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An update on oral cavity cancer: epidemiological trends, prevention strategies and novel approaches in diagnosis and prognosis

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In the UK, the incidence of oral cavity cancer continues to rise, with an increase of around 60% over the past 10 years. Many patients still present with advanced disease, often resulting in locoregional recurrence and poor outcomes, which has not changed significantly for over four decades. Changes in aetiology may also be emerging, given the decline of smoking in developed countries. Therefore, new methods to better target prevention, improve screening and detect recurrence are needed. High-throughput 'omics' technologies appear promising for future individual-level diagnosis and prognosis. However, given this is a relatively rare cancer with significant intra-tumour heterogeneity and variation in patient response, reliable biomarkers have been difficult to elucidate. From a public health perspective, implementing these novel technologies into current services would require substantial practical, financial and ethical considerations. This may be difficult to justify and implement at present, therefore focus remains on early detection using new patient-led follow-up strategies. This paper reviews the latest evidence on epidemiological trends in oral cavity cancer to help identify at risk groups, population-based approaches for prevention, in addition to potential cutting-edge approaches in the diagnosis and prognosis of this disease.

Keywords: Epidemiology, Oral Cancer, Survival, Risk Factors, Squamous Cell Carcinoma, Mouth Neoplasms

Introduction

Head and neck cancer, which includes the oral cavity is the 7th most common cancer globally, accounting for more than 660,000 new cases and 325,000 deaths each year. In the UK, the overall incidence of oral cavity cancer continues to rise, with an increase of around 60% over the past 10 years (Cancer Research UK (CRUK), 2015; Warnakulasuriya, 2009). Globally, incidence and mortality remain higher among males, with 150,000 more cases and 70,000 more deaths worldwide reported in males compared to females. Despite this however, the data suggest an increasing trend in oral cavity cancer amongst women and a decreasing trend for men in Europe and the United States (Miranda-Filho and Bray, 2020; Sung *et al.*, 2021). The highest age-standardised incidence rates (per 100,000 person-years) for oral cavity cancer are in Melanesia, namely Papua New Guinea (males= 22.2; females= 11.9), South Central Asia (males= 13.3; females= 4.6)) and Eastern Europe (males= 9.2; females= 1.9) (Sung *et al.*, 2021).

Ninety percent of all malignant tumours that arise from the oral mucosal epithelium are squamous cell carcinomas (OSCC) (Vigneswaran and Williams, 2014). The definition of oral cancer often varies between studies, with many combining oral and oropharyngeal cancer subsites, although differences in the aetiology, management and response to treatment means they should be considered as distinct disease entities (Conway, 2018; Thomas *et al.*, 2018). Therefore, the term oral cancer in the context of this review will focus only on cancer of the oral cavity. In addition to registries, the use of International Classification of Diseases (ICD-10) codes C00-C06 (World Health Organization (WHO), 2016), has helped standardise the collection and curation of cancer data (Table 1). The highest risk sites include lateral border of the tongue and the floor of mouth.

Table 1. International Classification of Diseases (ICD-10) codes for oral cavity cancer.

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

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Risk factors for oral cavity cancer

In developed countries, OSCC rarely occurs in people who neither smoke nor consume alcohol (Pelucchi *et al*., 2006). Both smoking and alcohol are well-established as carcinogens, with sufficient evidence in OSCC, according to the International Agency for Research on Cancer (Cogliano *et al*., 2011). Tobacco use both on its own and jointly with alcohol increases the risk of OSCC (Figure 1) (Hashibe *et al*., 2009; Rothman and Keller, 1972). Ethanol is oxidised to acetaldehyde, which has a direct carcinogenic effect and moreover alcohol may act as a 'solvent' for tobacco carcinogens, which are thought to bathe high-risk sites such as the floor of mouth (Homann *et al*., 1997). More recently it has been suggested that alcohol alone has an independent effect on OSCC risk, which may have been underestimated in previous observational analyses (Gormley *et al*., 2020). Higher alcohol consumption (of more than 3 drinks per day) over only a few years also appears to increase risk (Conway, 2018).

