings. Different sources attribute some sites to the oral cavity, whilst others define the same site as oropharynx. Yet others include some sites under both. Precision in what is termed “oral cavity” and “oropharynx” is thought increasingly important due to epidemiological data showing the emerging role of human

papillomavirus (HPV) in cancer aetiology. Understanding of the role played by HPV (especially in oropharynx cancer) is leading to the identification of differing trends and risk profiles alongside differing treatment regimen and prognoses [5]. Thus, oral cancer is increasingly being recognised as being two distinct diseases: oral cavity cancer (OCC) – “mouth cancer” and oropharyngeal cancer (OPP) – “throat cancer”.

This paper has three aims:

- to achieve clarity on the definitions of oral cavity cancer and oropharyngeal cancer,
- to present the recent global and UK trends in the incidence of these cancers,
- to describe the current evidence on their risk factors.

Methods

Defining oral cavity cancer and oropharyngeal cancer

The International Classification of Diseases for Oncology (ICD-O), published by the World Health Organization, is the standard classification tool for defining cancer subsites (along with morphologies). It is revised every ten years, most recently in 2013 [6]. This paper reviews the ICD-O codes used to define oral cavity cancer and oropharyngeal cancer within UK cancer registries and compares this with emerging definitions used in recent major epidemiology publications. Taking account of any variation in these definitions and considering both anatomical and aetiological differences in subsite grouping, this paper will try to present distinct standardised definitions of oral cavity cancer and oropharyngeal cancer.

Descriptive epidemiology of the burden and trends in oral cavity cancer and oropharyngeal cancer

The incidence (risk) burden of cancer in a population is best measured by incidence rates. Cancer incidence rates are the number of new cases diagnosed in the population over a given period of time (usually a year) expressed as a rate by dividing this by the total population at risk during that period (denominator). The denominator is usually adjusted to account for different age profiles in different populations referenced to a standard population, which has a known population age-structure – this is often the European Standard Population, which is a theoretical population adding up to a total of 100,000 persons. Incidence rate data are usually available from routinely collected data in Cancer Registries. Cancer Registration is the collection, maintenance, and management of data on every new diagnosis of cancer occurring in a population (obtained from multiple records including hospital medical and pathology records, death records). It uses the ICD-O to code the

topography (site) and morphology (histopathology) of the primary tumour along with basic demographic data.

This paper summarises the findings from recent global and UK epidemiological trend analyses peer-reviewed publications. Findings from global and UK studies which have analysed separately the recent trends in the incidence rates of oral cavity and oropharyngeal cancers are also reviewed. In addition up-to-date information requests were submitted to the UK Cancer Registries for annual incidence rates standardised to the 2013 European Standard Population (and number of new cases) of oral cavity and oropharyngeal cancer from 2000 to the most recently available year. In the UK there are 12 cancer registries, including one each for Northern Ireland (N.Ireland) [7], Scotland [8], and Wales [9], the English regional cancer registries collate their data via the National Cancer Registration and Analysis Service (NCRAS) in Public Health England [10]. Where available, these data will be presented separately by gender for each country of the UK – this will follow a more strictly defined subsite criteria of oral cavity cancer and oropharyngeal cancer. Epidemiological trends in mortality and survival of oral cavity and oropharyngeal cancer are beyond the scope of this paper.

Analytical epidemiology of risk factors for oral cavity cancer and oropharyngeal cancer

Risk factors for cancer studies are usually ascertained from observational studies – cohort or case-control studies. Given the relatively low volume of oral cancer and the long lag-time between exposure to risk factors and cancer diagnosis, case-control study designs are the mainstay of epidemiological investigations. In such case-control studies, a group of patients with oral cancer (“cases”) and a comparable group of study participants without oral cancer (“controls”) are recruited. Information on their histories of exposure to risk factors is collected and compared and differences allow assumptions to be made on possible risk and aetiological factors

The International Head And Neck Cancer Epidemiology (INHANCE) consortium is a collaboration of research groups of large epidemiological (case-control) studies investigating the risk factors for head and neck cancer including (separately) oral cavity and oropharyngeal cancer subsites [11, 12]. The consortium has pooled and standardised data from 35 studies including data on over 25,500 patients with head neck cancer (including cancers of the oral cavity and oropharynx) and 37,100 controls (participants without cancer). Over 30 peer-reviewed publications analysing aspects of the INHANCE data have been published. These have focused in detail on tobacco and alcohol risks, along with other key and emerging risk factors. This big dataset has major strengths including providing more

precise estimates of risk and has the ability to control for and assess interactions with potential confounding factors. The findings of the INHANCE data analyses with a particular focus on oral cavity and oropharyngeal cancers are presented below. Where there are gaps in the INHANCE analyses, these data have been complemented with other published systematic reviews or meta-analysis.

