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REVIEW

Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden

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Survival from head and neck cancers (HNCs) of the lip, oral cavity, pharynx, and larynx has increased by 10% over the past few decades. Little over half of patients who develop HNCs will survive beyond 5 years. Survival is lower for individuals in many countries where traditional risk factors such as tobacco smoking, alcohol drinking, and betel quid chewing are highly prevalent but tertiary health care center access is limited or unavailable. Early diagnosis of HNC is the most important prognostic factor for each tumor site. Molecular-based research on HNC tumors holds promise for early stage detection, screening, vaccination, disease follow-up, and progression. Future investments for HNC control must consider both effectiveness and sustainability for both high- and low-resource countries alike, with priority toward risk factor prevention and earlier diagnosis.

Key words: head and neck neoplasms, mouth neoplasms, early detection of cancer/statistics & numerical data, mouth neoplasms/diagnosis, dentists, cancer prevention

Introduction

Head and neck cancers (HNCs) of the lip, oral cavity, oropharynx, hypopharynx, and larynx predominantly begin in the squamous cells (∼90%) [1] that line mucosal surfaces. Approximately 30%–40% of HNC patients present with early-stage disease and have a 5-year survival of 70%–90% with treatment [2]. Most cases of HNC are diagnosed at advanced stages, when medical treatment is less effective and surgical treatment is mutilating to organs required for speech and swallowing. For individuals in countries with limited access to tertiary health care centers, survival rates are 30%–40% [3–6] compared with approximately two-thirds of HNC surviving in the United States [2]. Apart from tongue and oropharyngeal/tonsillar cancers, the 5-year survival has increased modestly in the past two decades within the United States [7]. The overall 5-year relative survival rate increased 20% from 54.7% in 1992–1996 to 65.9% in 2002–2006 [8].

The low HNC survival rate is driven by both late diagnostic stage and risk-associated behaviors with long-term health consequences. Among patients with predictive markers for metastatic disease, nodal involvement and extracapsular tumor spread, survival rates drop 10%–25% [9–11]. Even after treatment, 30%–60% of patients diagnosed at late stage with successful remission will develop recurrent locoregional cancer or second primary cancers [12–15]. Due to prior treatment effects on tumor cells, recurrent cancer has a higher likelihood of tissue infiltration by tumor cells, and multifocality [16].

HNCs are typically caused by tobacco, alcohol, and viral exposure as opposed to cancers due to germline variants in high penetrance genes. This is consistent with what is known about HNC tumors arising in environmentally exposed epithelial tissue and is consistent with large population attributable to exposure to well-established genotoxic agents, including tobacco, betel nut, and alcohol and now human papillomavirus (HPV). Considering low survival of late-stage HNCs, reduction of risky behaviors and early detection of HNCs are keys in reducing incidence, cost burden, and mortality. Thus, HNC prevention should aim to improve two fundamental domains of patient care: risk behavior reduction to decrease HNC incidence (primary prevention) and accuracy and precision of early diagnostic detection (secondary prevention).

Primary prevention: exposures, risk, and populations

An estimated 705 781 cases and 358 144 deaths worldwide due to lip, oral cavity, oropharyngeal, and hypopharyngeal cancers occurred in 2018 [17]. HNCs account for 3% of malignancies and ~51 540 HNC cases were diagnosed in the United States in 2018 [18]. Regionally estimated HNC incidence rates vary from 26.3 per 100 000 persons in Melanesia to 2.2 per 100 000 persons in Western Africa [19]. Wide variations are likely due to differences in risk factor exposure prevalence rates, including tobacco, alcohol consumption, betel quid chewing, and HPV.

Males are significantly more likely to develop HNC than females with an incidence ratio ranging from 2 : 1 to 4 : 1 [20]. The average age of diagnosis is 50–70 years [21]. The incidence rate in males exceeds 20 per 100 000 in France, Hong Kong, the Indian subcontinent, Central and Eastern Europe, Spain, Italy, and Brazil [22]. Mouth and tongue cancers are more common in the Indian subcontinent, contributing more to the overall cancer burden compared with other countries [23, 24]. Inherited susceptibility differences are small and may play a more important role in younger patients [25].

Established risk factors

Tobacco

Tobacco (smoked and smokeless) exposure is the largest known and most well-established contributor to HNCs (Table 1) [26–28]. An estimated 75% of lip, oral cavity, and pharyngeal cancers are attributable to tobacco smoking and alcohol consumption in Western Europe [29]. Heavy cigarette smokers have a 5- to 25-fold increased HNC risk compared with nonsmokers [30, 31]. Both cigar- and pipe smoking also increase HNC risk, even among those who have never smoked cigarettes [32].