Betel chewing, gutka and use of smokeless tobacco occur mostly in South Central Asian countries, where rates of OSCC continue to be some of the highest in the world (Figure 1) (Asthana *et al*., 2019; Miranda-Filho and Bray, 2020). Throughout India, Pakistan and Sri Lanka, tobacco is usually combined with areca nut wrapped with other ingredients in a betel leaf to form a quid which is chewed. Gutka is a combination of areca nut, slaked lime, paraffin, and catechu along with tobacco. In countries such as Papua New Guinea, the areca nut, betel inflorescence, or slaked lime are chewed without tobacco (Gupta and Warnakulasuriya, 2002; Thomas and MacLennan, 1992). One meta-analysis showed an increased risk of oral cancer with exposure to betel quid without tobacco in non-smokers (Thomas *et al*., 2007). However, tobacco smoking is still common across these populations, making it difficult to determine the independent effects of these agents (Figure 1).

Human papilloma virus (HPV), thought to be sexually transmitted (Heck *et al*., 2010; Hobbs *et al*., 2006), also increases OSCC risk (Figure 1). In developed countries such as the USA the proportion of oropharyngeal cancer attributed to HPV is 60–70% (Chaturvedi *et al*., 2013), whereas the aetiological fraction for oral sites is reported to be as low as 3% (Farsi *et al*., 2015; Gillison *et al*., 2015). Within the Head and Neck 5000 cancer study, the risk factors of those people with OSCC differed from those with laryngeal and oropharyngeal tumours. They were generally younger (43% <60 years old), more likely to be female (38%), less likely to smoke (25% never smokers) and no more likely to have performed oral sex (Thomas *et al*., 2018). Worryingly, these data suggest an emerging and distinct clinical entity of unknown aetiology.

Less well established risk factors as shown in Table 2 include, a family history of oral cavity cancer (Negri *et al*., 2009), lower body mass index (BMI) (Lubin *et al*., 2011), a diet lacking in fruit and vegetables (Chuang *et al*., 2009), type 2 diabetes (Tseng *et al*., 2014), poor oral