Results and discussion

Definitions

The debate over definitions is encapsulated and exemplified by the variation in routine publication of oral cancer statistics in the UK Cancer Registries (Table 1). Both the Cancer Registration statistics for England [10], published by the Office for National Statistics, and the Northern Ireland Cancer Registry [7], define oral cancers as one grouping “lip, oral cavity, and pharynx” – with the pharynx including oropharynx as well as nasopharynx and hypopharynx sites. The Cancer Registry for Wales [9], now known as the Welsh Cancer Intelligence and Surveillance Unit combine “oral & oropharynx cancer” together in their Cancer Incidence in Wales online publication. The Scottish Cancer Registry [8] report multiple subgroupings of head and neck cancer including “oral cavity cancer” and “oropharynx cancer” – however, there are a number of ICD codes included in both oral cavity and oropharynx definitions (Table 1).

Based on a review of major epidemiological studies [13-16], a “compromise” (anatomical and HPV-associated) method of defining oral cavity and oropharyngeal cancers separately was developed and is used here in a reanalysis of UK cancer data and proposed for future epidemiological studies (Table 1). Briefly, **oropharyngeal cancer** has been defined as including: the base of the tongue (C01), lingual tonsil (C2.4), tonsil (C09), oropharynx (C10), and pharynx not otherwise specified (C14); while **oral cavity cancer** includes: the inner lip (C00.3 - C00.9), other and unspecified parts of the tongue (C02) [excluding lingual tonsil (C2.4)], gum (C03), floor of the mouth (C04), palate (C05), and other and unspecified parts of the mouth (C06).

[INSERT TABLE 1 HERE]

Global burden and trends

The best and most recently available peer-reviewed analyses of global estimates by the World Health Organisation International Agency for Research on Cancer (WHO IARC) are for 2012 when 202,000 cases of oral cavity cancer and 100,500 cases of oropharyngeal cancer were newly diagnosed that year [17]. The global estimated age-standardised rate of

oral cavity cancer was 2.7 per 100,000 in 2012, with the largest proportion (48.7%) diagnosed in south-central Asia, and occurrence being consistently higher in men than women (M:F rate ratio 2:1). The global estimated rate for oropharyngeal cancer was lower at 1.4 per 100,000 in 2012, (but with a higher M:F ratio of 4.8:1), with the highest proportions being in North America (34.2%) and South-central Asia (35.1%) [17].

A series of detailed epidemiological studies on the worldwide and US trends in incidence rates for oral cavity and oropharyngeal cancers have been undertaken in recent years [13,14,17,18]. These analyses show that the incidence of oropharyngeal cancer is rising rapidly, especially in high income countries and especially in the US. In contrast oral cavity cancer incidence rates are flat-lining or decreasing in men globally and increasing slightly in women [14]. These changing trends are a global phenomenon and have been related to changing population risk factors. This has been described as “controlling a tobacco epidemic while a human papillomavirus epidemic emerges” [19].

UK burden and trends

Recently, there have been two studies of trends in oral cavity and oropharyngeal cancer in the UK. In England, oral cavity cancer increased per annum by 2.8% for men and 3.0% for women, while oropharynx cancer increased by 7.3% for men and 6.5% for women between 1995 and 2011 [15]. Further annual increases were projected from 2011 to 2025. In Scotland, a recent cancer registry analysis showed that between 2001 and 2012 oropharyngeal cancer increased by 85%, while oral cavity cancer increased by only 10% [16]. Oropharyngeal cancer has also been shown to be the most rapidly rising cancer in Scotland [20]. These observed trends are more marked among men [15, 16, 20], and the burden of both oral cavity and oropharyngeal cancer is greater among those from more deprived communities [16]. Analysed projections of these England and Scotland rates showed that the incidence burden of oropharyngeal would overtake oral cavity cancer within the next decade [15, 16].

Table 2 shows the most up-to-date available numbers and incidence rates of oral cavity and oropharyngeal cancer by males and females for England, N.Ireland, Scotland, and Wales.

[INSERT TABLE 2 HERE]

[INSERT FIGURE 1 HERE]

For the most recently available data – 2016, there were 3088 people diagnosed with oral cavity cancer in England, 80 in N.Ireland, 400 in Scotland, and in Wales (in 2015) there were 176 people diagnosed – giving a total of 3744 people diagnosed with oral cavity cancer in the UK. In 2016, there were 2977 cases of oropharyngeal cancer diagnosed in England, 73 in N.Ireland, and 324 in Scotland, and in Wales (in 2015), there were 207 people diagnosed – giving a total of 3581 people diagnosed with oropharyngeal cancer in the UK, and a total of 7325 cases of oral cavity and oropharynx cancers combined. This gives a total number of patients so far this century, recorded in the UK cancer registries as diagnosed with oral cancer of 90,880 (52,829 oral cavity and 38,051 oropharyngeal – Figure 1)).

