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

3  
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23

24 **Keywords:** Mouth Neoplasms; Oral Cancer; Squamous Cell Carcinoma; Epidemiology; Risk  
25 Factors; Survival; Therapeutics.

26 **Abstract**

27

28 In the UK, the overall incidence of oral cavity cancer continues to rise, with an increase of  
29 around 60% over the past 10 years. Many patients still present with advanced disease, often  
30 resulting in locoregional recurrence and poor outcomes, which has not changed significantly  
31 for over four decades. There may also be changes in aetiology emerging, given the decline of  
32 smoking in developed countries. Therefore, new methods to better target prevention, improve  
33 screening and to detect recurrence are needed. High-throughput ‘omics’ technologies appear  
34 promising for future individual-level diagnosis and prognosis. However, given this is a  
35 relatively rare cancer with significant intra-tumour heterogeneity and variation in patient  
36 response, reliable biomarkers have been difficult to elucidate. From a public health  
37 perspective, implementing these novel technologies into current services would require  
38 substantial practical, financial and ethical considerations. This papers reviews the latest  
39 evidence on epidemiological trends in oral cavity cancer to help identify at risk groups,  
40 population-based approaches for prevention, in addition to cutting-edge developments in the  
41 diagnosis and prognosis of this disease.

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## 51 **Introduction**

52

53 Head and neck cancer which includes the oral cavity is the 7<sup>th</sup> most common cancer globally,  
54 accounting for more than 660,000 new cases and 325,000 deaths each year. In the UK, the  
55 overall incidence of oral cavity cancer continues to rise, with an increase of around 60% over  
56 the past 10 years (Cancer Research UK (CRUK), 2015; Warnakulasuriya, 2009). Globally,  
57 incidence and mortality remain higher among males, with 150,000 more cases and 70,000  
58 more deaths worldwide reported in males compared to females. Despite this however, the  
59 data suggests an increasing trend in oral cavity cancer amongst women and a decreasing  
60 trend for men in Europe and the United States (Miranda-Filho and Bray, 2020; Sung *et al.*,  
61 2021). The highest age-standardised incidence rates (per 100,000 person-years) for oral  
62 cavity cancer are in Melanesia, namely Papua New Guinea (males= 22.2; females= 11.9),  
63 South Central Asia (males= 13.3; females= 4.6) and Eastern Europe (males= 9.2; females=  
64 1.9) (Sung *et al.*, 2021).

65

66 Ninety-percent of all malignant tumours which arise from the mucosal epithelium of the oral  
67 cavity are squamous cell carcinomas (OSCC) (Vigneswaran and Williams, 2014). The  
68 definition of oral cancer often varies between studies, with many combining oral and  
69 oropharyngeal cancer subsites, although differences in the aetiology, management and  
70 response to treatment means they should be considered as distinct disease entities (Conway,  
71 2018; Thomas *et al.*, 2018). Therefore, the term oral cancer in the context of this review will  
72 focus only on cancer of the oral cavity. In addition to registries, the use of International  
73 Classification of Diseases (ICD-10) codes C00-C06 (World Health Organization (WHO),  
74 2016), has helped standardise the collection and curation of cancer data (**Table 1**). The  
75 highest risk sites include lateral border of tongue and floor of mouth.

76 < **Table 1** near here >

77

78 **Risk factors for oral cavity cancer**

79

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

91

92 Betel chewing, gutka and use of smokeless tobacco occurs mostly in South Central Asian  
93 countries, where rates of OSCC continue to be some of the highest in the world (**Fig.1**)  
94 (Asthana *et al.*, 2019; Miranda-Filho and Bray, 2020). Throughout India, Pakistan and Sri  
95 Lanka, tobacco is usually combined with areca nut wrapped with other ingredients in a betel  
96 leaf to form a quid which is chewed. Gutka for example, is a combination of areca nut, slaked  
97 lime, paraffin, and catechu along with tobacco. In countries such as Papua New Guinea,  
98 tobacco is not chewed with the areca nut, betel inflorescence, or slaked lime, which are ~~often~~  
99 added separately (Gupta and Warnakulasuriya, 2002; Thomas and MacLennan, 1992). One  
100 meta-analysis showed an increased risk of oral cancer with exposure to betel quid without

101 tobacco in non-smokers (Thomas *et al.*, 2007). However, tobacco smoking is common across  
102 these populations, making it difficult to determine the independent effects of these agents  
103 (**Fig.1**).

104

105 Human papilloma virus (HPV), thought to be sexually transmitted (Heck *et al.*, 2010; Hobbs  
106 *et al.*, 2006), also increases OSCC risk (**Fig.1**). In developed countries such as the USA the  
107 proportion of oropharyngeal cancer attributed to HPV is 60–70% (Chaturvedi *et al.*, 2013),  
108 whereas the aetiological fraction for oral sites is reported to be as low as 3% (Farsi *et al.*,  
109 2015; Gillison *et al.*, 2015). Within the Head and Neck 5000 cancer study, the risk factors of  
110 those people with OSCC differed from those with laryngeal and oropharyngeal tumours.  
111 They were generally younger (43% <60 years old), more likely to be female (38%), less  
112 likely to smoke (25% never smokers) and no more likely to have performed oral sex (Thomas  
113 *et al.*, 2018). Worryingly, these data suggest an emerging and distinct clinical entity of  
114 unknown aetiology.

115

116 < **Figure 1** near here >

117

118 Less well established risk factors as shown in **Table 2** include, a family history of oral cavity  
119 cancer (Negri *et al.*, 2009), lower body mass index (BMI) (Lubin *et al.*, 2011), a diet lacking  
120 in fruit and vegetables (Chuang *et al.*, 2009), type 2 diabetes (Tseng *et al.*, 2014), poor oral  
121 health (Hashim *et al.*, 2016), socio-economic status, lower educational attainment and  
122 occupation (Conway *et al.*, 2021). While the relationships here may be confounded by  
123 smoking and drinking behaviour, further research to establish the value of these potentially  
124 modifiable risk factors is required.

125

126 < **Table 2** near here >

127

128 **Strategies for prevention**

129

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

140

141 Given the high recurrence and poor survival rates, OSCC is considered a major public health  
142 issue (Macpherson, 2018). Multiple population-based and individual-level approaches have  
143 been implemented in an attempt to both prevent the disease and to diagnose OSCC earlier  
144 (Ford and Farah, 2013; Macpherson, 2018). The effect of such interventions are complex,  
145 with oral examination screening of high-risk groups appearing to be more effective in areas  
146 of high disease prevalence, compared to low (Sankaranarayanan *et al.*, 2005). Ford and Farah  
147 (2013) found that those in lower socioeconomic groups at increased risk of OSCC, are likely  
148 to be poor dental attenders, which further reduces the efficacy of this approach. Moreover,  
149 the COVID-19 pandemic has decreased access to general dental services, resulting in a  
150 decline in oral cancer referrals to secondary care and prolonged waiting times. A recent call

151 has been made for long-term investment in public health programmes and transformation of  
152 the dental commissioning pathways targeted at those most in need (Stennett and Tsakos,  
153 2022). Public awareness campaigns (such as e.g., Mouth Cancer Action Month) can be used  
154 to improve symptom recognition, promote self-examination and awareness of risk factors  
155 (Austoker *et al.*, 2009; Macpherson, 2018). Previous studies have suggested that while the  
156 association between smoking and OSCC is publicly recognised, more could be done to  
157 increase awareness around the risk of alcohol (Monteiro *et al.*, 2016; Posorski *et al.*, 2014).  
158 Smoking cessation and brief alcohol interventions can be performed chairside by dentists,  
159 however funding, time and training are often quoted as barriers which need to be addressed  
160 (McAuley *et al.*, 2011). Ongoing trials such as the ENHANCE-D (ENHANCing smoking  
161 cEssation interventions in Dentistry) study, will help evaluate and evidence the impact of  
162 primary care dental professionals providing smoking cessation interventions such as Nicotine  
163 Replacement Therapy (NRT) or e-cigarettes (Holliday, 2022). Better collaboration, education  
164 and training of the wider healthcare team is key and the UK General Dental Council  
165 advocates continual professional development in oral cancer. Further training requirements  
166 for primary medical practitioners could help ensure appropriate urgent referrals are made for  
167 both malignant and potentially malignant oral conditions (Rodgers *et al.*, 2007).

