

# Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors

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## Key points

Head and neck cancer incidence is increasing and is projected to continue to rise, largely driven by increases in oropharyngeal cancer.

Mortality rates have started to increase within the last decade, reflecting a rising incidence and static survival rates.

Major risk factors that are associated with the risk of head and neck cancer are tobacco smoking and tobacco used in combination with alcohol consumption. Human papillomavirus is an additional major risk factor for oropharyngeal cancer. Cancers of the head and neck are clearly socioeconomically patterned but this socioeconomic risk is not entirely explained by smoking and alcohol behaviours.

## Abstract

**Introduction** Head and neck cancer appears to be increasing in incidence, with potential changes in aetiology proposed. This paper aims to provide a narrative overview of the epidemiological literature to describe the disease burden and trends in terms of incidence and mortality both in the UK and globally and to review the evidence on current risk factors.

**Methods** A search was performed on multiple databases (PubMed and Epistemonikos), applying filters to identify systematic reviews and meta-analyses which investigated head and neck cancer incidence, mortality and risk factors. International and UK cancer registries and sources were searched for incidence and mortality data.

**Results** Multiple definitions of head and neck cancer are employed in epidemiology. Globally, incidence rates have increased in recent decades, largely driven by oropharyngeal cancer. Mortality rates over the last decade have also started to rise, reflecting the disease incidence and static survival rates. Major risk factors include tobacco smoking alone and in combination with alcohol consumption, betel chewing (particularly in Southeast Asian populations) and the human papillomavirus in oropharyngeal cancer.

**Conclusions** These epidemiological data can inform clinical and preventive service planning for head and neck cancer.

## Introduction

Head and neck cancer (HNC) is the seventh most common cancer globally, accounting for more than 660,000 new cases and 325,000 deaths annually.<sup>1,2</sup> There appears to be an increasing incidence of this disease, with

potential changes in aetiology proposed given the decline of smoking, particularly in developed countries.<sup>3</sup> Epidemiology is both descriptive – describing the burden and trends of disease – and analytical – identifying risk factors. This paper aims to provide a narrative overview of the epidemiological literature, to describe the disease burden and trends in terms of incidence and mortality both in the UK and globally, and to review the evidence on current risk factors.

## Definitions of head and neck cancer

Approximately 90% of HNCs are squamous cell carcinoma, which arise from the epithelial lining of the oral cavity, pharynx and larynx.<sup>1</sup> There are many types of cancers affecting the head and neck, which are discretely categorised on the basis of their anatomical location using the International Classification of Diseases (ICD-10) from the World Health

Organisation (WHO).<sup>2</sup> A list of each subsite (including the individual ICD-10 code) is outlined in Table 1. Due to the differences in the presenting symptoms, treatment regimens and prognosis at each anatomical subsite, these are considered as separate entities.<sup>3</sup> A comprehensive review carried out by Kaste *et al.*<sup>4</sup> outlined the several differences in the contributory elements to the definition of HNC from major institutions such as the National Cancer Institute, International Agency for Research on Cancer (IARC) and Cancer Research UK (CRUK). The most important difference between these definitions is the inclusion of the oesophagus under the definition set out by CRUK. Several epidemiological studies include this subsite as a form of HNC, or under an overarching upper aerodigestive tract cancer definition. While some clinical definitions also include thyroid cancers, these are usually excluded in epidemiological studies. Due to variations

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in definition, it is important anatomical subsites are clearly specified when reviewing the literature (ideally by using corresponding ICD codes. See Table 1).