The trends in the incidence rates of oral cavity and oropharyngeal cancer for England, N.Ireland, and Scotland (2000-2016), and for Wales (2000-2015) are shown in Figure 1. A rapid increase in oropharyngeal cancer incidence is observed in all four countries. Oral cavity cancer incidence rates in Scotland have been relatively stable and consistently at the highest levels; in N.Ireland have a near similar magnitude, but are less stable (likely due to small numbers); while they have steadily risen in England and Wales over the period. Oropharyngeal cancer incidence rates are converging and catching up on oral cavity cancer rates in England, N.Ireland, and Scotland, but in Wales oropharyngeal cancer rates have already surpassed oral cavity cancer rates (Figure 1).

Risk factors review

Tobacco smoking and alcohol

Tobacco smoking and alcohol intake are well established risk factors for oral cancer. The INHANCE pooled dataset and analyses provide sufficiently high numbers of oral cavity and oropharyngeal cases who were non-smokers and/or non-alcohol consumers (thereby avoiding the problems associated with confounding) to enable a better understanding of these risks. This includes providing precise estimates of risk, understanding the joint tobacco-alcohol interaction, investigating the risk of smokeless tobacco and the benefits of quitting smoking or alcohol drinking.

Among smokers who never drank alcohol, there was a 2-fold risk estimate for oral cavity and oropharyngeal cancer, which increased with frequency and duration of smoking. A similar 2-fold risk of oral cavity and oropharyngeal cancer for alcohol drinking among those who never smoked tobacco was found, but only in heavier alcohol drinkers (three or more drinks per day) [21]. The highest risks are observed in those who both smoked tobacco and consumed alcohol heavily, with risk increased 5-fold [22].

INHANCE data show that there is a strong dose-response relationship for the risk of oral cavity and oropharyngeal cancer, with increasing frequency and duration of both smoking

and alcohol consumption. As is the case for lung cancer risk [23], smoking duration is more important than frequency for oral cancer – with fewer cigarettes per day over a longer number of years having a higher level of risk for oral cancer than more cigarettes per day over fewer years [24]. However, for alcohol consumption frequency is more important than duration – such that higher consumption (more than three drinks per day) over a short period (a few years) has a higher risk for oral cancer than a lower intake over a longer period (many years). Moreover, for both smoking and alcohol consumption there was no safety in low doses – low intakes of cigarettes and alcohol drinking increased risk of oral cancers [25]. In head and neck cancer risks – smoking risks were generally greater for larynx cancer, and alcohol drinking for oral cavity and pharyngeal cancers [24].

Betel quid

Betel quid, also known as “paan”, is a mixture of substances including areca nut with or without tobacco wrapped in a betel leaf and placed in the mouth [26]. It is common in south and southeast Asia and among people of south Asian origin in communities across the world including the UK [27, 28]. In a systematic review and meta-analysis of 15 case-controls, betel quid without tobacco was shown to have a near 3-fold increased risk association with “oral cancer” (undefined) [26].

Smokeless Tobacco

INHANCE analyses of smokeless tobacco – consumed as powdered snuff or tobacco chewing, found an increased risk association for oral cavity cancer, with a near 2-fold risk even among never cigarette smokers [29]. It therefore cannot be considered a risk reduction alternative.

The benefits of stopping smoking and drinking alcohol

Demonstrable benefits of quitting smoking were identified from the INHANCE data. Within 1 to 4 years after stopping smoking, risks reduced and reached a similar level to those who had never smoked after 20 years of quitting. In contrast, the risk effects associated with quitting heavy alcohol consumption take 20 years to begin to emerge [30].

Socioeconomic status

The other major risk association identified, on par with smoking and alcohol in terms of magnitude (2-fold increased risk), was socioeconomic status – specifically low educational attainment and low income. These risks were not fully explained by smoking and alcohol consumption – such that these socioeconomic effects were influencing risk behaviours (“the

cause of the cause”) and potentially having a more direct effect associated with socioeconomic circumstances [31].

Diet

There was limited new evidence in relation to dietary factors beyond confirming that a high intake of fresh fruits and vegetables were associated with reducing by half the oral cancer risk [32]. It is notable that, unlike for many cancers [33], obesity was not associated with an increased oral cancer risk. In fact, there are data to suggest that in young people (aged 30-years or less) oral cancer was more likely in those who self-reported a low body mass index (BMI) [34].