Smokeless tobacco products are also associated with an increased HNC risk, particularly for oral cavity cancer [31, 33]. HNC risk is increased in never smokers using snuff, compared with never-users of snuff [odds ratio (OR): 1.7; 95% confidence interval (CI): 1.1–2.7 for HNCs, and OR: 3.0; 95% CI 1.6–5.6 for oral cavity cancers] [31]. Secondhand tobacco smoke exposure may be a contributing factor toward HNC risk [34, 35], although due to the retrospective design of these studies a causal relationship has not been firmly established.

There is some evidence that the carcinogenic effects of tobacco may modify HNC risk among individuals with genetic predisposition in metabolic enzymes [36]. Individuals with the highest exposure to tobacco or alcohol are most prone to secondary cancers with a 4.7-fold risk for heavy smokers (>2 packs/day for 20 years) and a 3.8-fold risk for heavy drinkers (>15 beers/week) [37]. With smoking cessation, HNC risk is reduced to near pre-smoking risk after ≥20 years [38, 39].

A systematic review article examining the impact of interventions, nurse-delivered cognitive–behavior therapy, and pharmacotherapy reported significant improvements in smoking cessation rates for HNC patients [40]. There was no significant improvement in quit attempts or cigarettes smoked per day among patients who were briefly advised by a physician, nurse, or given enhanced advice with the help of self-help booklets and booster sessions by surgeon only [40]. Another systematic review of intervention studies for cancer patients overall has supported the use of combination of pharmacologic and non-pharmacologic approaches in smoking cessation [41].

Alcohol

Alcohol drinking without smoking has been estimated to contribute 4% of HNCs worldwide [42]. As the second major risk factor for HNCs, alcohol acts as a solvent to enhance mucosal exposure to carcinogens, increasing cellular uptake of other carcinogens such as those contained in smoking and diet [43]. In addition, acetaldehyde, the main metabolite of alcohol, forms DNA adducts, potentially leading to mutations [43].

The majority of ethanol is eliminated in the liver via enzymatic oxidation to acetaldehyde and acetate, catalyzed by the various isoenzymes of alcohol dehydrogenase (ADH). Aldehyde dehydrogenase (ALDH) is a superfamily of 19 human isoforms that metabolizes reactive aldehydes produced from alcohol into non-reactive acids [44]. For squamous cell HNCs, ALDH activity is elevated in subpopulations of cells that are chemo/radiotherapy-resistant and high levels of ALDH1 in HNC patient samples are correlated with poor prognosis [45]. The most recent systematic review found a significant interaction between the *ADH1C* variant genotype and alcohol consumption. The *ADH1C**2-2 genotype conferred a large, significant elevation in head and neck squamous cell carcinoma risk among the heavier alcohol drinkers (≥30 drinks/week) although the interaction had a less dramatic effect on HNC for heavy smoking. This suggests that the homozygous variant genotype of the *ADH1C* gene acts by increasing the HNC risk conferred by alcohol consumption [45].

The dose–response relationship has been consistent for both duration and amount of drinking and HNC risk [28, 30, 46]. It remains unclear whether the type of alcoholic beverage (wine, beer, or spirits) affects HNC risk after adjustment for total amount consumed and alcohol concentration [47, 48]. Among never/non-current smokers, pooled relative risks (RRs) were 1.3 (95% CI 1.1–1.7) for drinking and 2.5 (95% CI 1.8–3.6) for heavy drinking. A meta-analysis of case–control and cohort studies found RRs for any alcohol drinking, irrespective of smoking, were 2.1 (95% CI 1.4–3.3) for wine-, 2.4 (95% CI 1.9–3.1) for beer-, and 2.3 (95% CI 1.8–3.0) for spirits-only drinking. The corresponding RRs for heavy drinking were 4.9 (95% CI 2.8–8.7), 4.2 (95% CI 1.4–12.4), and 5.2 (95% CI 2.8–9.8) [42]. However, in an international pooled case–control study, authors observed similar associations with ethanol-standardized consumption frequency for beer-only drinkers [ORs = 1.6, 1.9, 2.2, and 5.4 for ≤5, 6–15, 16–30, and >30 drinks per week, respectively; P(trend) < 0.0001] and liquor-only drinkers (ORs = 1.6, 1.5, 2.3, and 3.6; $P < 0.0001$). Among wine-only drinkers, the ORs for moderate levels of consumption frequency approached the null. Only individuals with higher wine consumption levels were comparable to those of drinkers of other beverage types (ORs = 1.1, 1.2, 1.9, and 6.3; $P < 0.0001$) [49].