168

### 169 **Novel approaches to establishing oral cavity cancer diagnosis and prognosis**

170

171 The ‘gold standard’ approach for diagnosing OSCC is via clinical examination and a  
172 definitive incisional biopsy, sometimes with adjunctive panendoscopy, fine needle aspiration  
173 cytology, or imaging. Toluidine blue stain and chemiluminescence can aid diagnosis, but are  
174 not sensitive or specific enough to be used alone (Kim *et al.*, 2021) Computed tomography



175 (CT), positron emission tomography (PET) scans, ultrasound or magnetic resonance imaging  
176 (MRI) are often employed to investigate local or regional spread.

177

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

189

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

192

193 Germline genetics refers to the genetic code inherited from parents, and is found in every  
194 healthy cell in the body. Subtle variation in this genetic code, across populations, can alter  
195 anything from how quickly we metabolise alcohol to how quickly we feel hungry. The largest  
196 genome-wide association study (GWAS) of oral cavity cancer risk (n= 2,990 cases and n=  
197 6,585 controls) set out to identify these subtle variations across the genome that relate to  
198 OSCC risk. The study identified two new regions on chromosome position 2p23.3  
199 (rs6547741, *GPNI*) and 9q34.12 (rs928674, *LAMC3*), in addition to known cancer-related

200 loci, 9p21.3 (rs8181047, *CDKN2B-AS1*) and 5p15.33 (rs10462706, *CLPTMIL*).  
201 Polymorphisms within alcohol-related genes including alcohol-dehydrogenase 1B (*ADH1B*;  
202 4q23, rs1229984) were also implicated in OSCC susceptibility (Lesseur *et al.*, 2016).  
203 Genetic variants near other alcohol-metabolising genes, rs1573496 (*ADH7*), rs1042758  
204 (*ADH1C*) and rs4767364 (*ALDH2*) have also been associated with oral cavity cancer (McKay  
205 *et al.*, 2011). Findings such as these could help inform future risk prediction and targeted  
206 prevention strategies for certain high-risk patient groups.

207

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

218

219 *Tumour level changes which may help identify targets for predicting survival or treatment*  
220 *response*

221

222 Somatic mutations are mutations detected in the tumour tissue by genotyping resections or  
223 biopsies. The Cancer Genome Atlas (TCGA) program has sequenced and molecularly  
224 characterised OSCC tumour samples, with the most frequently mutated genes shown in **Fig.2**

225 (Weinstein *et al.*, 2013). This project demonstrated that the vast majority of HPV-negative  
226 OSCC have *TP53* loss-of-function mutations and *CDKN2A* inactivation, consistent with  
227 previous findings. *TP53* is a tumour suppressor gene which encodes for protein p53, regarded  
228 as the “guardian of the genome”, because of its role in promoting apoptosis and prohibiting  
229 the cell cycle, but these occur in almost every type of cancer, with reported frequency ranging  
230 from 38%–50% (Olivier *et al.*, 2010). *CDKN2A* codes for two proteins, including p16INK4  
231 which acts as a tumour suppressor by regulating the cell cycle (El-Naggar *et al.*, 1997). While  
232 less prevalent in oral cavity compared to oropharyngeal cancer, the presence of HPV that  
233 overexpresses p16 can be of significance in younger patients, particularly those without  
234 established risk factors (Kerawala *et al.*, 2016; Lingen *et al.*, 2013). Overexpression of  
235 epidermal growth factor receptor (*EGFR*) in OSCC has been associated with recurrent or  
236 metastatic disease (Kerawala *et al.*, 2016) and multiple successful trials (Bonner *et al.*, 2006;  
237 Bourhis *et al.*, 2006) have used cetuximab in combination with radiotherapy, when  
238 conventional treatment has failed. Programmed cell death protein-1/ligand-1 (PD-1/PD-L1)  
239 expression has also been associated with poor prognosis in OSCC (Maruse *et al.*, 2018).  
240 Immunotherapy which harnesses the patient’s own immune system to combat cancer, has  
241 resulted in the development of monoclonal antibodies which target PD-1 (Ferris *et al.*, 2016;  
242 Ferris *et al.*, 2018).

243

244 < **Figure 2** near here >

245

246 Whole-exome sequencing of tumour tissue is a transcriptomics approach which centres on  
247 the protein-coding regions of the genome. This technique revealed *NOTCH1* mutations in  
248 OSCC, which appears to function as a tumor suppressor gene, rather than an oncogene in this  
249 tumour type (Agrawal *et al.*, 2011; Stransky *et al.*, 2011). Other transcriptome profiling

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

261

#### 262 *Liquid biopsies to improve early detection*

263

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

273

#### 274 **Considerations for implementing precision medicine services**

275

276 The UK NHS Long Term Plan focuses on prevention and proposes investment in genomic  
277 testing and early detection for cancer (Department of Health & Social Care, 2019). However,  
278 implementing these services presents many challenges. Firstly, costs can range from £50 per  
279 individual for GWAS panels, to over £500 for whole genome sequencing. Another area of  
280 concern is that it that whole exome or genome testing often yields extensive, irrelevant  
281 information. Correct processing and interpretation of the results would require workforce  
282 training to correctly identify relevant variants, again with significant associated costs  
283 (Simpson *et al.*, 2019). Given the current state of underfunding for NHS dentistry and the  
284 healthcare service as a whole, this may be difficult to justify (British Dental Association,  
285 2022). The way in which ‘big genetic data’ is stored requires advanced computing  
286 infrastructure not currently in place across the NHS, which would need future investment.  
287 Secure handling of results from genomic testing to protect patient confidentiality is essential,  
288 as all genetic data is unique and potentially identifiable (Molnár-Gábor and Korbel, 2020).  
289 Other ethical dilemmas in genomic medicine, include that of consent and patient access to  
290 data (Conboy, 2020). When incidental discoveries arise which are outside of dental expertise,  
291 e.g., carrier status for disease, patients may need to referral onto geneticists for diagnosis and  
292 counselling, adding complexity to the pathway. Whilst clinicians have a duty of candour, the  
293 disclosure of genetic information can also lead to psychological distress or anxiety (Himes *et*  
294 *al.*, 2017).

295

### 296 **Strategies for clinical follow-up**

297

298 Follow-up after treatment aims to detect OSCC recurrence, as early detection is the key  
299 determinant of successful, curative salvage treatment. Current UK guidelines recommend

300 clinical review of oral cancer patients every 2 months for the first two years post-treatment,  
301 then 3-6 monthly for the next three years. Most (91%) of UK clinicians follow patients up for  
302 a minimum of 5 years, with a significant proportion (35%) for 10 years or longer (Joshi *et al.*,  
303 2010), but the current strategy is inadequate (Kothari *et al.*, 2011). An increase in OSCC  
304 cases in combination with higher survival rates is leading to an increasing number of oral  
305 cancer survivors who require follow-up, placing significant pressure on current resources. As  
306 there are no tumour biomarkers which reliably identify OSCC recurrence, surveillance  
307 therefore relies on clinical examination and conventional imaging, but their efficacy in  
308 asymptomatic patients is poor. A study of head and neck cancer in asymptomatic patients,  
309 attending routine follow-up, detected only 1 recurrence in every 99 consultations (Pagh *et al.*,  
310 2013). Unfortunately, routine follow-up detects most disease recurrence at a late stage, with  
311 only a small proportion of these patients suitable to receive salvage  
312 treatmentsurgery. Furthermore, patient's quality of life is impacted by a fear of cancer  
313 recurrence often triggered by forthcoming medical appointments (Mutsaers *et al.*, 2016). The  
314 inadequacy of the current follow-up strategy is being addressed in ongoing trials.  
315 PETNECK2 is investigating patient-initiated follow-up, with low risk head and neck cancer  
316 patients having a PET-CT scan one year after finishing treatment. If no cancer is detected,  
317 they will be receive nurse-led education about what symptoms of recurrent cancer to look out  
318 for, and an 'open urgent appointment' which guarantees clinical review within 2 weeks if  
319 they develop symptoms, instead of regular clinic visits (Lorenc *et al.*, 2022).