## Methods

A search was performed on multiple databases (PubMed and Epistemonikos), applying filters to identify systematic reviews and meta-analyses which investigated HNC incidence, mortality and risk factors, using the IARC definition and corresponding ICD-10 codes described in Table 1. International and UK cancer registries and sources were searched for incidence and mortality data.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium has performed the largest pooled analyses using individual level data from studies from around the world, with the overall aim to better understand the aetiology and risks associated with HNC. These analyses have the advantage of harmonising definitions of disease outcomes, definition of risk factors and the ability to obtain robust estimates, adjusting for confounding and other potential effect modifiers. The INHANCE methods have been described in detail elsewhere and further information is available on the INHANCE consortium website, hosted by the University of Utah.<sup>5</sup> Briefly, there are 35 pooled case-control studies with a total of over 25,700 HNC cases and 37,100 controls. Included studies have minimal criteria on sample size and data availability and are usually multicentre studies, with 15 from North America, 13 from Europe, 3 from Latin America, 3 from Asia and 1 from multiple continents. There are important limitations of these INHANCE analyses which have been acknowledged, mainly related to inherent drawbacks in the original case-control source studies and despite the greatest global burden of disease being in Southeast Asia, there are few studies included from this region (with no studies from India and Bangladesh) or from Africa. INHANCE have published over 45 peer-reviewed papers, including analyses on the following HNC risks: tobacco smoking, alcohol drinking, diet/anthropometrics, oral health/hygiene, medical history, sexual history, genetics, occupation and socioeconomics. All of the INHANCE results to date have been summarised in two overview papers<sup>6,7</sup> and key findings will be summarised here.

**Table 1 Anatomical subsites of the head and neck based on ICD-10**

Main site	ICD-10 code
Malignant neoplasms of lip	C00
Malignant neoplasm of base of tongue	C01
Malignant neoplasm of other and unspecified part of tongue	C02
Malignant neoplasm of gum	C03
Malignant neoplasm of floor of mouth	C04
Malignant neoplasm of palate	C05
Malignant neoplasm of other and unspecified parts of mouth	C06
Malignant neoplasm of parotid gland	C07
Malignant neoplasm of other and unspecified major salivary glands	C08
Malignant neoplasm of tonsil	C09
Malignant neoplasm of oropharynx	C10
Malignant neoplasm of nasopharynx	C11
Malignant neoplasm of piriform sinus	C12
Malignant neoplasm of hypopharynx	C13
Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	C14
Malignant neoplasm of nasal cavity and middle ear	C30
Malignant neoplasm of accessory sinuses	C31
Malignant neoplasm of larynx	C32
Malignant neoplasm of other and ill-defined sites	C76

## Results

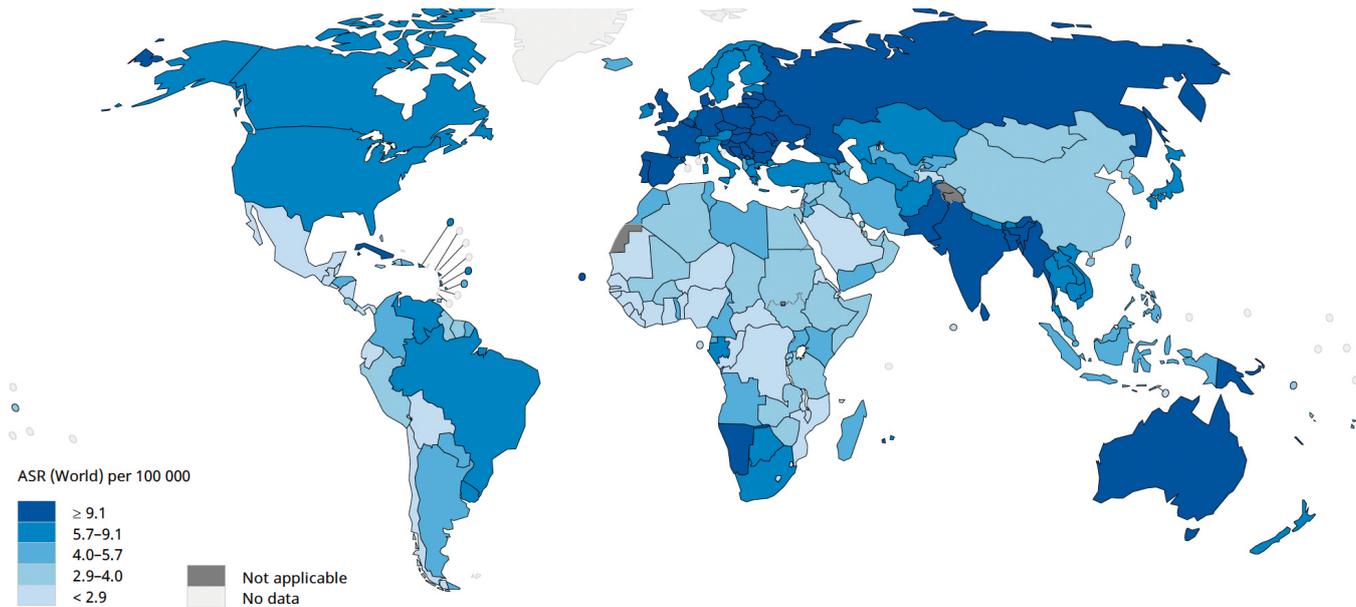
Understanding the cancer burden is key to developing, managing and improving services for disease prevention and treatment. Here, peer-reviewed literature and cancer registry data are used to describe the latest incidence, mortality and risk factor trends for HNC.