Control of heavy drinking remains an important target for HNC control as well as for several other cancers. Individuals consuming 50 or more grams of alcohol per day (~3.5 or more drinks per day) have at least a two to three times greater risk of

Table 1. Summary of population attributable fractions for head and neck cancers

Cancer site	Risk agent	Population attributable fraction (%)	Population	Region	Outcome	Study design	Reference
Oral cavity	Betel quid without tobacco	53.7	T	Taiwan and China	Incidence	Meta-analysis	[66]
	Betel quid with tobacco	49.5	T	India			
	Tobacco	2.8	T	Multicenter East Asian		Case–control	[153]
	Poor oral hygiene	8.9	T	Multicenter international		Case–control	[154]
	Tobacco	9.8	M	France			[158]
		22.4	F				
	Alcohol	31.5	T	Multicenter East Asian			[153]
	Tobacco and alcohol together	74.0	M	France			[158]
		45.4	F				
Oral and pharynx	Tobacco	69.5	M	UK		National survey	[156]
		54.9	F				
	Alcohol	37.3	M				
		16.9	F				
	Low fruit and vegetable intake	57.2	M				
		53.6	F				
	Infections (predominantly HPV)	12.3	M				
		14.0	F				
	Occupation	0.6	M				
		0.2	F				
Orophaynx	Tobacco	24.6	M	China	Mortality		[155]
		2.8	F				
	Tobacco	10.8	T	Multicenter East Asian	Incidence	Case–control	[153]
	Alcohol	34.0	M	China	Mortality	National survey	[155]
		5.5	F				
	Alcohol	34.0	M	Lebanon	Incidence	Nationwide survey	[157]
		4.0	F				
	Low fruit and vegetable intake	61.4	Urban	China	Mortality	National survey	[155]
		57.1	Rural				
	Human papilloma virus (HPV)	39.7	T				
Larynx	Tobacco	24.6	M				
		2.8	F				
	Tobacco	74.0	M	Taiwan and China	Incidence	Meta-analysis	[66]
		65.0	F	Taiwan and China			
	Alcohol	8.7	M	China	Mortality	National survey	[155]
		1.1	F				

T, total; M, male; F, female.

developing HNCs than nondrinkers [50]. The European Code against Cancer, a list of cancer-preventive strategies for public health initiatives, recommends limiting daily alcohol consumption or completely avoiding alcohol for overall cancer prevention [51].

Combined risk of alcohol and tobacco

Risk is more than multiplicative for those who use tobacco and alcohol together. More frequently, HNC occurs when both alcohol and tobacco are used in combination, explaining 85% of hypopharyngeal/laryngeal cancers, 75% (in some series) of non-HPV oropharyngeal cancers (OPCs), and 61% of oral cavity cancers [52]. Indeed, concurrent heavy exposure to tobacco and alcohol increases HNC risk 40-fold [43]. Two carcinogenic agents, such as tobacco or alcohol, can interact to modify HNC risk on a multiplicative scale [53]. After repeated exposure of a long duration, multiple primary and secondary tumors (arising among patients cured of a primary tumor) can occur in the area affected by the accumulation of carcinogenic alterations at the mucosal surface, a phenomenon described as 'field cancerization' [54, 55]. Thus, although smoking and alcohol each have separate effects on HNCs, they also have a harmful combined effect. Worldwide, tobacco or alcohol was attributed to 72% (95% CI 61% to 79%) of HNC cases, of which 35% were due to tobacco and alcohol combined [42].

Although the prevalence of tobacco smoking and alcohol drinking has been decreasing or stable in most high-income countries such as the United States, both tobacco and alcohol risk factors have been increasing in low- to middle-income countries

in Africa, Asia, and South America with some regional variation for alcohol use [56, 57]. Even within the United States, racial disparities may be explained only partly by risk factor prevalence differences. A large and pooled case–control study was able to more precisely estimate associations between cigarette smoking and alcohol use and HNC by subsite in blacks in the United States [58]. Associations for cigarette smoking and HNC were modestly higher among blacks compared with whites, whereas estimates of association of alcohol use and HNC were similar or slightly higher. After the exclusion of oropharyngeal cases, which are known to be more likely HPV-negative among black Americans [42], the differences by race for tobacco use remained but were attenuated while alcohol use associations were not [58]. The reason for these differences in risk by race is not known, but could possibly be due to differences in alcohol and tobacco metabolism, differing usage, and cessation patterns by race [58].

Betel quid

In South Asia, Southeast Asia, and the Pacific islands, a large proportion of oropharyngeal and oral cavity cancers can be attributed to betel quid chewing [25, 59, 60]. Betel quid chewing prevalence has been reported to vary from 33.8% in rural Sri Lanka [61] to 76.8% in the Solomon Islands [62], and is rare in North America and Western Europe. In endemic countries, betel quid chewing dates back thousands of years and is integrated into both ceremonial situations and daily life [63]. Betel quid users chew recreationally and during working hours for pharmacological effects: euphoria, heightened alertness, focused attention, appetite suppression, and improved digestion [64]. Approximately 600 million people worldwide chew betel quid [61], and it is the fourth most commonly consumed psychoactive substance behind alcohol, nicotine, and caffeine [65].