320

## 321 **Conclusion**

322

323 Recent epidemiological trends in OSCC suggest a potential change in aetiology, with rising  
324 numbers of younger patients who do not have the established risk factors, including tobacco

325 use and alcohol. The role of less established risks such as BMI, diet, oral health, socio-  
326 economic status, occupation, and family history (genetics) warrant further investigation, as  
327 they could play a contributing role in this disease. Going forward, both conventional and  
328 genetic epidemiology could help in identifying high-risk groups to target with prevention  
329 strategies. While the evidence is clear for smoking, betel quid/ gutka and smokeless tobacco  
330 cessation, more emphasis should be placed on alcohol reduction in future cancer control  
331 policies, given its potential independent effect as shown using genetic techniques. Delayed  
332 presentation contributes to poor overall survival in OSCC, with low levels of public  
333 awareness associated strongly with social and economic determinants of health. Improved  
334 public awareness campaigns, greater access and support to attend services, as well as better  
335 informed primary care personnel are needed (Macpherson, 2018). Advancements in high-  
336 throughput ‘omics’ technologies appear promising for individual-level diagnosis and  
337 prognosis in OSCC. However, reproducible profiles for such biomarkers remain to be  
338 elucidated. This is likely due to the lower prevalence of OSCC compared with other cancers,  
339 in addition to significant intra-tumour heterogeneity and variation in patient response. Cancer  
340 registries linked to large datasets such as UK Biobank, in addition to consortia which bring  
341 together larger numbers of accurately phenotyped and genotyped OSCC cases offer the best  
342 possibility of such biomarker development. Given the considerable practical, financial and  
343 ethical costs involved with precision medicine, this may be difficult to justify and implement  
344 at present and the focus is currently on early detection using new follow-up strategies. For the  
345 meantime therefore, genomic testing remains funded within the context of academic research.

346

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350 **References**

351

352 Agrawal, N., Frederick, M.J., Pickering, C.R., Bettegowda, C., Chang, K., Li, R.J., Fakhry,  
353 C., Xie, T.X., Zhang, J., Wang, J., Zhang, N., El-Naggar, A.K., Jasser, S.A.,  
354 Weinstein, J.N., Treviño, L., Drummond, J.A., Muzny, D.M., Wu, Y., Wood, L.D.,  
355 Hruban, R.H., Westra, W.H., Koch, W.M., Califano, J.A., Gibbs, R.A., Sidransky, D.,  
356 Vogelstein, B., Velculescu, V.E., Papadopoulos, N., Wheeler, D.A., Kinzler, K.W.  
357 and Myers, J.N. (2011): Exome sequencing of head and neck squamous cell  
358 carcinoma reveals inactivating mutations in NOTCH1. *Science* **333**, 1154-1157.

359 Ambatipudi, S., Langdon, R., Richmond, R.C., Suderman, M., Koestler, D.C., Kelsey, K.T.,  
360 Kazmi, N., Penfold, C., Ho, K.M., McArdle, W., Ring, S.M., Pring, M., Waterboer,  
361 T., Pawlita, M., Gaunt, T.R., Davey Smith, G., Thomas, S., Ness, A.R. and Relton,  
362 C.L. (2018): DNA methylation derived systemic inflammation indices are associated  
363 with head and neck cancer development and survival. *Oral Oncology* **85**, 87-94.

364 Asthana, S., Labani, S., Kailash, U., Sinha, D.N. and Mehrotra, R. (2019): Association of  
365 Smokeless Tobacco Use and Oral Cancer: A Systematic Global Review and Meta-  
366 Analysis. *Nicotine Tob Res* **21**, 1162-1171.

367 Austoker, J., Bankhead, C., Forbes, L.J.L., Atkins, L., Martin, F., Robb, K., Wardle, J. and  
368 Ramirez, A.J. (2009): Interventions to promote cancer awareness and early  
369 presentation: systematic review. *British Journal of Cancer* **101**, S31-S39.

370 Babji, D., Nayak, R., Bhat, K. and Kotrashetti, V. (2019): Cell-free tumor DNA: Emerging  
371 reality in oral squamous cell carcinoma. *Journal of oral and maxillofacial pathology :*  
372 *JOMFP* **23**, 273-279.



373 Beynon, R.A., Ingle, S.M., Langdon, R., May, M., Ness, A., Martin, R., Suderman, M.,  
374 Ingarfield, K., Marioni, R., McCartney, D., Waterboer, T., Pawlita, M., Relton, C.,  
375 Smith, G.D. and Richmond, R. (2020): Epigenetic biomarkers of ageing are predictive  
376 of mortality risk in a longitudinal clinical cohort of individuals diagnosed with  
377 oropharyngeal cancer. *medRxiv*, 2020.2002.2004.20020198.

378 Bonner, J.A., Harari, P.M., Giralt, J., Azarnia, N., Shin, D.M., Cohen, R.B., Jones, C.U., Sur,  
379 R., Raben, D., Jassem, J., Ove, R., Kies, M.S., Baselga, J., Youssoufian, H., Amellal,  
380 N., Rowinsky, E.K. and Ang, K.K. (2006): Radiotherapy plus cetuximab for  
381 squamous-cell carcinoma of the head and neck. *N Engl J Med* **354**, 567-578.

382 Bourhis, J., Rivera, F., Mesia, R., Awada, A., Geoffrois, L., Borel, C., Humblet, Y., Lopez-  
383 Pousa, A., Hitt, R., Vega Villegas, M.E., Duck, L., Rosine, D., Amellal, N., Schueler,  
384 A. and Harstrick, A. (2006): Phase I/II study of cetuximab in combination with  
385 cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic  
386 squamous cell carcinoma of the head and neck. *J Clin Oncol* **24**, 2866-2872.

387 British Dental Association (2022): Urgent action needed as millions miss out on NHS  
388 dentistry. From [https://bda.org/news-centre/press-releases/Pages/Urgent-action-](https://bda.org/news-centre/press-releases/Pages/Urgent-action-needed-as-millions-miss-out-on-NHS-dentistry.aspx)  
389 [needed-as-millions-miss-out-on-NHS-dentistry.aspx](https://bda.org/news-centre/press-releases/Pages/Urgent-action-needed-as-millions-miss-out-on-NHS-dentistry.aspx).

390 Cancer Research UK (CRUK) (2015): Mouth cancer rates are increasing, but why? From  
391 [https://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-](https://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-increasing-but-why/#:~:text=Overall%20the%20rates%20of%20tongue,a%20year%20in%20the%20UK.)  
392 [increasing-but-](https://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-increasing-but-why/#:~:text=Overall%20the%20rates%20of%20tongue,a%20year%20in%20the%20UK.)  
393 [why/#:~:text=Overall%20the%20rates%20of%20tongue,a%20year%20in%20the%20](https://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-increasing-but-why/#:~:text=Overall%20the%20rates%20of%20tongue,a%20year%20in%20the%20UK.)  
394 [UK.](https://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-increasing-but-why/#:~:text=Overall%20the%20rates%20of%20tongue,a%20year%20in%20the%20UK.)

395 Chaturvedi, A.K., Anderson, W.F., Lortet-Tieulent, J., Curado, M.P., Ferlay, J., Franceschi,  
396 S., Rosenberg, P.S., Bray, F. and Gillison, M.L. (2013): Worldwide Trends in  
397 Incidence Rates for Oral Cavity and Oropharyngeal Cancers. *Journal of Clinical*  
398 *Oncology* **31**, 4550-4559.