### Global incidence trends in head and neck cancer

The overall incidence of HNC continues to rise, with a predicted 30% increase annually by 2030.<sup>12</sup> This increase has been recorded across both developed and developing countries.<sup>6</sup> Southeast Asia and Asia-Pacific regions have a particularly high incidence of oral cancer, associated with chewing of areca nut (betel quid), with or without tobacco.<sup>8</sup> Oral cancer is therefore expected to rise within Southeast Asia, in line with population growth.<sup>9</sup> The increasing incidence rates of HNC in the USA and Europe have been attributed to a rise in oropharyngeal cancer, linked to human papillomavirus (HPV) infection<sup>10,11</sup> (Fig. 1).

Recent studies have demonstrated a global trend towards increasing incidence in HPV-related subsites, accompanied by decreasing incidence in HPV-unrelated subsites in countries such as the USA, Canada, Hong Kong and Korea.<sup>12</sup> Over the next 20 years, it is expected that the majority of HNC will be HPV-positive, with projections that in some European countries, such as the UK, oropharyngeal cancer incidence will overtake cancer of the oral cavity.<sup>13</sup>

Worldwide, laryngeal cancers have increased by 23% over the past ten years. However, age-adjusted rates for new laryngeal cancer cases have been falling in countries with a higher sociodemographic index, again reflecting changes in smoking and alcohol drinking behaviour.<sup>14</sup> Overall, HNC affects men two to four times more than women, with estimates reaching over 20 per 100,000.<sup>15</sup> For men in developing countries, lip and oral cavity cancer is the second most common cancer (10 per 100,000). Male incidence of oral and oropharyngeal cancer has declined over recent years in France (-12.6%), Slovakia (-4.0%), Spain (-10.8%), Brazil (-26.7%) and Hong



**Fig. 1** Global age-standardised incidence rates of head and neck cancer. Reprinted from International Agency For Research On Cancer, 'Cancer today – Data visualization tools for exploring the global cancer burden in 2020', Copyright 2022, <http://gco.iarc.fr/today> (accessed August 2021). The map was generated using the GLOBOCAN website mapping tool (<https://gco.iarc.fr/today/online-analysis-map>) by selecting the 'lip, oral cavity', 'oropharynx', 'hypopharynx' and 'larynx' cancer sites. Estimated age-standardised rates of head and neck cancer incidence worldwide are shown for both sexes

Kong (-10.5%), while it increased in the UK (18.8%), Australia (8.7%), Japan (21.3%) and in the US (3.7%).<sup>16</sup> The risk of HNC increases with age across populations, with the majority of cases diagnosed in those over 50 years.<sup>17</sup> Similarly, there has been a rise in cases among younger women, predominantly in European countries, which may be explained by sex-specific patterns of tobacco and alcohol consumption.<sup>15,16</sup>