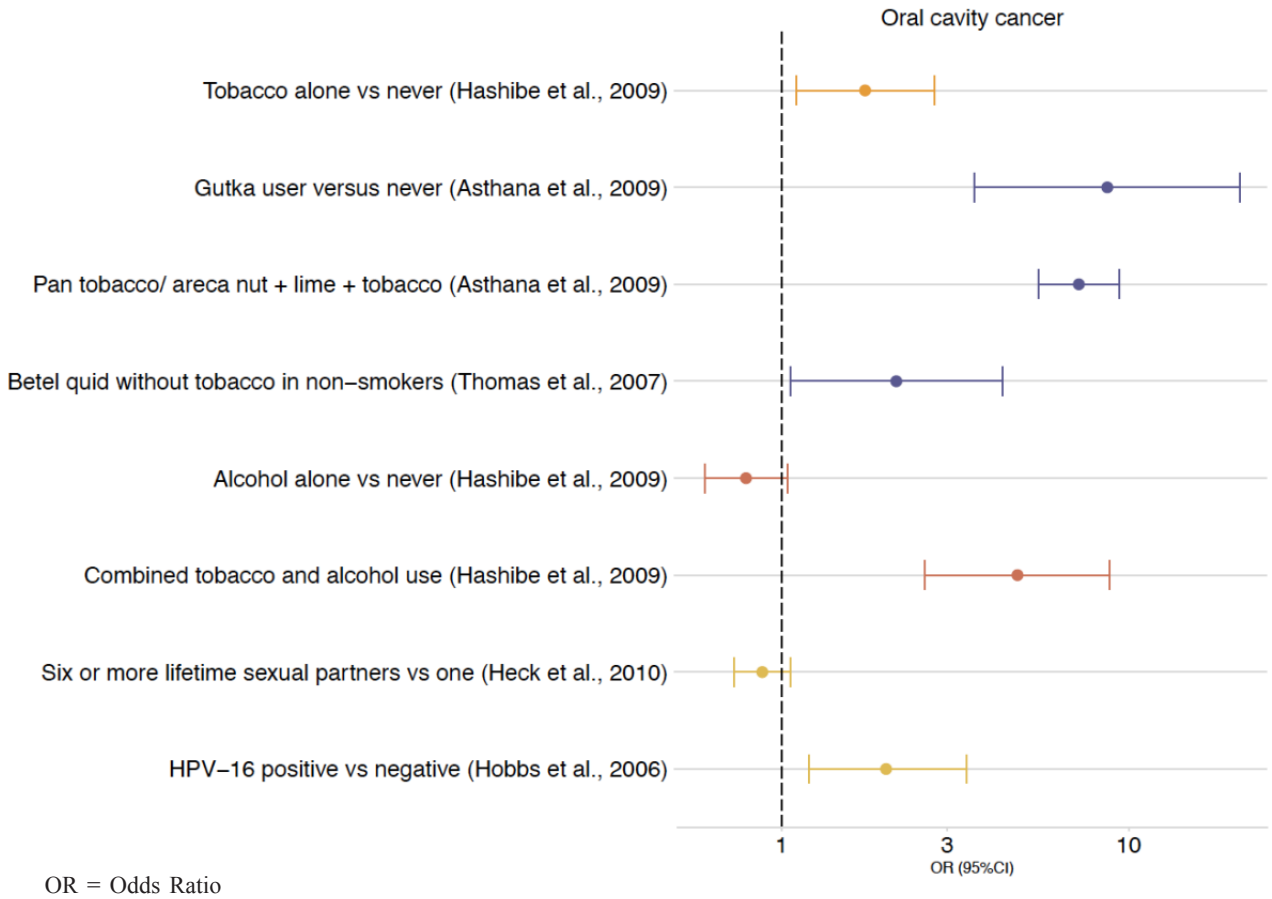

Figure 1. *Risk Factors for Oral Cancer*

Table 2. Less well-established risk factor associations for oral cavity cancer.

Risk factor	*Level of exposure*	*Odds risk (95% CI) for oral cancer*	*Reference*
Family history	Oral cavity cancer in first degree relatives	OR 1.53 (1.11, 2.11)	(Negri *et al*., 2009)
BMI	<18.5	OR 2.58 (2.00, 3.40)	(Lubin *et al*., 2011)
Diet	Vegetable intake (4^{th} vs 1^{st} quartile)	OR 0.69 (0.61, 0.79)	(Chuang *et al*., 2009)
	Fruit intake (4^{th} vs 1^{st} quartile)	OR 0.46 (0.38, 0.56)	
Type 2 Diabetes Mellitus	History of diabetes vs no diabetes	OR 1.74 (1.47, 2.06)	(Tseng *et al*., 2014)
Oral health / hygiene	<5 missing teeth vs ≥ missing teeth	OR 0.69 (0.64, 0.76)	(Hashim *et al*., 2016)
	No gum disease vs gum disease	OR 0.83 (0.77, 0.89)	
	Annual dentist vs < once a year	OR 0.82 (0.76, 0.89)	
	Daily toothbrushing vs <once a day	OR 0.81 (0.75, 0.88)	
Socioeconomic factors	Low educational attainment	OR 1.85 (1.60, 2.15)	(Conway *et al*., 2021)
	Low vs high income	OR 2.41 (1.59, 3.65)	
	Low vs high occupational SES	OR 1.84 (1.47, 2.31)	(Conway *et al*., 2021)

health (Hashim *et al.*, 2016), socio-economic status, lower educational attainment and occupation (Conway *et al.*, 2021). While the relationships here may be confounded by smoking and drinking behaviour, further research to establish the value of these potentially modifiable risk factors is required.

Strategies for prevention

Delay in OSCC diagnosis is often associated with increased disfigurement and poorer survival rates (Gómez *et al.*, 2009), dropping to 50% or below for advanced-stage 3 or 4 disease (Gigliotti *et al.*, 2019; Warnakulasuriya, 2009). Forty to sixty percent of head and neck cancer patients still present with advanced disease, a figure which has not decreased for over four decades, despite marginally higher survival rates (McGurk *et al.*, 2005). Cervical lymph node metastasis occurs in up to 40% of patients with OSCC, leading to loco-regional recurrence (Fan *et al.*, 2011). In response to the guidance for improving head and neck cancer outcomes in the UK, many providers have moved towards a centralised or 'hub and spoke' model, with higher numbers of patients being treated by a smaller number of specialised units (Stafford *et al.*, 2016).