Betel quid consists of areca nut in ripe, unripe, or baked form and often includes slaked lime (calcium oxide and calcium hydroxide) obtained from coral, shellfish, or limestone. These ingredients are wrapped in the leaf, stem, or inflorescence from the *Piper betle* plant, and may include the addition of other regionally variable ingredients: catechu (an extract of acacia trees), tobacco (in raw or processed form), and/or other spices and herbs [61]. Tobacco is commonly added to betel quid in India, Pakistan, and Bangladesh [65]. Catechu, an astringent vegetable extract containing tannin, is sometimes added in Sri Lanka, West Malaysia, and Melanesia [61]. Similar to tobacco snuff, betel quid is placed in contact with the oral mucosa and absorbed. HNC risk from betel quid chewing is thus highest for oral cavity cancers followed by pharyngeal cancers.

Betel quid, regardless of whether or not tobacco is added, is an independent risk factor for HNCs [66]. Given variations in betel quid preparation, RRs for oral cancer/OPC were calculated regionally and were all elevated. In the Indian subcontinent, the RR was increased nearly threefold based on 15 studies for betel quid without tobacco added and nearly eightfold based on 31 studies for betel quid with tobacco [66]. In Taiwan, the RR for betel quid without tobacco was over 10-fold based on 13 studies [66]. Positive dose–response curves were observed for number of betel quid chewed per day and duration of chewing in years in separate studies from India and Taiwan [66, 67].

A meta-analysis based on surveys of 40 346 cases from India, Taiwan, and China estimated that eliminating the most common betel quid combination in each country would prevent roughly half of oral cancers in these countries [66]. In Northern Thailand, the age-standardized annual incidence of oral cancer per 100 000 males dropped from 3.6 (1988–1991) to 1.2 in 1999 ($P_{trend} = 0.0002$) and in females from 2.6 (1988–1991) to 1.1 in 1999 ($P_{trend} = 0.01$) [68]. The decrease was linked to the changing behavior of betel quid chewing among the teenage and young adult population, many of whom admitted to not habitually incorporating betel quid chewing in their daily life [69, 70]. However, in Taiwan, HNC patients who used betel quid were significantly younger than HNC patients who did not chew [67].

A study in Guam reported that smokers made two times as many quit attempts on average as quid chewers (11.5 versus 5.2) [71]. Given that physiological or physiological dependence has not been established, treatment with cessation intervention adapted for betel quid chewers should focus on two core aspects: education about the health risks associated with betel quid chewing and a focus on social and psychological aspects of betel quid chewing. A strong social/cultural component should teach chewers skills for effectively dealing with social pressure to chew and culturally tailored training in refusal [72]. There is a gap of knowledge between betel quid cancer risk and preventive strategies aimed at betel quid chewing cessation. To inform public health measures, future domains of investigation should include: psychosocial causes of dependence, betel quid chewing patterns, and withdrawal symptoms.

Human papillomavirus

HPV serotypes are distinguished by genetic sequence diversity of the L1 viral capsid protein and as many as 20 high-risk serotypes have been identified. Although multiple high-risk serotypes cause HNC, type 16 is the most frequently associated with oropharynx and anal cancer [43]. HPV16 is responsible for 85%–90% of HPV-related OPC in North America [43]. Other high-risk serotypes account for the remaining 10%–15% [73]. This is distinctly different from cervical cancer where HPV16 and 18 are both frequent and combined account for 50%–75% of cervical cancer cases [74]. HPV oncogenesis is contingent on direct viral access to basal keratinocytes, occurring on specific subsites: primarily in the tonsil and base of tongue and occasionally in watershed areas of the supraglotiic larynx and nasopharynx [75]. In the epidermis and anogenital region, viral access is mediated largely through microabrasions secondary to sexual contact [75].

OPC incidence has been increasing in the United States, the UK, and other high-income countries in recent years, particularly among individuals without traditional risk factors [43, 76–78]. The recent increase may be driven by increasing oral exposure to HPV infection as HPV accounts for up to 72% of all OPCs in high-income countries and to a much less extent (13% of OPC) in lower income countries [77, 78]. Although oropharyngeal and cervical cancers share a common etiology, OPC incidence has surpassed that of cervical cancers in the United States [79, 80]. The incidence of HPV-positive OPC increased by 225%, whereas the incidence of HPV-negative OPC declined by 50% in 271 OPCs from 1984 to 2004 [81]. In contrast to OPC, HPV16 only represents 60% of type-specific infections in cervical cancer, with

HPV18 being the next most common type-specific infection in cervical cancer [82].