Genetics

Some limited risk associations associated with oral cancer have been identified – including genetic variants associated with alcohol metabolism, DNA repair pathways, and genes involved in the metabolism of nicotine [35]. This work has demonstrated the potential of genetic-environmental risk interactions. A moderately strong family history hereditary risk was also identified. An increased risk associated with having a first degree relative with head and neck cancer has been suggested [36].

Young people

Interestingly, risk factors reported above were generally consistent across age-groups (and indeed genders), with the major risk factors observed among younger adults being tobacco smoking and alcohol drinking [37].

Oral health

The risks associated with poor oral health are also beginning to become clear through analysis of the INHANCE dataset. After adjusting for smoking and alcohol consumption: few missing teeth, regular dental attendance, and daily toothbrushing may modestly reduce the risk of oral cavity and oropharyngeal cancer, but wearing a denture per se was not associated with increased risk [38, 39]. There was also a slightly elevated risk associated with mouthwash use over a prolonged period (greater than 35 years) and use more than once per day – although it was not possible to completely disentangle smoking and alcohol consumption in this analysis [40], and an earlier systematic review of estimates from published studies reported non-significant increased risk associations for regular mouthwash use [41]

Human papillomavirus (HPV)

Oral human papillomavirus (HPV) is mainly associated with oropharyngeal (rather than oral cavity) cancer risk. There are over 200 HPV types, but as with cervical cancer, HPV 16 and 18 subtypes are the main high-risk oncogenic types [42]. Substantial increased risk for oropharyngeal cancer (as high as 15 times greater) in those with HPV 16 have been identified – as in the groundbreaking 2007 *New England Journal of Medicine* study [43].

However, the natural history (prevalence, persistence, and determinants) of oral HPV infection is not well understood, nor is how carriage of oral HPV leads to oropharyngeal cancer. A large US population survey of oral prevalence of HPV infection found an overall 7% prevalence, with bimodal peaks at 10% in 25-30 and 50-55-year-olds in men [44]. Risk factors for oral HPV carriage were also identified. These included smoking, alcohol, number of sexual partners, number of oral sex partners, and open mouth kissing. A small feasibility study in Scotland replicated these broad prevalence findings [45].

Oral HPV is sexually transmitted [42]. INHANCE studies also point to a slight increased risk for oropharyngeal cancer with 6 or more lifetime sexual partners, 4 or more lifetime oral sex partners, and early age (<18 years) of sexual debut [46].

World-wide, the estimated HPV-attributable fraction of oropharyngeal cancer was 18-28%, but with estimates approaching 70% in the US [47]. A meta-analysis, including 5,396 oropharyngeal cancer cases, observed increases from 40.5% before 2000 to 72.2% after 2005, with significant increases observed in North America and Europe [48]. A recent international multi-centre case-control study, which included UK data and harmonised analyses, found HPV positive oropharyngeal cancer case proportions of 60% of US, and 31% in Europe (data collected on cases diagnosed in 2002-2004) [49]. Similarly, older European estimates of around 30% population attributable fraction for oropharyngeal cancer have been reported previously [50]. Thus, given that the epidemiology trends of rapid increases in oropharyngeal cancer, it seems reasonable to assume that the attributable proportion (in UK and Europe) is rising from around one-third of cases and perhaps approaching the US proportion of around two-thirds. It should be noted (even from US data) that the aetiological fraction for other cancers of the head and neck is considerably lower – perhaps as low as 3% for oral cavity cancer [51].

Conclusions

When discussing “oral cancer”, it is important to be clear and use the distinct terms: oral cavity cancer and oropharyngeal cancer. There is a need for agreed and standardised (ICD-based) definitions of oral cavity cancer and oropharyngeal cancer to be adopted in

descriptive epidemiological reporting of disease burden and trends in Cancer Registries, and in analytical epidemiological analysis of risk. This is important given the increasing evidence of the differing and changing trends and risk factors across these cancers.

The recent and projected increases of oral cavity and especially oropharyngeal cancer in the UK underlines the need for prioritising the development of cancer control strategies and cancer treatment services for those diagnosed.

The risk data reviewed has demonstrated the well known role of tobacco and alcohol in the aetiology of oral and oropharyngeal cancer. The strengthening evidence around HPV (in the case of oropharyngeal cancer), evidence on the benefits of quitting tobacco and alcohol use and further understanding of the role of diet, oral health, and genetics combined with the dominant role of socioeconomic factors and inequalities are all important in designing and managing both population and individual risk reduction strategies.

Acknowledgements

We acknowledge Professor John Gibson, University of Aberdeen Dental School, who provided clinical advice in relation to defining oral cavity and oropharyngeal cancers.