Given the high recurrence and poor survival rates, OSCC is considered a major public health issue (Macpherson, 2018). Multiple population-based and individual-level approaches have been implemented in attempts to both prevent the disease and to diagnose OSCC earlier (Ford and Farah, 2013; Macpherson, 2018). The effects of such interventions are complex, with oral screening of high-risk groups appearing to be more effective in areas of high disease prevalence, compared to low (Sankaranarayanan *et al.*, 2005). Ford and Farah (2013) found that those in lower socioeconomic groups at increased risk of OSCC, are likely to be poor dental attenders, which further reduces the efficacy of this approach. Moreover, the COVID-19 pandemic has decreased access to general dental services, resulting in a decline in oral cancer referrals to secondary care and prolonged waiting times. A recent call has been made for long-term investment in public health programmes and transformation of the dental commissioning pathways targeted at those most in need (Stennett and Tsakos, 2022). Public awareness campaigns (such as e.g., Mouth Cancer Action Month) can be used to improve symptom recognition, promote self-examination and awareness of risk factors (Austoker *et al.*, 2009; Macpherson, 2018). Previous studies have suggested that while the association between smoking and OSCC is publicly recognised, more could be done to increase awareness of the risk of alcohol (Monteiro *et al.*, 2016; Posorski *et al.*, 2014). Smoking cessation and brief alcohol interventions can be performed chairside by dentists, however funding, time and training are often quoted as barriers that need to be addressed (McAuley *et al.*, 2011). Ongoing trials such as the ENHANCE-D (ENHANCing smoking cEssation interventions in Dentistry) study, will help evaluate the impact of primary care dental professionals providing smoking cessation interventions such as Nicotine Replacement Therapy (NRT) or e-cigarettes (Holliday, 2022). Better collaboration, education and training of the wider healthcare team is key and the UK General Dental Council advocates continual professional development in oral cancer. Further training requirements for primary medical practitioners could help ensure appropriate urgent referrals are made for both malignant and potentially malignant oral conditions (Rodgers *et al.*, 2007).

Novel approaches to establishing oral cavity cancer diagnosis and prognosis

The 'gold standard' approach for diagnosing OSCC is via clinical examination and a definitive incisional biopsy, sometimes with adjunctive panendoscopy, fine needle aspiration cytology, or imaging. Toluidine blue stain and chemiluminescence can aid diagnosis, but are

neither sensitive nor specific enough to be used alone (Kim *et al.*, 2021). Computed tomography (CT), positron emission tomography (PET) scans, ultrasound or magnetic resonance imaging (MRI) are often employed to investigate local or regional spread.

Oral carcinogenesis is a complex process, in which multiple genetic events occur to alter the normal functions of both oncogenes and tumour suppressor genes, resulting in increased cell proliferation, loss of cell cohesion and potential for metastasis (Williams, 2000). Given the significant intra-tumour heterogeneity (Weinstein *et al.*, 2013), differences in environmental exposures to carcinogens and variation in patients' response (possibly as a result of genetic predisposition, metabolic, or epigenetic factors), a precision medicine approach has been proposed (Garraway *et al.*, 2013; Sankar and Parker, 2017). With the evolution of high-throughput 'omics' technologies, researchers are now focusing on the development of new diagnostic and prognostic biomarkers for the disease. However, implementing these would clearly require substantial practical, financial and ethical considerations as we will discuss (D'Adamo *et al.*, 2021).