399 Chuang, S.C., Jenab, M., Heck, J., Olshan, A., Bencko, V., Schantz, S., Curado, M.P., Mates,  
400 D., McClean, M., Daudt, A., Franceschi, S., Zaridze, D., Koifman, S., Lazarus, P.,  
401 Herrero, R., Fabianova, E., Luigino, D.M., Zhang, Z.F., Muscat, J., Talamini, R.,  
402 Rudnai, P., Fernandez, L., Lissowska, J., Menezes, A., Levi, F., Hayes, R.,  
403 Benhamou, S., Eluf-Neto, J., Boccia, S. and Matos, E. (2009): Diet and the risk of  
404 head and neck cancer: A pooled analysis in the INHANCE consortium. *Cancer*  
405 *Research* **69**.

406 Cogliano, V.J., Baan, R., Straif, K., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F.,  
407 Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Freeman, C., Galichet, L. and Wild,  
408 C.P. (2011): Preventable exposures associated with human cancers. *J Natl Cancer*  
409 *Inst* **103**, 1827-1839.

410 Conboy, C. (2020): Consent and Privacy in the Era of Precision Medicine and Biobanking  
411 Genomic Data. *American Journal of Law & Medicine* **46**, 167-187.

412 Conway, D.I., Hovanec, J., Ahrens, W., Ross, A., Holcatova, I., Lagiou, P., Serraino, D.,  
413 Canova, C., Richiardi, L., Healy, C., Kjaerheim, K., Macfarlane, G.J., Thomson, P.,  
414 Agudo, A., Znaor, A., Brennan, P., Luce, D., Menvielle, G., Stucker, I., Benhamou,  
415 S., Ramroth, H., Boffetta, P., Vilensky, M., Fernandez, L., Curado, M.P., Menezes,  
416 A., Daudt, A., Koifman, R., Wunsch-Filho, V., Yuan-Chin, A.L., Hashibe, M.,  
417 Behrens, T. and McMahon, A.D. (2021): Occupational socioeconomic risk  
418 associations for head and neck cancer in Europe and South America: individual

419 participant data analysis of pooled case–control studies within the INHANCE  
420 Consortium. *Journal of Epidemiology and Community Health* **75**, 779-787.

421 Conway, D.I., Purkayastha, M., Chestnutt, I. G. (2018): The changing epidemiology of oral  
422 cancer: definitions, trends, and risk factors. *British Dental Journal* **225**, 867-873.

423 D’Adamo, G.L., Widdop, J.T. and Giles, E.M. (2021): The future is now? Clinical and  
424 translational aspects of “Omics” technologies. *Immunology & Cell Biology* **99**, 168-  
425 176.

426 Dawson, M.A. and Kouzarides, T. (2012): Cancer epigenetics: from mechanism to therapy.  
427 *Cell* **150**, 12-27.

428 Department of Health & Social Care (2019): The NHS Long Term Plan. From  
429 <https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/>.

430 Dickinson, A., Saraswat, M., Joenväärä, S., Agarwal, R., Jyllikoski, D., Wilkman, T.,  
431 Mäkitie, A. and Silén, S. (2020): Mass spectrometry–based lipidomics of oral  
432 squamous cell carcinoma tissue reveals aberrant cholesterol and glycerophospholipid  
433 metabolism — A Pilot study. *Translational Oncology* **13**, 100807.

434 El-Naggar, A.K., Lai, S., Clayman, G., Lee, J.K., Luna, M.A., Goepfert, H. and Batsakis, J.G.  
435 (1997): Methylation, a major mechanism of p16/CDKN2 gene inactivation in head  
436 and neck squamous carcinoma. *Am J Pathol* **151**, 1767-1774.

437 Fan, S., Tang, Q.-L., Lin, Y.-J., Chen, W.-L., Li, J.-S., Huang, Z.-Q., Yang, Z.-H., Wang, Y.-  
438 Y., Zhang, D.-M., Wang, H.-J., Dias-Ribeiro, E., Cai, Q. and Wang, L. (2011): A  
439 review of clinical and histological parameters associated with contralateral neck

440 metastases in oral squamous cell carcinoma. *International journal of oral science* **3**,  
441 180-191.

442 Farsi, N.J., El-Zein, M., Gaied, H., Lee, Y.C., Hashibe, M., Nicolau, B. and Rousseau, M.C.  
443 (2015): Sexual behaviours and head and neck cancer: A systematic review and meta-  
444 analysis. *Cancer Epidemiol* **39**, 1036-1046.

445 Ferris, R.L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, A.D., Licitra, L., Harrington,  
446 K., Kasper, S., Vokes, E.E., Even, C., Worden, F., Saba, N.F., Iglesias Docampo,  
447 L.C., Haddad, R., Rordorf, T., Kiyota, N., Tahara, M., Monga, M., Lynch, M., Geese,  
448 W.J., Kopit, J., Shaw, J.W. and Gillison, M.L. (2016): Nivolumab for Recurrent  
449 Squamous-Cell Carcinoma of the Head and Neck. *New England Journal of Medicine*  
450 **375**, 1856-1867.

451 Ferris, R.L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A.D., Licitra, L.,  
452 Harrington, K.J., Kasper, S., Vokes, E.E., Even, C., Worden, F., Saba, N.F.,  
453 Docampo, L.C.I., Haddad, R., Rordorf, T., Kiyota, N., Tahara, M., Lynch, M.,  
454 Jayaprakash, V., Li, L. and Gillison, M.L. (2018): Nivolumab vs investigator's choice  
455 in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-  
456 term survival update of CheckMate 141 with analyses by tumor PD-L1 expression.  
457 *Oral Oncol* **81**, 45-51.

458 Ford, P.J. and Farah, C.S. (2013): Early detection and diagnosis of oral cancer: Strategies for  
459 improvement. *Journal of Cancer Policy* **1**, e2-e7.

460 Garraway, L.A., Verweij, J. and Ballman, K.V. (2013): Precision oncology: an overview. *J*  
461 *Clin Oncol* **31**, 1803-1805.

462 Gigliotti, J., Madathil, S. and Makhoul, N. (2019): Delays in oral cavity cancer. *International*  
463 *Journal of Oral and Maxillofacial Surgery* **48**, 1131-1137.

464 Gillison, M.L., Chaturvedi, A.K., Anderson, W.F. and Fakhry, C. (2015): Epidemiology of  
465 Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin*  
466 *Oncol* **33**, 3235-3242.

467 Gómez, I., Seoane, J., Varela-Centelles, P., Diz, P. and Takkouche, B. (2009): Is diagnostic  
468 delay related to advanced-stage oral cancer? A meta-analysis. *Eur J Oral Sci* **117**,  
469 541-546.

470 Gormley, M., Dudding, T., Sanderson, E., Martin, R.M., Thomas, S., Tyrrell, J., Ness, A.R.,  
471 Brennan, P., Munafo, M., Pring, M., Boccia, S., Olshan, A.F., Diergaard, B., Hung,  
472 R.J., Liu, G., Davey Smith, G. and Richmond, R.C. (2020): A multivariable  
473 Mendelian randomization analysis investigating smoking and alcohol consumption in  
474 oral and oropharyngeal cancer. *Nat Commun* **11**, 6071.

475 Grossman, R.L., Heath, A.P., Ferretti, V., Varmus, H.E., Lowy, D.R., Kibbe, W.A. and  
476 Staudt, L.M. (2016): Toward a Shared Vision for Cancer Genomic Data. *New*  
477 *England Journal of Medicine* **375**, 1109-1112.

478 Gupta, P.C. and Warnakulasuriya, S. (2002): Global epidemiology of areca nut usage. *Addict*  
479 *Biol* **7**, 77-83.

480 Hashibe, M., Brennan, P., Chuang, S.C., Boccia, S., Castellsague, X., Chen, C., Curado,  
481 M.P., Dal Maso, L., Daudt, A.W., Fabianova, E., Fernandez, L., Wunsch-Filho, V.,  
482 Franceschi, S., Hayes, R.B., Herrero, R., Kelsey, K., Koifman, S., La Vecchia, C.,  
483 Lazarus, P., Levi, F., Lence, J.J., Mates, D., Matos, E., Menezes, A., McClean, M.D.,  
484 Muscat, J., Eluf-Neto, J., Olshan, A.F., Purdue, M., Rudnai, P., Schwartz, S.M.,

485 Smith, E., Sturgis, E.M., Szeszenia-Dabrowska, N., Talamini, R., Wei, Q.Y., Winn,  
486 D.M., Shangina, O., Pilarska, A., Zhang, Z.F., Ferro, G., Berthiller, J. and Boffetta, P.  
487 (2009): Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck  
488 Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology  
489 Consortium. *Cancer Epidemiology Biomarkers & Prevention* **18**, 541-550.