### The incidence of head and neck cancer in the UK

HNC rates are also rising in the UK. Studies have shown that from 1995–2011, oropharyngeal cancer incidence increased by 7.3% for men and 6.5% for women in England, with oral cavity cancer showing a 2.8% rise in men and 3.0% rise in women over the same period.<sup>18</sup> Incidence rates are highest in Scotland, where oropharyngeal cases were shown to have increased by 85% from 2001–2012.<sup>19</sup> These increasing rates are continuing to rise according to the most-recent UK Cancer Registry data, which show a 34% increase in total cases diagnosed across the four nations from 2011–2018. The burden of HNC is strongly socioeconomically patterned, with the highest rates being observed among people living in the most socioeconomically deprived

communities.<sup>19</sup> These Cancer Registry data also demonstrate that the majority of HNCs are diagnosed at an advanced stage.<sup>20</sup> For the UK as a whole, 58.5% of HNCs are diagnosed at stage III or IV, in accordance with the seventh edition of the TNM (tumor-node-metastasis) Atlas.<sup>21</sup> Overall, stage IV is the most common stage at diagnosis for oral and oropharyngeal cancer, whereas stage I is most common for laryngeal cancer.<sup>20</sup>

### Mortality and survival trends in head and neck cancer

In 2018, there were 4,078 deaths attributable to HNC in the UK, accounting for approximately 2% of all cancer deaths annually.<sup>22</sup> There is apparent variation in national HNC mortality rates (European age-standardised rates [ASR]; ASR per 100,000 population) between nations of the UK. Scotland (ASR 8.7) and Northern Ireland (ASR 8.4) had worse outcomes than England (ASR 6.2) and Wales (ASR 5.8). Age-specific mortality that is attributable to HNC rises from the fifth decade onwards, towards a peak mortality in those over the age of 90 years; a phenomenon most pronounced in men. In the UK, since the early 1970s, the combined HNC mortality for men and women has fallen by 11% overall (1971: ASR 7.3; 2018: ASR 6.5); however, the last decade has seen a

gradual rise in mortality rates from a low in 2006 (ASR 5.6), possibly reflecting the changes in disease incidence and static survival rates.<sup>22</sup>

Globally, five-year survival for HNC averages at 50% of cases, with hypopharynx experiencing the worst outcomes.<sup>17</sup> A recent analysis of WHO death certification data showed that there has been little change in mortality generally over recent decades for both men and women.<sup>16</sup> Survival rates can vary significantly across geographical location, tumour site and, most prominently, stage at diagnosis. Those diagnosed with advanced disease have notably poorer outcomes than those with early disease. Analysis of a large cohort in the USA showed that HPV-positive cancers had a better chance of long-term survival compared to non-HPV cancers, confirming previous studies also suggesting this phenomenon.<sup>23</sup> There are several studies exploring the factors associated with relatively poor survival among people with HNC, including Head and Neck 5000<sup>24</sup> and the recently established HEADSpAcE.<sup>25</sup> Analysis of routinely collected data and from large prospective cohort studies, such as Head and Neck 5000, have demonstrated that significant socioeconomic inequalities in HNC survival exist in the UK, not all of which can be explained by behavioural factors.<sup>26</sup>

Table 2 Risk factors for head and neck cancer (cont. on page 791)