The increasing annual incidence of OPC is also more apparent among men, although incidence has been increasing in females, and is likely due to increases in HPV exposure [83]. From 1973 to 2012, HNCs have increased annually by 0.6% and for white men during 2008–2012 there has been a 5.1% annual increase [84]. Prevalence is increasing in young people who have never smoked or have a relatively short smoking history [22]. Incidence has increased in the last decade, particular for those <45 years and especially among men [22], although the highest OPC incidence rate remains between the ages of 55–64 [85].

Incidence of HPV-related OPCs has been increasing worldwide, particularly in North America and northern Europe. In the UK, the incidence of oral cancer and OPC in men rose 51%, from 7 to 11 per 100 000 person-years between 1989 and 2006 [86]. HPV-positive OPC occurs more frequently among white than black Americans, underscoring that HNC incidence disparities within the United States [83]. Survivors are also more likely to be white and younger at age of diagnosis [87]. The incidence of non-HPV-associated HNCs is now ∼50% higher in black American men [88]. The higher mortality among black American men associated with OPCs may reflect the lower prevalence of HPV positivity and a higher rate of smoking [43, 88]. It is also possible that a delayed increase in incidence among nonwhite individuals could be partly due to changes in behaviors and exposures that occurred earlier among white men than among black American men [89]. The rise in female OPC incidence is more likely related to a delayed decline in tobacco-related OPC as the decline in smoking rates is observed in women after men, following the Lopez et al.'s descriptive model of tobacco prevalence trends [90, 91].

HPV-positive OPC has a favorable prognosis compared with HPV-negative OPC. HPV-positive patients have a longer median survival than HPV-negative patients (130 versus 20 months, respectively) [81], and survival is significantly better for HPV-positive patients both at the time of the primary diagnosis and at disease recurrence [26, 92]. HPV-status independently reduced the risk of death due to OPC by 64%, independent of age, tumor stage, and prognostic Eastern Cooperative Oncology Group performance scores [93]. The more favorable prognosis for HPV-positive tumors has led to new staging criteria for HPV-positive OPC reflective of the higher range of survival probability for these cancers [76].

HPV vaccination

For both high- and low-income countries, vaccination programs hold great promise in reducing the incidence of anogenital cancers as well as very highly likely protection against OPC, although this is yet to be studied in a vaccinated population [94].

Vaccines targeted against HR HPV infection have diagnostic applications via the induction of antibody-mediated immunity against HPV capsid antigens [95]. Gardasil®, Gardasil-9® (Merck & Co., Inc., Whitehouse Station, NJ), and Cervarix® [GlaxoSmithKline (GSK), Research Triangle Park, NC], approved by the US Food and Drug Administration for cervical cancer prevention, target the most common HPV types associated with cancer (both HPV16 and 18) but have not yet been evaluated for oropharyngeal sites. Approximately 70% of cervical cancers and a larger proportion of HPV-associated non-cervical cancers (∼86%–95%) are caused by HPV16 and 18 [96].

The biologic efficacy of HPV vaccines Gardasil [82] and Cervarix [97–99] in prevention of cervical infection and cancer was established through four large blinded randomized phase III clinical trials performed in women ages 15–26. Approved HPV vaccines can prevent non-cervical HPV infections, including anogenital and precancerous lesions that lead to HPV-associated cancers. Randomized trials have provided strong evidence for Cervarix [100] and Gardasil™ in protecting against female genital diseases including vaginal and vulvar HPV-associated lesions [101] and against female anal HPV-related infections [102]. A randomized trial in Costa Rica showed that Cervarix was also highly effective in preventing oral infection with HPV16 and 18, suggesting that HPV vaccination may protect against HPV-associated OPCs [100]. A cross-sectional study on a representative US population found that the prevalence of oral HPV16, 18, 6, and 11 infections was reduced in vaccinated versus unvaccinated individuals (0.11% versus 1.61%; $P_{adj} = 0.008$), corresponding to an 88.2% (95% CI 5.7% to 98.5%) prevalence reduction [85].