Mitana Purkayastha worked on this paper as part of her PhD studies (which she recently successfully completed) funded by NHS Education for Scotland.

David Conway is a member of the International Head And Neck Cancer Epidemiology (INHANCE) consortium.

Thanks to all involved with data collection in the UK Cancer Registries. And a special thanks to the data providers involved in analysing the information requests from the four countries: Matthew Peet (Cancer Analysis Team, Health Analysis and Life Events, Public Policy Analysis Office for National Statistics - England); Dr Eileen Morgan (N. Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast – N. Ireland Cancer Registry is funded by the Public Health Agency; this work uses data provided by patients and collected by NHS as part of their care and support); Cavan Gallagher (Population Health, Information Services Division, NHS National Services Scotland); Ceri White and Jamie Sullivan (Welsh Cancer Intelligence and Surveillance Unit, Public Health Wales).

References

1. Buck C, Llopis A, Nájera E, Terris. The challenge of epidemiology: issues and selected readings. Sci Publ No. 505. Pan American Health Organisation: Washington DC, 1988.

2. dos Santos Silva I. Cancer Epidemiology: Principles and Methods. International Agency for Research on Cancer: Lyon, 1999. <https://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CancerEpi.pdf> (Accessed July 2018).
3. Tapia JL, Goldberg L J. The challenges of defining oral cancer: Analysis of an ontological approach. *Head and neck pathology* 2011; 5(4): 376-384.
4. Moreno Lopez LA, Esparza Gomez GC. Oral cancer versus oropharyngeal cancer versus head and neck cancer. *Oral Oncol.* 1998; 34:576-577.
5. Taberna M, Mena M, Pavón MA, Alemany L, Gillison ML, Mesía R. Human papillomavirus-related oropharyngeal cancer. *Ann Oncol.* 201;28(10):2386-2398.
6. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Sobin L, Parkin DM, Whelan S (eds). *International Classification of Diseases for Oncology (ICD – O) Third Edition, First Revision.* World Health Organisation: Geneva, 2013.
7. The Northern Irish Cancer Registry. Lip Oral Cavity & Pharynx 1993-2016. Queens University Belfast, 2018. <https://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/BySite/LipOralCavityPharynx/> (Accessed July 2018).
8. Scottish Cancer Registry. Head and Neck Cancer Statistics. Information Services Division, NHS National Services Scotland, Edinburgh, 2018. <http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Head-and-Neck/> (Accessed July 2018).
9. Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence in Wales 2016. Public Health Wales <http://www.wcisuwales.nhs.uk/definitions-icd10-codes> (Accessed July 2018).
10. Office of National Statistics. Cancer Registration Statistics, England. 2018 <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> (Accessed July 2018)
11. International Head And Neck Epidemiology (INHANCE) consortium. University of Utah: Utah, 2018. <https://www.inhance.utah.edu/> (Accessed July 2018).
12. Conway DI, Hashibe M, Boffetta P; INHANCE consortium, Wunsch-Filho V, Muscat J, La Vecchia C, Winn DM. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. *Oral Oncol.* 2009;45(9):743-6.
13. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruze S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011 Nov 10;29(32):4294-301.
14. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol.* 2013;31(36):4550-9.
15. Louie KS, Mehanna H, Sasieni P. Trends in head and neck cancers in England from 1995 to 2011 and projections up to 2025. *Oral Oncol.* 2015;51(4):341-8.

16. 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.
17. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, Soerjomataram I. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA Cancer J Clin.* 2017;67(1):51-64.
18. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol.* 2014;50(5):387-403.
19. Hashibe M, Sturgis EM. Epidemiology of oral-cavity and oropharyngeal carcinomas: controlling a tobacco epidemic while a human papillomavirus epidemic emerges. *Otolaryngol Clin North Am* 2013; 46(4):507-20.
20. Junor EJ, Kerr GR, Brewster DH. Oropharyngeal cancer. Fastest increasing cancer in Scotland, especially in men. *BMJ.* 2010;340:c2512.
21. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P. 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.
22. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Kelsey K, Koifman S, La Vecchia C, Lazarus P, Levi F, Lence JJ, Mates D, Matos E, Menezes A, McClean MD, Muscat J, Eluf-Neto J, Olshan AF, Purdue M, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Shangina O, Pilarska A, Zhang ZF, Ferro G, Berthiller J, Boffetta P. 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.
23. Peto J. That the effects of smoking should be measured in pack-years: misconceptions 4. *Br J Cancer.* 2012;107(3):406-7.
24. Lubin JH, Purdue M, Kelsey K, Zhang ZF, Winn D, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Smith E, Shangina O, Schwartz SM, Rudnai P, Neto JE, Muscat J, Morgenstern H, Menezes A, Matos E, Mates IN, Lissowska J, Levi F, Lazarus P, La Vecchia C, Koifman S, Herrero R, Franceschi S, Wünsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Maso LD, Curado MP, Chen C, Castellsague X, Brennan P, Boffetta P, Hashibe M, Hayes RB. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol.* 2009;170(8):937-47.
25. Berthiller J, Straif K, Agudo A, Ahrens W, Bezerra Dos Santos A, Boccia S, Cadoni G, Canova C, Castellsague X, Chen C, Conway D, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Franceschi S, Fukuyama EE, Hayes RB, Healy C, Herrero R, Holcatova I, Kelsey K, Kjaerheim K, Koifman S, Lagiou P, La Vecchia C, Lazarus P, Levi F, Lissowska J, Macfarlane T, Mates D, McClean M, Menezes A, Merletti F, Morgenstern H, Muscat J, Olshan AF, Purdue M, Ramroth H, Rudnai P, Schwartz SM, Serraino D, Shangina O, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Thomson P, Vaughan TL, Vilensky M, Wei Q, Winn DM, Wünsch-Filho V, Zhang ZF, Znaor A, Ferro G, Brennan P, Boffetta