Risk factor for HNC (unless specified)	Level of exposure	Range of OR or population attributable risk (PAR) (95% CI)	Reference
Tobacco smoking in never-alcohol drinkers	Cigarette smoking vs never	OR 2.13 (1.53, 2.98)	Hashibe <i>et al.</i> , 2007 <sup>29</sup>
Tobacco smoking by type of product	Cigarettes (+ dose response)	OR 3.46 (3.24, 3.70)	Wyss <i>et al.</i> , 2013 <sup>47</sup>
	Cigars (+ dose response)	OR 2.54 (1.93, 3.34)	
	Pipes (+ dose response)	OR 2.08 (1.55, 2.81)	
Passive smoking	Home vs never	OR 1.60 (1.12, 2.28)	Lee <i>et al.</i> , 2008 <sup>48</sup>
	Work vs never	OR 1.55 (1.04, 2.30)	
Smokeless tobacco	Snuff vs never	OR 1.71 (1.08, 2.70)	Wyss <i>et al.</i> , 2016 <sup>49</sup>
	Chewing tobacco vs never	OR 1.20 (0.81, 1.77)	
Smokeless tobacco (oral cancer)	Gutka vs never	OR 8.67 (3.59, 20.93)*	Asthana <i>et al.</i> , 2019 <sup>50</sup>
	Pan/areca nut/lime/betel liquid	OR 7.18 (5.48, 9.41)*	
	Manipuri vs never	OR 3.32 (1.32, 8.36)*	
Alcohol in never users of tobacco	Three or more drinks per day vs never	OR 2.04 (1.29, 3.21)	Hashibe <i>et al.</i> , 2007 <sup>29</sup>
Alcohol beverage type	Wine >30 drinks/week vs never	OR 6.3 (2.2, 18.6)	Purdue <i>et al.</i> , 2009 <sup>51</sup>
	Beer >30 drinks/week vs never	OR 5.4 (3.1, 9.2)	
	Liquor >30 drinks/week vs never	OR 3.6 (2.2, 5.8)	
Combined effects of alcohol and drinking	Never users	OR 1.00 (Ref.)	Hashibe <i>et al.</i> , 2009 <sup>27</sup>
	Tobacco alone	OR 2.37 (1.66, 3.39)	
		PAR 33.0 (42.6, 25.9)	
	Alcohol alone	OR 1.06 (0.88, 1.28)	
		PAR 4.0 (1.5, 5.3)	
	Tobacco and alcohol joint effect	OR 5.73 (3.62, 9.06)	
PAR 34.9 (17.2, 48.0)			
Racial differences in alcohol risk	Never to <20 years	OR 1.00 (Ref.)	Voltzke <i>et al.</i> , 2018 <sup>52</sup>
	≥20 to 30 years	White 1.62 (1.36, 1.94)	
		Black 2.01 (1.07, 3.79)	
	≤30 years	White 1.38 (1.20, 1.58)	
Black 2.20 (1.38, 3.50)			
Marijuana	Ever use vs never	OR 0.88 (0.67, 1.16)	Berthiller <i>et al.</i> , 2009 <sup>53</sup>
Diet – consumption of food items/types	High fruit vs low	OR 0.52 (0.43, 0.62)	Chuang <i>et al.</i> , 2012 <sup>31</sup>
	High vegetables vs low	OR 0.66 (0.49, 0.90)	
	High red meat vs low	OR 1.40 (1.13, 1.74)	
	High processed meat vs low	OR 1.37 (1.14, 1.65)	
	Low (<18.5) vs normal	OR 1.69 (1.10, 2.50)	
BMI (larynx)	Overweight/obese vs normal	OR 0.60 (0.3, 1.3)	Lubin <i>et al.</i> , 2011 <sup>28</sup>
Recreational physical activity	Moderate vs none/low	OR 0.78 (0.66, 0.91)	Nicolotti <i>et al.</i> , 2011 <sup>32</sup>
Diabetes	History of diabetes vs no history	OR 1.09 (0.95, 1.24)	Stott-Miller <i>et al.</i> , 2012 <sup>54</sup>
Sexual behaviours (oropharyngeal cancer)	≥6 lifetime sexual partners vs 1	OR 1.25 (1.01, 1.54)	Heck <i>et al.</i> , 2010 <sup>35</sup>
	≥4 lifetime oral sex partners vs 0–1	OR 2.25 (1.42, 3.58)	