490 Hashim, D., Sartori, S., Brennan, P., Curado, M.P., Wünsch-Filho, V., Divaris, K., Olshan,  
491 A.F., Zavallos, J.P., Winn, D.M., Franceschi, S., Castellsagué, X., Lissowska, J.,  
492 Rudnai, P., Matsuo, K., Morgenstern, H., Chen, C., Vaughan, T.L., Hofmann, J.N.,  
493 D'Souza, G., Haddad, R.I., Wu, H., Lee, Y.C., Hashibe, M., Vecchia, C.L. and  
494 Boffetta, P. (2016): The role of oral hygiene in head and neck cancer: results from  
495 International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Annals*  
496 *of oncology : official journal of the European Society for Medical Oncology* **27**, 1619-  
497 1625.

498 Heck, J.E., Berthiller, J., Vaccarella, S., Winn, D.M., Smith, E.M., Shan'gina, O., Schwartz,  
499 S.M., Purdue, M.P., Pilarska, A., Eluf-Neto, J., Menezes, A., McClean, M.D., Matos,  
500 E., Koifman, S., Kelsey, K.T., Herrero, R., Hayes, R.B., Franceschi, S., Wunsch-  
501 Filho, V., Fernandez, L., Daudt, A.W., Curado, M.P., Chen, C., Castellsague, X.,  
502 Ferro, G., Brennan, P., Boffetta, P. and Hashibe, M. (2010): Sexual behaviours and  
503 the risk of head and neck cancers: a pooled analysis in the International Head and  
504 Neck Cancer Epidemiology (INHANCE) consortium. *International Journal of*  
505 *Epidemiology* **39**, 166-181.

506 Himes, P., Kauffman, T.L., Muessig, K.R., Amendola, L.M., Berg, J.S., Dorschner, M.O.,  
507 Gilmore, M., Nickerson, D.A., Reiss, J.A., Richards, C.S., Rope, A.F., Simpson,  
508 D.K., Wilfond, B.S., Jarvik, G.P. and Goddard, K.A.B. (2017): Genome sequencing

509 and carrier testing: decisions on categorization and whether to disclose results of  
510 carrier testing. *Genet Med* **19**, 803-808.

511 Hobbs, C.G., Sterne, J.A., Bailey, M., Heyderman, R.S., Birchall, M.A. and Thomas, S.J.  
512 (2006): Human papillomavirus and head and neck cancer: a systematic review and  
513 meta-analysis. *Clinical Otolaryngology* **31**, 259-266.

514 Holliday, R. (2022): ENHANCE-D Study. From  
515 [https://blogs.ncl.ac.uk/northerndentres/currentprojects/enhance-d-study-expression-](https://blogs.ncl.ac.uk/northerndentres/currentprojects/enhance-d-study-expression-of-interest/)  
516 [of-interest/](https://blogs.ncl.ac.uk/northerndentres/currentprojects/enhance-d-study-expression-of-interest/).

517 Homann, N., Karkkainen, P., Koivisto, T., Nosova, T., Jokelainen, K. and Salaspuro, M.  
518 (1997): Effects of acetaldehyde on cell regeneration and differentiation of the upper  
519 gastrointestinal tract mucosa. *J Natl Cancer Inst* **89**, 1692-1697.

520 Hulls, P.M., de Vocht, F., Bao, Y., Relton, C.L., Martin, R.M. and Richmond, R.C. (2020):  
521 DNA methylation signature of passive smoke exposure is less pronounced than active  
522 smoking: The Understanding Society study. *Environ Res* **190**, 109971.

523 Joshi, A., Calman, F., O'Connell, M., Jeannon, J.P., Pracy, P. and Simo, R. (2010): Current  
524 Trends in the Follow-up of Head and Neck Cancer Patients in the UK. *Clinical*  
525 *Oncology* **22**, 114-118.

526 Kerawala, C., Roques, T., Jeannon, J.P. and Bisase, B. (2016): Oral cavity and lip cancer:  
527 United Kingdom National Multidisciplinary Guidelines. *The Journal of laryngology*  
528 *and otology* **130**, S83-S89.

529 Kim, D.H., Song, E.A., Kim, S.W. and Hwang, S.H. (2021): Efficacy of toluidine blue in the  
530 diagnosis and screening of oral cancer and pre-cancer: A systematic review and meta-  
531 analysis. *Clinical Otolaryngology* **46**, 23-30.

532 Kothari, P., Trinidad, A., Hewitt, R.J.D., Singh, A. and O'Flynn, P. (2011): The follow-up of  
533 patients with head and neck cancer: an analysis of 1,039 patients. *Eur Arch*  
534 *Otorhinolaryngol* **268**, 1191-1200.

535 Kukurba, K.R. and Montgomery, S.B. (2015): RNA Sequencing and Analysis. *Cold Spring*  
536 *Harbor protocols* **2015**, 951-969.

537 Langdon, R., Beynon, R.A., Ingarfield, K., Marioni, R.E., McCartney, D.L., Martin, R.M.,  
538 Ness, A.R., Pawlita, M., Waterboer, T., Relton, C., Thomas, S.J. and Richmond, R.C.  
539 (2020): Epigenetic prediction of complex traits and mortality in a cohort of  
540 individuals with oropharyngeal cancer. *Clin Epigenetics* **12**, 58.

541 Lesueur, C., Diergaard, B., Olshan, A.F., Wunsch, V., Ness, A.R., Liu, G., Lacko, M., Eluf-  
542 Neto, J., Franceschi, S., Laggiou, P., Macfarlane, G.J., Richiardi, L., Boccia, S.,  
543 Polesel, J., Kjaerheim, K., Zaridze, D., Johanson, M., Menezes, A.M., Curado, M.P.,  
544 Robinson, M., Ahrens, W., Canova, C., Znaor, A., Castellsague, X., Conway, D.I.,  
545 Holcatova, I., Mates, D., Vidensky, M., Healy, C.M., Szeszenia-Dbrowska, N.,  
546 Fabianova, E., Lissowska, J., Grandis, J.R., Weissler, M.C., Tajara, E.H., Nunes,  
547 F.D., de Carvalho, M.B., Thomas, S., Hung, R.J., Peters, W.H.M., Herrero, R.,  
548 Cadoni, G., Bueno-De-Mesquita, H.B., Steffen, A., Agudo, A., Shangina, O., Xiao,  
549 X.J., Gaborieau, V., Chabrier, A., Anantharaman, D., Boffetta, P., Amos, C.I., McKay,  
550 J.D. and Brennan, P. (2016): Genome-wide association analyses identify new  
551 susceptibility loci for oral cavity and pharyngeal cancer. *Nature Genetics* **48**, 1544-  
552 1550.



553 Lim, Y., Sun, C.X., Tran, P. and Punyadeera, C. (2016): Salivary epigenetic biomarkers in  
554 head and neck squamous cell carcinomas. *Biomark Med* **10**, 301-313.

555 Lingen, M.W., Xiao, W., Schmitt, A., Jiang, B., Pickard, R., Kreinbrink, P., Perez-Ordenez,  
556 B., Jordan, R.C. and Gillison, M.L. (2013): Low etiologic fraction for high-risk  
557 human papillomavirus in oral cavity squamous cell carcinomas. *Oral Oncol* **49**, 1-8.

558 Lorenc, A., Wells, M., Fulton-Lieuw, T., Nankivell, P., Mehanna, H., Jepson, M. and Team,  
559 P.R. (2022): Clinicians' Views of Patient-initiated Follow-up in Head and Neck  
560 Cancer: a Qualitative Study to Inform the PETNECK2 Trial. *Clinical oncology*  
561 *(Royal College of Radiologists (Great Britain))* **34**, 230-240.