Changes in the genetic and epigenetic profile which may aid risk prediction and prognostication

Germline genetics refers to the genetic code inherited from parents and is found in every healthy cell in the body. Subtle variation in this genetic code, across populations, can alter anything from how quickly we metabolise alcohol to how quickly we feel hungry. The largest genome-wide association study (GWAS) of oral cavity cancer risk (n= 2,990 cases and n= 6,585 controls) set out to identify variations across the genome that relate to OSCC risk. The study identified two new regions on chromosome position 2p23.3 (rs6547741, *GPN1*) and 9q34.12 (rs928674, *LAMC3*), in addition to known cancer-related loci, such as 9p21.3 (rs8181047, *CDKN2B-AS1*). Polymorphisms within alcohol-related genes including alcohol-dehydrogenase 1B (*ADH1B;* 4q23, rs1229984*)* were also implicated in OSCC susceptibility (Lesseur *et al.*, 2016). Genetic variants near other alcohol-metabolising genes have also been associated with OSCC (McKay *et al.*, 2011). Findings such as these could help inform future risk prediction and targeted prevention strategies for certain high-risk patient groups.

The effect of epigenetic changes in blood have also been explored in people with OSCC. DNA methylation (DNAm) is an epigenetic modification involving the addition of methyl groups at cytosine-phosphate-guanine (CpG) sites, which influence gene expression (Dawson and Kouzarides, 2012; Hulls *et al.*, 2020). Many genes have presented an altered methylation profile in OSCC, including galanin (*GAL*), which has been reported to modulate perineural invasion in head and neck cancer (Russo *et al.*, 2018; Scanlon *et al.*, 2015). Further studies have revealed that blood-based DNAm predictors of smoking, alcohol consumption, body mass index (Langdon *et al.*, 2020), ageing (Beynon *et al.*, 2020), and inflammation (Ambatipudi *et al.*, 2018), are predictive of all-cause mortality among participants with head and neck cancer.

Tumour level changes that may help identify targets for predicting survival or treatment response

Somatic mutations are mutations detected in the tumour tissue by genotyping resections or biopsies. The Cancer Genome Atlas (TCGA) program has sequenced and molecularly characterised OSCC tumour samples, with the most frequently mutated genes shown in Figure 2 (Weinstein *et al.*, 2013). The vast majority of HPV-negative OSCC have *TP53* loss-of-function mutations and *CDKN2A* inactivation, consistent with previous findings. *TP53* is a tumour suppressor gene which encodes for protein p53, regarded as the "guardian of the genome", because of its role in promoting apoptosis and prohibiting