P, Hashibe M, Lee YC. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol.* 2016;45(3):835-45.

26. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. *PLoS One.* 2014;9(11):e113385

27. Croucher R, Dahiya M, Gowda KK. Contents and price of vendor assembled paan quid with tobacco in five London localities: a cross-sectional study. *Tob Control.* 2013;22(2):141-3.

28. Siddiqi K, Gupta PC, Prasad VM, Croucher R, Sheikh A. Smokeless tobacco use by south Asians. *Lancet Glob Health.* 2013;1(2):e71.

29. Wyss AB, Hashibe M, Lee YA, Chuang SC, Muscat J, Chen C, Schwartz SM, Smith E, Zhang ZF, Morgenstern H, Wei Q, Li G, Kelsey KT, McClean M, Winn DM, Schantz S, Yu GP, Gillison ML, Zavallos JP, Boffetta P, Olshan AF. Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium. *Am J Epidemiol.* 2016;184(10):703-716.

30. Marron M, Boffetta P, Zhang ZF, Zaridze D, Wünsch-Filho V, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Smith E, Schwartz SM, Rudnai P, Purdue MP, Olshan AF, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, McClean M, Matos E, Mates IN, Lissowska J, Levi F, Lazarus P, La Vecchia C, Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Cadoni G, Chen C, Castellsague X, Boccia S, Benhamou S, Ferro G, Berthiller J, Brennan P, Møller H, Hashibe M. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *Int J Epidemiol.* 2010;39(1):182-96.

31. Conway DI, Brenner DR, McMahon AD, Macpherson LM, Agudo A, Ahrens W, Bosetti C, Brenner H, Castellsague X, Chen C, Curado MP, Curioni OA, Dal Maso L, Daudt AW, de Gois Filho JF, D'Souza G, Edefonti V, Fabianova E, Fernandez L, Franceschi S, Gillison M, Hayes RB, Healy CM, Herrero R, Holcatova I, Jayaprakash V, Kelsey K, Kjaerheim K, Koifman S, La Vecchia C, Lagiou P, Lazarus P, Levi F, Lissowska J, Luce D, Macfarlane TV, Mates D, Matos E, McClean M, Menezes AM, Menvielle G, Merletti F, Morgenstern H, Moysich K, Müller H, Muscat J, Olshan AF, Purdue MP, Ramroth H, Richiardi L, Rudnai P, Schantz S, Schwartz SM, Shangina O, Simonato L, Smith E, Stucker I, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Thomson P, Vaughan TL, Wei Q, Winn DM, Wunsch-Filho V, Yu GP, Zhang ZF, Zheng T, Znaor A, Boffetta P, Chuang SC, Ghodrat M, Amy Lee YC, Hashibe M, Brennan P. 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

32. Edefonti V, Hashibe M, Ambrogi F, Parpinel M, Bravi F, Talamini R, Levi F, Yu G, Morgenstern H, Kelsey K, McClean M, Schantz S, Zhang Z, Chuang S, Boffetta P, La Vecchia C, Decarli A. Nutrient-based dietary patterns and the risk of head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. *Ann Oncol.* 2012;23(7):1869-80.

33. Arnold M, Leitzmann M, Freisling H, Bray F, Romieu I, Renehan A, Soerjomataram I. Obesity and cancer: An update of the global impact. *Cancer Epidemiol.* 2016;41:8-15.

34. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, Zaridze D, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Schwartz SM, Rudnai P, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, Matos E, Bucur A, Levi F, Lazarus P, La Vecchia C, Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Wunsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Chen C, Castellsague X,

Benhamou S, Boffetta P, Brennan P, Hashibe M. 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.

35. Winn DM, Lee YC, Hashibe M, Boffetta P; INHANCE consortium. The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer. *Oral Dis*. 2015;21(6):685-93.

36. Negri E, Boffetta P, Berthiller J, Castellsague X, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, Lazarus P, Lence JJ, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Shangina O, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Lissowska J, Zhang ZF, Ferro G, Brennan P, La Vecchia C, Hashibe M. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Int J Cancer*. 2009;124(2):394-401.

37. Toporcov TN, Znaor A, Zhang ZF, Yu GP, Winn DM, Wei Q, Vilensky M, Vaughan T, Thomson P, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Smith E, Shangina O, Schwartz SM, Schantz S, Rudnai P, Richiardi L, Ramroth H, Purdue MP, Olshan AF, Eluf-Neto J, Muscat J, Moyses RA, Morgenstern H, Menezes A, McClean M, Matsuo K, Mates D, Macfarlane TV, Lissowska J, Levi F, Lazarus P, La Vecchia C, Lagiou P, Koifman S, Kjaerheim K, Kelsey K, Holcatova I, Herrero R, Healy C, Hayes RB, Franceschi S, Fernandez L, Fabianova E, Daudt AW, Curioni OA, Maso LD, Curado MP, Conway DI, Chen C, Castellsague X, Canova C, Cadoni G, Brennan P, Boccia S, Antunes JL, Ahrens W, Agudo A, Boffetta P, Hashibe M, Lee YC, Filho VW. 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

38. Ahrens W, Pohlbeln H, Foraita R, Nelis M, Lagiou P, Lagiou A, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane TV, Macfarlane GJ, Lee YC, Talamini R, Barzan L, Canova C, Simonato L, Thomson P, McKinney PA, McMahan AD, Znaor A, Healy CM, McCartan BE, Metspalu A, Marron M, Hashibe M, Conway DI, Brennan P. Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: the ARCAGE study. *Oral Oncol*. 2014;50(6):616-25

39. Hashim D, Sartori S, Brennan P, Curado MP, Wünsch-Filho V, Divaris K, Olshan AF, Zevallos JP, Winn DM, Franceschi S, Castellsagué X, Lissowska J, Rudnai P, Matsuo K, Morgenstern H, Chen C, Vaughan TL, Hofmann JN, D'Souza G, Haddad RI, Wu H, Lee YC, Hashibe M, Vecchia CL, Boffetta P. The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Ann Oncol*. 2016;27(8):1619-25.

40. Boffetta P, Hayes RB, Sartori S, Lee YC, Muscat J, Olshan A, Winn DM, Castellsagué X, Zhang ZF, Morgenstern H, Chen C, Schwartz SM, Vaughan TL, Wunsch-Filho V, Purdue M, Koifman S, Curado MP, Vilensky M, Gillison M, Fernandez L, Menezes A, Daudt AW, Schantz S, Yu G, D'Souza G, Haddad RI, La Vecchia C, Hashibe M. Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium. *Eur J Cancer Prev*. 2016;25(4):344-8.

41. Gandini S, Negri E, Boffetta P, La Vecchia C, Boyle P. Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies. *Ann Agric Environ Med*. 2012;19(2):173-80.

42. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 2015;33(29):3235-42.

43. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-56.
44. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, Graubard BI, Chaturvedi AK. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA*. 2012;307(7):693-703.
45. Human Papilloma Virus (HPV) Oral Prevalence in Scotland (HOPSCOTCH): A Feasibility Study in Dental Settings. Conway DI, Robertson C, Gray H, Young L, McDaid LM, Winter AJ, Campbell C, Pan J, Kavanagh K, Kean S, Bhatia R, Cubie H, Clarkson JE, Bagg J, Pollock KG, Cuschieri K. *PLoS One*. 2016 Nov 18;11(11):e0165847.
46. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, Schwartz SM, Purdue MP, Pilarska A, Eluf-Neto J, Menezes A, McClean MD, Matos E, Koifman S, Kelsey KT, Herrero R, Hayes RB, Franceschi S, Wünsch-Filho V, Fernández L, Daudt AW, Curado MP, Chen C, Castellsagué X, Ferro G, Brennan P, Boffetta P, Hashibe M. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol*. 2010;39(1):166-81.
47. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 2015;33(29):3235-42.
48. Mehanna H, Beech T, Nicholson T, et al. The prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer: Systematic review and meta-analysis of trends by time and region. *Head Neck*. 2013;35:747-755.
49. Anantharaman D, Abedi-Ardekani B, Beachler DC, Gheit T, Olshan AF, Wisniewski K, Wunsch-Filho V, Toporcov TN, Tajara EH, Levi JE, Moyses RA, Boccia S, Cadoni G, Rindi G, Ahrens W, Merletti F, Conway DI, Wright S, Carreira C, Renard H, Chopard P, McKay-Chopin S, Scelo G, Tommasino M, Brennan P, D'Souza G. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. *Int J Cancer*. 2017;140(9):1968-197.
50. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, Clifford GM. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*. 2007;121(3):621-32.
51. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 2015;33(29):3235-42.