Table 2 Risk factors for head and neck cancer (cont. from page 790)

Risk factor for HNC (unless specified)	Level of exposure	Range of OR or population attributable risk (PAR) (95% CI)	Reference
HPV	Oropharynx tonsil HPV16 vs negative	OR 15.1 (6.8, 33.7)	Hobbs <i>et al.</i> , 2006 <sup>34</sup>
	Oropharynx other HPV16 vs negative	OR 4.3 (2.1, 8.9)	
	Oral cavity HPV16 vs negative	OR 2.0 (1.2, 3.4)	
	Larynx HPV16 vs negative	OR 2.0 (1.0, 4.2)	
Oral health/hygiene	<5 missing teeth vs ≥missing teeth	OR 0.78 (0.74, 0.82)	Hashim <i>et al.</i> , 2016 <sup>33</sup>
	No gum disease vs gum disease	OR 0.94 (0.89, 0.99)	
	Annual dentist vs <once a year	OR 0.82 (0.78, 0.87)	
	Daily toothbrushing vs <once a day	OR 0.83 (0.79, 0.88)	
Family history	First degree relative with HNC	OR 1.7 (1.2, 2.3)	Negri <i>et al.</i> , 2009 <sup>55</sup>
Increased duration in occupations	Cooks	OR 1.36 (1.09, 1.68)	Khetan <i>et al.</i> , 2019 <sup>56</sup>
	Cleaners	OR 1.38 (1.13, 1.69)	
	Painters	OR 1.82 (1.42, 2.35)	
Socioeconomic factors	Low vs high education	OR 2.50 (2.02, 3.09)	Conway <i>et al.</i> , 2015 <sup>57</sup>
	Low vs high income	OR 2.44 (1.62, 3.67)	
	Low vs high occupational socioeconomic status	OR 1.88 (1.64, 2.17)	Conway <i>et al.</i> , 2021 <sup>58</sup>

Key:  
\* = Risk estimates adjusted for confounders unless indicated

### Risk factors associated with head and neck cancer

Tobacco smoking and alcohol drinking behaviours, separately and in combination, are major risk factors for HNC, accounting for 72% of cases when used in combination.<sup>27</sup> However, this was slightly less for oral cavity cancer (64%) and slightly more for laryngeal cancer (89%) and much lower for women and among younger age groups.<sup>27</sup> Risk factors are generally similar across subsites of the head and neck, although the magnitude of risk associated with particular risks may vary, for example tobacco smoking risks are greatest for laryngeal cancer and alcohol for oral cavity and oropharyngeal cancer.<sup>28</sup> In a large pooled analysis, Hashibe *et al.* investigated the independent effects of tobacco smoking in never alcohol drinkers and found an increased odds risk (odds ratio [OR] 2.13; 95% confidence interval [CI] = 1.53, 2.98) of HNC,<sup>29</sup> with a further study examining interaction suggesting a multiplicative joint effect of tobacco and alcohol (Table 2).<sup>27</sup> More recent studies have demonstrated evidence for an independent causal effect of alcohol consumption in oral and oropharyngeal cancer when controlling for smoking, suggesting the role of alcohol may have been previously underestimated.<sup>30</sup> Dietary<sup>31</sup> and other lifestyle factors, such as physical activity<sup>32</sup> and oral

hygiene,<sup>33</sup> are currently considered relatively minor risk factors (Table 2).