As HPV-vaccination has been licensed in 2006 [95] the latency period has not yet been sufficient to observe the full impact of current HPV vaccines on oropharyngeal HPV-related cancers. Recent reports on HPV prevalence and HPV-related infections are encouraging. The US Centers for Disease Control and Prevention compared HPV infection rates before vaccination (2003–2006) and after vaccination (2009–2012) [103]. The prevalence of HPV6, 11, 16, and 18 decreased by 64% in sexually active girls and women aged 14–19 years and by 34% in those aged 20–24 years [103]. Likewise, an Australian study had shown that the proportion of girls and women, as well as boys and men, developing genital warts decreased significantly after the implementation of a national HPV vaccination program in 2007 [89]. Although previously HPV vaccination programs have focused on girls, vaccination of boys is particularly because HPV-related OPCs are increasing in high-income countries, and men make up a large proportion of the OPC burden [104]. Primary prevention with HPV vaccination of both girls and boys has the potential to prevent the increasing burden of OPCs [104]. However, the impact of HPV-vaccination for OPC prevention has not yet been tested in large clinical trials and will take decades to be evident.

Secondary prevention: identifying high-risk individuals and earlier diagnosis

For the past two decades, reducing HNC burden through earlier detection has been a major challenge. Secondary HNC prevention has thus focused on two primary aims: identifying high-risk individuals and screening modalities.

Identifying high-risk individuals

The highest risk of developing HNC is having a medical history of a primary HNC tumor; even after lifestyle modification, previous HNC patients have a 2%–7% increased risk of HNC second

primary tumor per year [105, 106]. Reasons include shared risk factors such as tobacco smoking and alcohol drinking, genetic instability and mutations, pre-existing genetic susceptibility, and immunodeficiency following chemotherapy, radiotherapy, immunosuppression for autoimmune diseases and transplant, and/or surgical treatments [107]. Individuals with the premalignant dysplastic oral leukoplakia have an ~12% overall oral cancer risk, with a malignant transformation range from 1% to 5% at 5 years, and 30% increased risk at 10 years following treatment [108, 109]. Individuals with the hereditary diseases and syndromes, Fanconi anemia, Li–Fraumeni syndrome, Dyskeratosis congenital, and Plummer–Vinson syndrome, are also at increased risk [110].

Individuals most susceptible to late-stage HNC diagnosis are individuals without medical history or comorbid disease because early HNC symptoms are often nonspecific and do not provide adequate information for early diagnosis [110]. Apart from strong hereditary risk factors, the most effective and strategic approach aimed at HNC reduction is to identify high-risk people and to inquire about risk factors: tobacco smoking/chewing, betel quid chewing particularly from individuals from the Pacific rim and India, high alcohol intake, and sexual activity. This can be accomplished in new patient encounters after identifying high lifestyle risk factors through medical history-taking, although the effectiveness of this procedure as a screening strategy remains an understudied area of research.

There is evidence that repeat oral cavity inspection and examinations may be an effective screening tool for patients who have considerable prior contact with primary health care providers. Continuity of care with the same primary care provider alone was independently associated with an earlier diagnosis for HNCs. A dose–response pattern for continuous primary care was associated with earlier stage diagnosis for oral cavity cancers, but not for laryngeal cancers or pharyngeal cancers [107, 111].

Screening approaches

Several approaches have been considered for oral cavity cancer screening, including visual inspection, genetic-based tests, and HPV testing. However, the three major barriers to large-scale implementation of secondary HNC prevention measures are as follows: (i) no strong evidence to date that secondary HNC prevention is effective in substantially reducing HNC mortality when applied, (ii) a lack of consensus of which population should be screened and (iii) no risk-based systematic screening protocol or algorithm for HNCs that can readily be applied.

As of 2017, clinicians are required to perform an oral examination as part of patient encounters [112, 113]. The National Institute for Dental and Craniofacial Research (NIDCR) provides a website-based pictorial oral cancer examination protocol for dental practitioners [73]. Recommendations recently published by the American Dental Association (ADA) Council on Scientific Affairs include: (i) obtaining an updated medical, social, and dental history and performing an intraoral and extraoral conventional visual and tactile examination in all adult patients; (ii) performing biopsy of suspicious lesion or specialist referral and (iii) salivary and light-based adjuncts are not recommended for evaluating lesions for malignancy [112, 113]. However, whether this will decrease the burden of HNC and the effect estimate of the evidence that these ADA recommendations are based on has been reported to be low [112, 113].

For average-risk or asymptomatic people, oral cancer screening is also recommended as part of a cancer-related checkup during routine medical physical examinations by the American Cancer Society [114]. In most physician–patient encounters, this oral examination often includes looking for leukoplakia and erythroplakia lesions, which can progress to cancer [94]. *Healthy People 2020* review, managed by the US Department of Health and Human Services, set goals to increase the number of adults with an annual oral cancer screening and the proportion of oral cancer diagnosed at the local stage from 23% to 29% [115]. Despite these recommendations, only 15%–19% of adults aged ≥40 years report receipt of an oral cancer examination in their lifetime [116–118]. There is currently no standard or routine screening test to diagnose lip, oral cavity, and pharyngeal cancers, and no screening guidelines have been provided for the early detection of lip, oral cavity, and pharyngeal leukoplakia and erythroplakia lesions or cancers in the general population.