562 Lousada-Fernandez, F., Rapado-Gonzalez, O., Lopez-Cedrun, J.-L., Lopez-Lopez, R.,  
563 Muinelo-Romay, L. and Suarez-Cunqueiro, M.M. (2018): Liquid Biopsy in Oral  
564 Cancer. *International journal of molecular sciences* **19**, 1704.

565 Lubin, J.H., Muscat, J., Gaudet, M.M., Olshan, A.F., Curado, M.P., Dal Maso, L., Wünsch-  
566 Filho, V., Sturgis, E.M., Szeszenia-Dabrowska, N., Castellsague, X., Zhang, Z.F.,  
567 Smith, E., Fernandez, L., Matos, E., Franceschi, S., Fabianova, E., Rudnai, P., Purdue,  
568 M.P., Mates, D., Wei, Q., Herrero, R., Kelsey, K., Morgenstern, H., Shangina, O.,  
569 Koifman, S., Lissowska, J., Levi, F., Daudt, A.W., Neto, J.E., Chen, C., Lazarus, P.,  
570 Winn, D.M., Schwartz, S.M., Boffetta, P., Brennan, P., Menezes, A., La Vecchia, C.,  
571 McClean, M., Talamini, R., Rajkumar, T., Hayes, R.B. and Hashibe, M. (2011): An  
572 examination of male and female odds ratios by BMI, cigarette smoking, and alcohol  
573 consumption for cancers of the oral cavity, pharynx, and larynx in pooled data from  
574 15 case-control studies. *Cancer Causes Control* **22**, 1217-1231.

575 Macpherson, L.M.D. (2018): Raising awareness of oral cancer from a public and health  
576 professional perspective. *British Dental Journal* **225**, 809-814.

577 Maruse, Y., Kawano, S., Jinno, T., Matsubara, R., Goto, Y., Kaneko, N., Sakamoto, T.,  
578 Hashiguchi, Y., Moriyama, M., Toyoshima, T., Kitamura, R., Tanaka, H., Oobu, K.,  
579 Kiyoshima, T. and Nakamura, S. (2018): Significant association of increased PD-L1  
580 and PD-1 expression with nodal metastasis and a poor prognosis in oral squamous cell  
581 carcinoma. *International Journal of Oral and Maxillofacial Surgery* **47**, 836-845.

582 McAuley, A., Goodall, C.A., Ogden, G.R., Shepherd, S. and Cruikshank, K. (2011):  
583 Delivering alcohol screening and alcohol brief interventions within general dental  
584 practice: rationale and overview of the evidence. *British Dental Journal* **210**, E15-  
585 E15.

586 McGurk, M., Chan, C., Jones, J., O'Regan, E. and Sherriff, M. (2005): Delay in diagnosis and  
587 its effect on outcome in head and neck cancer. *Br J Oral Maxillofac Surg* **43**, 281-  
588 284.

589 McKay, J.D., Truong, T., Gaborieau, V., Chabrier, A., Chuang, S.-C., Byrnes, G., Zaridze,  
590 D., Shangina, O., Szeszenia-Dabrowska, N., Lissowska, J., Rudnai, P., Fabianova, E.,  
591 Bucur, A., Bencko, V., Holcatova, I., Janout, V., Foretova, L., Laggiou, P.,  
592 Trichopoulos, D., Benhamou, S., Bouchardy, C., Ahrens, W., Merletti, F., Richiardi,  
593 L., Talamini, R., Barzan, L., Kjaerheim, K., Macfarlane, G.J., Macfarlane, T.V.,  
594 Simonato, L., Canova, C., Agudo, A., Castellsagué, X., Lowry, R., Conway, D.I.,  
595 McKinney, P.A., Healy, C.M., Toner, M.E., Znaor, A., Curado, M.P., Koifman, S.,  
596 Menezes, A., Wunsch-Filho, V., Neto, J.E., Garrote, L.F., Boccia, S., Cadoni, G.,  
597 Arzani, D., Olshan, A.F., Weissler, M.C., Funkhouser, W.K., Luo, J., Lubiński, J.,  
598 Trubicka, J., Lener, M., Oszutowska, D., Schwartz, S.M., Chen, C., Fish, S., Doody,

599 D.R., Muscat, J.E., Lazarus, P., Gallagher, C.J., Chang, S.-C., Zhang, Z.-F., Wei, Q.,  
600 Sturgis, E.M., Wang, L.-E., Franceschi, S., Herrero, R., Kelsey, K.T., McClean, M.D.,  
601 Marsit, C.J., Nelson, H.H., Romkes, M., Buch, S., Nukui, T., Zhong, S., Lacko, M.,  
602 Manni, J.J., Peters, W.H.M., Hung, R.J., McLaughlin, J., Vatten, L., Njølstad, I.,  
603 Goodman, G.E., Field, J.K., Liloglou, T., Vineis, P., Clavel-Chapelon, F., Palli, D.,  
604 Tumino, R., Krogh, V., Panico, S., González, C.A., Quirós, J.R., Martínez, C.,  
605 Navarro, C., Ardanaz, E., Larrañaga, N., Khaw, K.-T., Key, T., Bueno-de-Mesquita,  
606 H.B., Peeters, P.H.M., Trichopoulou, A., Linseisen, J., Boeing, H., Hallmans, G.,  
607 Overvad, K., Tjønneland, A., Kumle, M., Riboli, E., Vålk, K., Voodern, T., Metspalu,  
608 A., Zelenika, D., Boland, A., Delepine, M., Foglio, M., Lechner, D., Blanché, H., Gut,  
609 I.G., Galan, P., Heath, S., Hashibe, M., Hayes, R.B., Boffetta, P., Lathrop, M. and  
610 Brennan, P. (2011): A Genome-Wide Association Study of Upper Aerodigestive  
611 Tract Cancers Conducted within the INHANCE Consortium. *PLOS Genetics* **7**,  
612 e1001333.

613 Miranda-Filho, A. and Bray, F. (2020): Global patterns and trends in cancers of the lip,  
614 tongue and mouth. *Oral Oncology* **102**, 104551.

615 Molnár-Gábor, F. and Korbelt, J.O. (2020): Genomic data sharing in Europe is stumbling-  
616 Could a code of conduct prevent its fall? *EMBO molecular medicine* **12**, e11421-  
617 e11421.

618 Monteiro, L.S., Warnakulasuriya, S., Cadilhe, S., Sousa, D., Trancoso, P.F., Antunes, L.,  
619 Salazar, F. and Pacheco, J.J. (2016): Oral cancer awareness and knowledge among  
620 residents in the Oporto city, Portugal. *Journal of Investigative and Clinical Dentistry*  
621 **7**, 294-303.

622 Mutsaers, B., Jones, G., Rutkowski, N., Tomei, C., Séguin Leclair, C., Petricone-Westwood,  
623 D., Simard, S. and Lebel, S. (2016): When fear of cancer recurrence becomes a  
624 clinical issue: a qualitative analysis of features associated with clinical fear of cancer  
625 recurrence. *Support Care Cancer* **24**, 4207-4218.

626 Negri, E., Boffetta, P., Berthiller, J., Castellsague, X., Curado, M.P., Dal Maso, L., Daudt,  
627 A.W., Fabianova, E., Fernandez, L., Wünsch-Filho, V., Franceschi, S., Hayes, R.B.,  
628 Herrero, R., Koifman, S., Lazarus, P., Lence, J.J., Levi, F., Mates, D., Matos, E.,  
629 Menezes, A., Muscat, J., Eluf-Neto, J., Olshan, A.F., Rudnai, P., Shangina, O.,  
630 Sturgis, E.M., Szeszenia-Dabrowska, N., Talamini, R., Wei, Q., Winn, D.M., Zaridze,  
631 D., Lissowska, J., Zhang, Z.-F., Ferro, G., Brennan, P., La Vecchia, C. and Hashibe,  
632 M. (2009): Family history of cancer: pooled analysis in the International Head and  
633 Neck Cancer Epidemiology Consortium. *International Journal of Cancer* **124**, 394-  
634 401.