High-risk HPV, especially HPV type 16, is a major risk factor for oropharyngeal cancer,<sup>34</sup> thought to be sexually transmitted via oro-genital contact (Table 2).<sup>11</sup> Heck *et al.* demonstrated that >4 oral sex partners greatly increased the risk of oropharyngeal cancer (OR 2.25; 95% CI = 1.42, 3.58).<sup>35</sup> HPV has been associated with over 50% of cases in the UK<sup>36</sup> but there is wide global variation<sup>37,38</sup> and smoking has been shown to interact with HPV and increase risk.<sup>39</sup> Those who have HPV-negative oropharyngeal tumours are more likely to be heavier smokers, with an increased risk of death for every additional pack-year, compared to HPV-positive cases.<sup>40</sup> HPV-positive cases present with an almost 60% reduction in the risk of mortality after adjustment for prognostic factors, such as age, ethnicity, staging, smoking status and treatment regime.<sup>40</sup> This could be because people with HPV-positive disease are slightly younger, with less comorbidity, or that they have enhanced anti-tumour immunity. It has also been postulated that HPV-positive tumours harbour fewer genetic mutations or may be more radiosensitive (with an intact apoptotic response), associated with an overall better response to radiotherapy.<sup>41</sup>

Genetic susceptibility to HNC has been investigated,<sup>42</sup> with the largest genome-wide association study (GWAS) of oral and pharyngeal cancer (6,034 cases and 6,585 controls from Europe, North America and South America), detecting seven unique loci.<sup>43</sup> Of note, oropharyngeal subgroup analysis revealed a strong protective association at chromosome 6p21.32 (lead variant rs3828805, mapping to HLA-DQB1) within the human leucocyte antigen (HLA) Class II region. A more recent GWAS in an independent dataset supports these findings.<sup>44</sup> Follow-up is required to determine the extent and specificity of the HLA effect in HPV-positive tumours, which could help explain why some individuals are more at risk of developing the disease following HPV infection. Genetic variants in alcohol-metabolising genes, such as alcohol dehydrogenase, have also been associated with increased HNC risk.<sup>45,46</sup>

Tobacco smoking and alcohol consumption are established risk factors for HNC.<sup>27</sup> However, a detailed understanding of these somewhat complex behaviours in terms of precise estimates of risk, understanding the joint tobacco-alcohol effect, the dose-response, and the benefits of quitting both smoking and alcohol, remain less well established. The role of other potential risk

factors, such as smokeless tobacco, betel chewing, diet, oral health and hygiene and hormonal, genetic, occupational and socioeconomic status in HNC risk, are not well understood. A major challenge in elucidating detailed information from the epidemiological literature is the heterogeneity in study designs and populations often being from small observational studies. The dominant effect of tobacco smoking and alcohol drinking also overshadow other potential risk factors. While a number of the systematic reviews and meta-analyses presented aggregated estimates from epidemiological studies, these were usually focused on specific risk factors and/or subsites of the head and neck. Furthermore, these studies often encountered difficulties harmonising data from observational studies and adjusting for appropriate confounding factors. Observational studies also suffer from other methodological issues, such as reverse causality. Given that multiple HNC definitions were used, this adds complexity to the interpretation of results.

## Conclusions

Both globally and in the UK, HNC incidence has increased over recent decades and is projected to continue to rise, largely driven by increases in oropharyngeal cancer. Mortality rates in the UK have started to increase within the last decade, reflecting rising incidence and static survival rates. In summary, the major risk factors that are associated with the risk of HNC are tobacco smoking and tobacco used in combination with alcohol consumption. Betel chewing is an established risk in Southeast Asian countries and in people from Southeast Asian minority ethnic groups. HPV is an additional major risk factor for oropharyngeal cancer. Cancers of the head and neck are clearly socioeconomically patterned, with those from the poorest backgrounds having the greatest burden, but this socioeconomic risk is not entirely explained by smoking and alcohol behaviours. Moreover, HNCs are higher among men than women (although the trends are diverging) and more common in older age-groups, although oropharyngeal cancer incidence peaks around ten years younger, at around 60–65 years.

### Ethics declaration

The authors declare no conflicts of interest.

As this was a narrative review using existing literature, no ethical approval was required.

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### Author contributions

David I. Conway conceived the study and all authors (Mark Gormley, Grant Creaney, Andrew Schache, Kate Ingarfield and David I. Conway) carried out data curation and analysis. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors read and approved the final manuscript.

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