The lack of HNC screening consensus is due to the paucity of well-designed, randomized prospective trials. The US Preventive Services Task Force has concluded that current evidence is insufficient to assess the balance of benefits versus harms of oral cancer screening in asymptomatic adults [116].

It is possible that high-risk individuals visit their medical doctors more frequently than they visit their dentists. Although physicians are more likely to provide risk-factor counseling (tobacco cessation or alcohol reduction), they are less likely than dentists to perform oral cancer examinations [119]. Depending on population characteristics, targeting individuals at highest risk may also not necessarily identify the most disease [107]. Community-based screening events attract a significantly greater proportion of participants with HNC behavioral risk factors, but hospital-based screening events attract a substantially greater proportion of patients with a past medical history of otolaryngologic cancer or treatment and substantial medical comorbidities. As these two HNC screening scenarios attract fundamentally different types of participants, they require different allocation of resources. For a community-based approach, the high-risk factor population may present with more early-stage HNCs, which are highly treatable. For a hospital-based approach, drawing from a population with a higher rate of concerning signs and symptoms [107], screening might be used not only to diagnose but also to rule out or monitor HNC in patients with a past medical history [107].

Visual inspection

As oral cavity cancer occurs in a region that is generally visible to the patient, dentists, and physicians, visual examination is the most common accessible and opportunistic screening modality available in many countries. In the US National Health Interview Survey, over 93% of older adults who developed localized tumors and 88% of persons who developed advanced tumors had one or more physician visits in the year before diagnosis [116].

In the largest randomized controlled trial to date, enrolling over 100 000 Indian patients, visual screening for oral cavity cancers was efficacious in early detection for high-risk tobacco and

alcohol users [120]. Eligible participants had no known comorbidities, were aged 35 years and older with no past history of oral cavity cancer, and were questioned about occupation and lifestyle habits, including tobacco smoking/chewing and alcohol use. Trained health care workers screened individuals with high-risk behaviors by inspecting the labial and buccal mucosa, retromolar area, gingiva, anterior tongue, floor of mouth, and hard palate under bright daylight and/or with the aid of a flashlight. The findings were recorded as: normal or non-referable lesions (e.g. fissures in the tongue, aphthous ulcers, black patches, blanching), referable lesions that were suggestive of precancerous lesions (e.g. white lesions, ulcerated or nodular white lesions, verrucous lesions, red lesions, oral submucous fibrosis), or lesions suggestive of cancer (e.g. suspicious ulcers or growths). A positive screening test was defined as the presence of one or more of the referable lesions. Screen-positive individuals were referred for further investigation, and screen-negative individuals were advised to receive repeat screening after 3 years for a maximum of three rounds.

At the end of the trial, the mortality rate ratio (RR) for those who were in the screening intervention group compared with patients not in the intervention group was 0.8 (95% CI 0.5–1.2). Among tobacco and alcohol users, the mortality rate ratio was even lower [MRR 0.6 (0.4–0.9)] for males and MRR 0.8 (0.4–1.4) for females. There was a qualitative difference in screening effect for non-tobacco or alcohol users: 3.0 versus 0.9 per 100 000 person-years in the screened versus controlled arms (RR 3.5; 95% CI 0.1–96.5). Although there were a higher number of early-stage (I and II) cases in the screened arm versus the control arm (85 versus 37), the number of late-stage (III and IV) cancers was similar (104 versus 105); the proportion of cases with early-stage disease was higher in the screened arm.

A large study of patients in India and Sri Lanka detecting oral cavity cancer lesions found no evidence of reduced mortality due to poor compliance following initial screening [75]. Rather, evidence supports a benefit from continuous and repeated screening. A cluster-randomized controlled trial in Kerala, India, found that a larger reduction in oral cavity cancer morality was observed for patients who adhered to repeated inspection rounds. A 38% reduction in oral cavity cancer incidence (95% CI 8% to 59%) and 81% reduction in oral cavity cancer mortality (95% CI 69% to 89%) were observed for tobacco and/or alcohol users attending four screening rounds performed by trained health workers [121]. A cost-effectiveness study published by the same group found that visual screening could be offered at a reasonable cost for low-income settings—under 6 US dollars (USD) per person [122]. The incremental cost per life-year saved was 835 USD for all eligible individuals and 156 USD for high-risk tobacco and/or alcohol users [122]. After 9 years (three screening program cycles), the benefit was 269 life-years saved per 100 000 individuals and 1437 life-years for those at high risk. This fulfilled the target set by the World Health Organization (WHO) Commission on Macroeconomics and Health, defining the benchmark of cost-effective intervention to be when its cost-effectiveness ratio is less than a country's gross domestic product per capita [123]. It remains to be determined whether the screening program can reduce oral cavity cancer mortality in Western or low risk populations.