635 Olivier, M., Hollstein, M. and Hainaut, P. (2010): TP53 mutations in human cancers: origins,  
636 consequences, and clinical use. *Cold Spring Harbor perspectives in biology* **2**,  
637 a001008-a001008.

638 Pagh, A., Vedtofte, T., Lynggaard, C.D., Rubek, N., Lonka, M., Johansen, J., Andersen, E.,  
639 Kristensen, C.A., von Buchwald, C., Andersen, M., Godballe, C., Overgaard, J. and  
640 Grau, C. (2013): The value of routine follow-up after treatment for head and neck  
641 cancer. A national survey from DAHANCA. *Acta Oncol* **52**, 277-284.

642 Pelucchi, C., Gallus, S., Garavello, W., Bosetti, C. and La Vecchia, C. (2006): Cancer risk  
643 associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver.  
644 *Alcohol research & health : the journal of the National Institute on Alcohol Abuse*  
645 *and Alcoholism* **29**, 193-198.

646 Posorski, E., Boyd, L., Giblin, L.J. and Welch, L. (2014): Oral Cancer Awareness Among  
647 Community-Dwelling Senior Citizens in Illinois. *Journal of Community Health* **39**,  
648 1109-1116.

649 Rodgers, J., Macpherson, L.M., Smith, G.L., Crighton, A.J., Carton, A.T. and Conway, D.I.  
650 (2007): Characteristics of patients attending rapid access clinics during the West of  
651 Scotland Cancer Awareness Programme oral cancer campaign. *Br Dent J* **202**, E28;  
652 discussion 680-681.

653 Rothman, K. and Keller, A. (1972): The effect of joint exposure to alcohol and tobacco on  
654 risk of cancer of the mouth and pharynx. *J Chronic Dis* **25**, 711-716.

655 Russo, D., Merolla, F., Varricchio, S., Salzano, G., Zarrilli, G., Mascolo, M., Strazzullo, V.,  
656 Di Crescenzo, R.M., Celetti, A. and Ilardi, G. (2018): Epigenetics of oral and  
657 oropharyngeal cancers. *Biomedical reports* **9**, 275-283.

658 Sankar, P.L. and Parker, L.S. (2017): The Precision Medicine Initiative's All of Us Research  
659 Program: an agenda for research on its ethical, legal, and social issues. *Genet Med* **19**,  
660 743-750.

661 Sankaranarayanan, R., Ramadas, K., Thomas, G., Muwonge, R., Thara, S., Mathew, B. and  
662 Rajan, B. (2005): Effect of screening on oral cancer mortality in Kerala, India: a  
663 cluster-randomised controlled trial. *Lancet* **365**, 1927-1933.

664 Scanlon, C.S., Banerjee, R., Inglehart, R.C., Liu, M., Russo, N., Hariharan, A., van Tubergen,  
665 E.A., Corson, S.L., Asangani, I.A., Mistretta, C.M., Chinnaiyan, A.M. and D'Silva,  
666 N.J. (2015): Galanin modulates the neural niche to favour perineural invasion in head  
667 and neck cancer. *Nature Communications* **6**, 6885.

668 Schaaij-Visser, T.B., Brakenhoff, R.H., Leemans, C.R., Heck, A.J. and Slijper, M. (2010):  
669 Protein biomarker discovery for head and neck cancer. *J Proteomics* **73**, 1790-1803.

670 Simpson, S., Seller, A. and Bishop, M. (2019): Using the Findings of a National Survey to  
671 Inform the Work of England's Genomics Education Programme. *Frontiers in genetics*  
672 **10**, 1265-1265.

673 Stafford, F., Ah-See, K., Fardy, M. and Fell, K. (2016): Organisation and provision of head  
674 and neck cancer surgical services in the United Kingdom: United Kingdom National  
675 Multidisciplinary Guidelines. *The Journal of laryngology and otology* **130**, S5-S8.

676 Stennett, M. and Tsakos, G. (2022): The impact of the COVID-19 pandemic on oral health  
677 inequalities and access to oral healthcare in England. *British Dental Journal* **232**, 109-  
678 114.

679 Stransky, N., Egloff, A.M., Tward, A.D., Kostic, A.D., Cibulskis, K., Sivachenko, A.,  
680 Kryukov, G.V., Lawrence, M.S., Sougnez, C., McKenna, A., Shefler, E., Ramos,  
681 A.H., Stojanov, P., Carter, S.L., Voet, D., Cortés, M.L., Auclair, D., Berger, M.F.,  
682 Saksena, G., Guiducci, C., Onofrio, R.C., Parkin, M., Romkes, M., Weissfeld, J.L.,  
683 Seethala, R.R., Wang, L., Rangel-Escareño, C., Fernandez-Lopez, J.C., Hidalgo-  
684 Miranda, A., Melendez-Zajgla, J., Winckler, W., Ardlie, K., Gabriel, S.B., Meyerson,  
685 M., Lander, E.S., Getz, G., Golub, T.R., Garraway, L.A. and Grandis, J.R. (2011):  
686 The mutational landscape of head and neck squamous cell carcinoma. *Science* **333**,  
687 1157-1160.

688 Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F.  
689 (2021): Global cancer statistics 2020: GLOBOCAN estimates of incidence and

690 mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for*  
691 *Clinicians*.

692 Thomas, S.J., Bain, C.J., Battistutta, D., Ness, A.R., Paissat, D. and MacLennan, R. (2007):  
693 Betel quid not containing tobacco and oral cancer: A report on a case-control study in  
694 Papua New Guinea and a meta-analysis of current evidence. *International Journal of*  
695 *Cancer* **120**, 1318-1323.

696 Thomas, S.J. and MacLennan, R. (1992): Slaked lime and betel nut cancer in Papua New  
697 Guinea. *Lancet* **340**, 577-578.

698 Thomas, S.J., Penfold, C.M., Waylen, A. and Ness, A.R. (2018): The changing aetiology of  
699 head and neck squamous cell cancer: A tale of three cancers? *Clinical Otolaryngology*  
700 **43**, 999-1003.

701 Tseng, K.S., Lin, C., Lin, Y.S. and Weng, S.F. (2014): Risk of head and neck cancer in  
702 patients with diabetes mellitus: a retrospective cohort study in Taiwan. *JAMA*  
703 *Otolaryngol Head Neck Surg* **140**, 746-753.

704 van Hooff, S.R., Leusink, F.K., Roepman, P., Baatenburg de Jong, R.J., Speel, E.J., van den  
705 Brekel, M.W., van Velthuisen, M.L., van Diest, P.J., van Es, R.J., Merkx, M.A.,  
706 Kummer, J.A., Leemans, C.R., Schuurin, E., Langendijk, J.A., Lacko, M., De Herdt,  
707 M.J., Jansen, J.C., Brakenhoff, R.H., Slootweg, P.J., Takes, R.P. and Holstege, F.C.  
708 (2012): Validation of a gene expression signature for assessment of lymph node  
709 metastasis in oral squamous cell carcinoma. *J Clin Oncol* **30**, 4104-4110.

710 Vigneswaran, N. and Williams, M.D. (2014): Epidemiologic trends in head and neck cancer  
711 and aids in diagnosis. *Oral and maxillofacial surgery clinics of North America* **26**,  
712 123-141.

713 Warnakulasuriya, S. (2009): Global epidemiology of oral and oropharyngeal cancer. *Oral*  
714 *Oncol* **45**, 309-316.

715 Weinstein, J.N., Collisson, E.A., Mills, G.B., Shaw, K.R., Ozenberger, B.A., Ellrott, K.,  
716 Shmulevich, I., Sander, C. and Stuart, J.M. (2013): The Cancer Genome Atlas Pan-  
717 Cancer analysis project. *Nature Genetics* **45**, 1113-1120.