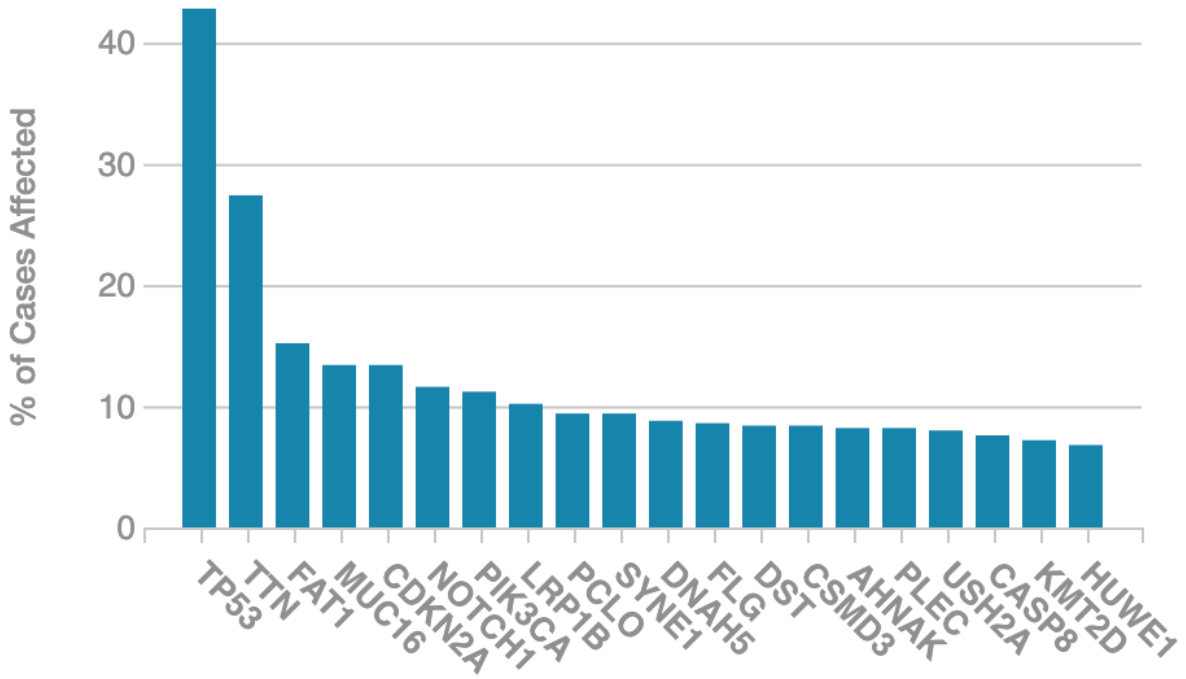

Figure 2. *Frequently mutated genes in OSCC tumour samples.*

the cell cycle, but these occur in almost every type of cancer, with reported frequency ranging from 38%–50% (Olivier *et al.*, 2010). *CDKN2A* codes for two proteins, including p16INK4 which acts as a tumour suppressor by regulating the cell cycle (El-Naggar *et al.*, 1997). While less prevalent in oral cavity compared to oropharyngeal cancer, the presence of HPV that overexpresses p16 can be of significance in younger patients, particularly those without established risk factors (Kerawala *et al.*, 2016; Lingen *et al.*, 2013). Overexpression of epidermal growth factor receptor (*EGFR*) in OSCC has been associated with recurrent or metastatic disease (Kerawala *et al.*, 2016) and successful trials (Bonner *et al.*, 2006; Bourhis *et al.*, 2006) have used cetuximab in combination with radiotherapy, when conventional treatment has failed. Programmed cell death protein-1/ligand-1 (PD-1/PD-L1) expression has also been associated with poor prognosis in OSCC (Maruse *et al.*, 2018). Immunotherapy that harnesses the patient's own immune system to combat cancer, has resulted in the development of monoclonal antibodies that target PD-1 (Ferris *et al.*, 2016; Ferris *et al.*, 2018).

Other transcriptome profiling techniques such as RNA-Seq could play a future role in clinical diagnostics and in determining individual genetic response to treatment (Kukurba and Montgomery, 2015; van Hooff *et al.*, 2012). Initial studies have also suggested that metabolomic, proteomic and lipidomic profiling using mass spectrometry techniques may be collectively beneficial in identifying molecular mechanisms and signalling pathways in OSCC, but clear patterns have not yet emerged (Dickinson *et al.*, 2020; Schaaij-Visser *et al.*, 2010; Yonezawa *et al.*, 2013). This could be due to small sample sizes (given that OSCC is a relatively rare cancer) and significant intra-tumour heterogeneity. Furthermore, whether the same DNA methylation signals identified in blood are also present in tumour tissue or saliva, which are more proximal to the disease of interest and easier to obtain, representative of those found in tumour tissue requires further investigation (Lim *et al.*, 2016).

Liquid biopsies to improve early detection

As conventional biopsies are limited by the area of tissue sampled usually following visual inspection, so called 'liquid biopsies' detecting circulating tumour cells (CTCs), circulating tumour DNA (ctDNA), circulating tumour RNA (ctRNA), proteins or exosomes from blood or saliva could enhance cancer detection (Babji *et al.*, 2019). This could be particularly beneficial in posterior regions of the oral cavity, oropharynx, or in cases of unknown primary tumour. Liquid biomarkers could also allow for the 'real-time' monitoring of tumour progression or personalised therapeutic responses, however again, a reproducible panel of sensitive and specific profiles for these biomarkers has not yet been established (Lousada-Fernandez *et al.*, 2018).