Table 1 Oral cancer definitions used in routine Cancer Registry publications in the 4 countries of the UK

Oral Cancer Subsite (ICD code)	England	N.Ireland	Scotland		Wales	Proposed Standardised Definition
External lip (C00.0 - C00.2)	L OC P	L OC P	X		OC OP	X
Lip (C00.3 - C00.9)	L OC P	L OC P	OC		OC OP	OC
Base of tongue, NOS (C01.0 - C1.09)	L OC P	L OC P	OP	OC	OC OP	OP
Dorsal surface of tongue, NOS (C02.0 - C02.3)	L OC P	L OC P	OC		OC OP	OC
Lingual tonsil (C02.4)	L OC P	L OC P	OC		OC OP	OP
Overlapping lesion of tongue, or tongue NOS (C02.8 - C02.9)	L OC P	L OC P	OC		OC OP	OC
Gum (C03)	L OC P	L OC P	OC		OC OP	OC
Floor of mouth (C04)	L OC P	L OC P	OC		OC OP	OC
Soft palate (C05.1)	L OC P	L OC P	OC	OC	OC OP	OC
Uvula (C05.2)	L OC P	L OC P	OC	OC	OC OP	OC
Overlapping lesion of palate or palate NOS (C05.8)	L OC P	L OC P	OC	OC	OC OP	OC
Cheek mucosa (C06.0)	L OC P	L OC P	OC		OC OP	OC
Overlapping lesion of other and unspecified mouth (C06.8- C06.9)	L OC P	L OC P	OC		OC OP	OC
Mouth, NOS (C06.9)	L OC P	L OC P	OC		OC OP	OC
Salivary glands and parotid gland (C07 - C08)	L OC P	L OC P	X		X	X
Tonsil (C09)	L OC P	L OC P	OC		OC OP	OP
Anterior surface of epiglottis (C10.1)	L OC P	L OC P	OC		OC OP	OP
Lateral wall of oropharynx (C10.2)	L OC P	L OC P	OC		OC OP	OP
Nasopharynx (C11)	L OC P	L OC P	X		X	X
Pyriform sinus (C12.9)	L OC P	L OC P	X		X	X
Hypopharynx (C13)	L OC P	L OC P	X		X	X
Pharynx NOS (C14.0)	L OC P	L OC P	X		X	OP
Waldeyer's ring (C14.2)	L OC P	L OC P	X		X	OP

ICD : International Classification of Diseases;
NOS : Not Otherwise Specified
L OC P : Lip Oral Cavity Pharynx cancer
OC : Oral Cavity cancer
OP : Oropharyngeal cancer
OC OP : Oral Cavity and Oropharyngeal cancer (combined)
OPC: Oropharyngeal Cancer
X : Excluded

Table 2 Cancer Registry data from 4 UK countries showing oral cavity cancer and oropharyngeal cancer numbers (n) and (European) Age-Standardised incidence rates per 100,000 person-years by gender

Country / gender	OCC Incidence rate (n)	OPC Incidence rate (n)	Year - most recently available data
England Females	4.8 per 100,000 (1309)	2.7 per 100,000 (712)	2016
Males	7.3 per 100,000 (1779)	9.1 per 100,000 (2265)	
N.Ireland Females	3.9 per 100,000 (34)	2.1 per 100,000 (18)	2016
Males	5.9 per 100,000 (46)	6.8 per 100,000 (55)	
Scotland Females	5.6 per 100,000 (160)	2.7 per 100,000 (77)	2016
Males	10.0 per 100,000 (240)	9.7 per 100,000 (247)	
Wales Females	3.7 per 100,000 (64)	2.9 per 100,000 (48)	2015
Males	7.4 per 100,000 (112)	10.5 per 100,000 (159)	

OCC : Oral Cavity Cancer

OPC : Oropharyngeal Cancer

Figure 1 Trends in (European) Age-Standardised incidence rates (EASRs) of oral cavity cancer (OCC) and oropharyngeal cancer (OPC), males and females combined, for England, N.Ireland, and Scotland (2000-2016) and Wales (2000-2015), with total number of cases in period (n).