718 Williams, H.K. (2000): Molecular pathogenesis of oral squamous carcinoma. *Molecular*  
719 *Pathology* **53**, 165-172.

720 World Health Organization (WHO) (2016): World Health Organization (WHO): International  
721 statistical classification of diseases and related health problems (10th ed.). From  
722 <https://icd.who.int/browse10/2019/en#/>.

723 Yonezawa, K., Nishiumi, S., Kitamoto-Matsuda, J., Fujita, T., Morimoto, K., Yamashita, D.,  
724 Saito, M., Otsuki, N., Irino, Y., Shinohara, M., Yoshida, M. and Nibu, K. (2013):  
725 Serum and tissue metabolomics of head and neck cancer. *Cancer Genomics*  
726 *Proteomics* **10**, 233-238.

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737 **Tables**

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

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	<b>Main site</b>	<b>ICD-10 Code</b>
	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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756 **Table 2.** Less well established risk factor associations for oral cavity cancer

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<b>Risk factor</b>	<b>Level of exposure</b>	<b>Odds risk (95% CI) for oral cancer</b>	<b>Reference</b>
<b>Family history</b>	Oral cavity cancer in first degree relatives	OR 1.53 (1.11, 2.11)	(Negri <i>et al.</i> , 2009)
<b>BMI</b>	<18.5	OR 2.58 (2.00, 3.40)	(Lubin <i>et al.</i> , 2011)
<b>Diet</b>	Vegetable intake (4 <sup>th</sup> vs 1 <sup>st</sup> quartile)	OR 0.69 (0.61, 0.79)	(Chuang <i>et al.</i> , 2009)
	Fruit intake (4 <sup>th</sup> vs 1 <sup>st</sup> quartile)	OR 0.46 (0.38, 0.56)	
<b>Type 2 Diabetes Mellitus</b>	History of diabetes vs no diabetes	OR 1.74 (1.47, 2.06)	(Tseng <i>et al.</i> , 2014)
<b>Oral health / hygiene</b>	<5 missing teeth vs $\geq$ missing teeth	OR 0.69 (0.64, 0.76)	(Hashim <i>et al.</i> , 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)	
<b>Socioeconomic factors</b>	Low educational attainment	OR 1.85 (1.60, 2.15)	(Conway <i>et al.</i> , 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 <i>et al.</i> , 2021)

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771 **Figures**

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773 **Figure 1.** Established risk factor associations for oral cavity cancer

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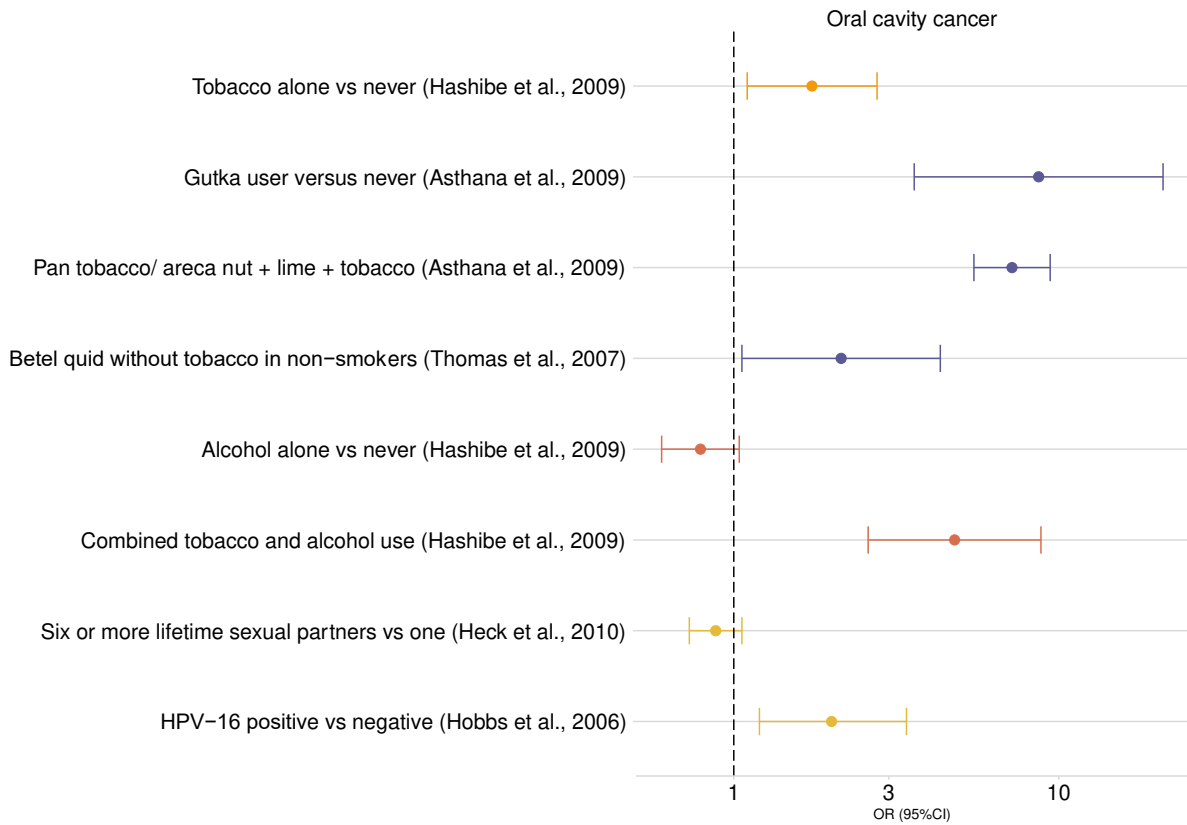


Figure adapted from results taken from the largest pooled analyses by Hashibe et al. (2009), Asthana et al. (2019), Thomas et al. (2007), Heck et al. (2010) and Hobbs et al. (2006). Error bars represent 95% confidence intervals (95%CI).

803 **Figure 2.** Distribution of the most frequently mutated genes in oral squamous cell carcinoma

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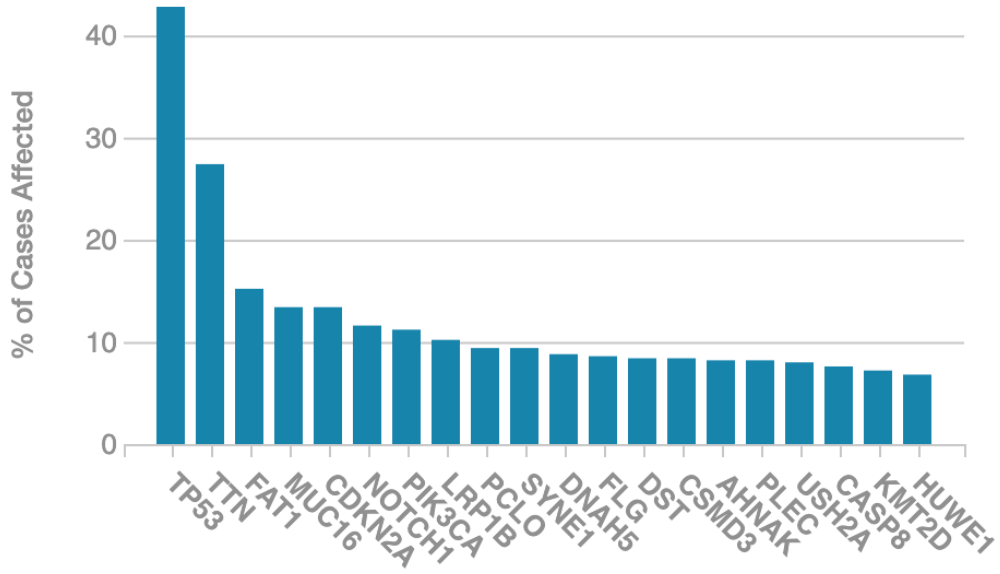
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814 The Cancer Genome Atlas (TCGA) data available on the Genomic Data Commons results published here are in whole or

815 part based upon data generated by the TCGA Research Network: <https://www.cancer.gov/tcga>. Copyright free graphics

816 (Grossman *et al.*, 2016).

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