Considerations for implementing precision medicine services

The UK NHS Long Term Plan focuses on prevention and proposes investment in genomic testing and early detection for cancer (Department of Health & Social Care, 2019). However, implementing these services presents many challenges. Firstly, costs can range from £50 per individual for GWAS panels, to over £500 for whole genome sequencing. Another area of concern is that it that whole exome or genome testing often yields extensive, irrelevant information. Correct processing and interpretation of the results would require workforce training to correctly identify relevant variants, again with significant associated costs (Simpson *et al.*, 2019). Given the current underfunding for NHS dentistry and the healthcare service as a whole, this may be difficult to justify (British Dental Association, 2022). The way in which 'big genetic data' are stored requires advanced computing infrastructure not currently in place across the NHS, which would need future investment. Secure handling of results from genomic testing to protect patient confidentiality is essential, as all genetic data are unique and potentially identifiable (Molnár-Gábor and Korbel, 2020). Other ethical dilemmas in genomic medicine, include that of consent and patient access to data (Conboy, 2020). When incidental discoveries arise that are outside of a clinician's expertise, for example, carrier status for disease, patients may need referral on to geneticists for diagnosis and counselling, adding complexity to the pathway. Whilst practitioners have a duty of candour, the disclosure of genetic information can also lead to psychological distress or anxiety (Himes *et al.*, 2017).

Strategies for clinical follow-up

Follow-up after treatment aims to detect OSCC recurrence, as early detection is the key determinant of successful, curative salvage treatment. Current UK guidelines recommend clinical review of oral cancer patients every 2 months for the first two years post-treatment, then 3-6 monthly for the next three years. Most (91%) of UK clinicians follow patients up for a minimum of five years, with a significant proportion (35%) for ten years or longer (Joshi *et al.*, 2010). The increase in OSCC cases in combination with higher survival rates is leading to more oral cancer survivors who require follow-up. This is placing significant pressure on current resources, making the current strategy inadequate (Kothari *et al.*, 2011). As there are no tumour biomarkers that reliably identify OSCC recurrence, surveillance therefore relies on clinical examination and conventional imaging, but their efficacy in asymptomatic patients is poor. A study of head and neck cancer in asymptomatic patients attending routine follow-up, detected only 1 recurrence in every 99 consultations (Pagh *et al.*, 2013). Unfortunately, routine follow-up also detects most disease recurrence at a late stage, with only a small proportion of these patients suitable to receive salvage treatment. Furthermore, patient's quality of life is impacted by a fear of cancer recurrence, often triggered by forthcoming medical appointments (Mutsaers *et al.*, 2016). The inadequacy of the current follow-up strategy is being addressed in ongoing trials. PETNECK2 is investigating patient-initiated follow-up, with low-risk head and neck cancer patients having a PET-CT scan one year after finishing treatment. If no cancer is detected, they will receive nurse-led education about what symptoms of recurrent cancer to look out for, and an 'open urgent appointment' which guarantees clinical review within 2 weeks if they develop symptoms, instead of regular clinic visits (Lorenc *et al.*, 2022).

Conclusion

Recent epidemiological trends in OSCC suggest a potential change in aetiology, with rising numbers of younger patients who do not have the established risk factors, including tobacco use and alcohol. The role of less established risks such as BMI, diet, oral health, socio-economic status, occupation, and family history (genetics) warrant further investigation, as they could play a contributing role in this disease. Going forward, both conventional and genetic epidemiology could help in identifying high-risk groups to target with prevention strategies. While the evidence is clear for smoking, betel quid/ gutka and smokeless tobacco cessation, more emphasis should be placed on alcohol reduction in future cancer control policies, given its potential independent effect as shown using genetic techniques. Delayed presentation contributes to poor overall survival in OSCC, with low levels of public awareness associated strongly with social and economic determinants of health. Improved public awareness campaigns, greater access and support to attend services, as well as better informed primary care personnel are needed (Macpherson, 2018). Advances in high-throughput 'omics' technologies appear promising for individual-level diagnosis and prognosis in OSCC. However, reproducible profiles for such biomarkers remain to be elucidated. This is likely due to the lower prevalence of OSCC compared with other cancers, in addition to significant intra-tumour heterogeneity and variation in patient response. Cancer registries linked to large datasets such as UK Biobank, in addition to consortia which bring together larger numbers of accurately phenotyped and genotyped OSCC cases offer the best possibility of such biomarker development. Given the considerable practical, financial and ethical costs involved with precision medicine, this may be difficult to justify and implement at present and therefore the focus is currently on early detection using new follow-up strategies. For the meantime therefore, genomic testing remains funded within the context of academic research.

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