Adjunctive techniques to visual examination

Compared with visual examination, toluidine blue staining, brush biopsy/cytology, or fluorescence imaging have not been shown to have superior sensitivity and specificity as the primary screening tool or adjunct for screening [94, 124]. A systematic review of oral cancer screening randomized controlled trials evaluated the effectiveness of visual examination with adjunctive technologies. Apart from oral examination, oral cavity cancer mortality was not reduced when patients were screened using toluidine blue, brush biopsy, or fluorescence imaging [94]. A mortality risk reduction of 24% was found for oral visual inspection for individuals who used alcohol or tobacco [94]. In a randomized control trial conducted in Taiwan, 7975 individuals at high risk due to cigarette smoking or betel quid chewing were randomly assigned to receive a one-time oral cancer examination after gargling with toluidine blue or a blue placebo dye [125]. Positive test rates were 9.5% versus 8.3%, respectively ($P = 0.047$). The detection of premalignant lesions was not different between either group (RR 1.1; 95% CI 0.7–1.4) and the number of oral cancers diagnosed within the short follow-up period (5 years) was too small for valid comparison (six in each group).

A systematic literature review of toluidine blue, a variety of other visualization adjuncts, and cytopathology in the screening setting showed a broad range of reported sensitivities, specificities, and positive predictive values when using biopsy confirmation as the gold standard outcome [126]. The clinical practicality of oral visual examination adjunct techniques are not well-established and require further study in various populations and screening settings, a larger sample size, and standardization of high-risk screening criteria.

Novel and proposed screening methods

For distally located HNCs (oropharyngeal, hypopharyngeal, and laryngeal cancers), inspection and direct flexible laryngoscopy after initial suspicion have been used in high-resource countries. Evaluation under anesthesia or an in-office fiberoptic examination may be needed to visualize the full extent of hypopharyngeal tumors. As laryngeal cancer is the second most common HNC worldwide (incidence 3.9 per 100 000 persons worldwide) and has a low survival at late stages [20], a less-invasive screening method would substantially facilitate early-stage diagnosis and reduce cancer mortality. Although molecular-based screening tests have been proposed based on tumor suppression genes and oncogenes, further advances are needed in molecular characterization of laryngeal cancer and the effectiveness of molecular screening, staging, and surveillance before molecular-based screening can be used for HNC detection [127].

HPV-specific OPC screening

The improved prognosis and median survival of HPV-positive OPC has galvanized further research on molecular-based modalities optimized to less invasive and earlier OPC detection. If properly integrated to the current clinical parameters in the management of HNC, molecular diagnostic tests can stratify the risk of developing HNC, HNC prognosis if diagnosed, and management. To date, there are no present guidelines or recommendations for any HPV-specific primary screening tests for OPCs.

However, for newly diagnosed squamous cell cancers, the College of American Pathologists' protocol recommends testing newly diagnosed OPC patients for high-risk HPV, either from the primary tumor or from cervical nodal metastases, using p16 immunohistochemistry with a 70% nuclear and cytoplasmic staining cut-off [85]. Routinely testing non-squamous oropharyngeal carcinomas or non-oropharyngeal carcinomas for HPV is not recommended [85].

HPV detection techniques that might be used clinically consist of three main categories: (i) direct HPV tests, (ii) indirect tests correlating with HPV, and (iii) proxy measures of HPV infection [127]. The gold standards for assessing HPV infection both involve direct molecular methods: polymerase chain reaction (PCR) (direct) or *in situ* hybridization (ISH) of a tumor biopsy. Both tests can be used on fresh/frozen samples or formalin-fixed paraffin-embedded tissue specimens, and are commercially available.

Although highly sensitive and cost-effective, standard PCR techniques require stringent quality control and are highly subject to incidental contamination if no rigorously performed. Reverse transcriptase (RT) PCR amplification of viral E6/E7 messenger RNA is now considered the most accurate test for detecting functionally causal HPV within tumor specimens as it detects transcriptionally active HPV [128].

ISH for high-risk HPV has a high specificity of 100% [129]. Although ISH can differentiate between episomal and integrated HPV DNA by evaluating the presence of diffuse versus punctuate signals, this has been found to not be important for cancer prognosis [130]. Although sensitivity is low at 83% [129] and can be improved with ISH kits with signal enhancement and ISH assays, these assays are insufficiently clinically validated for sensitivity to be used in routine screening, are technically difficult, and do not detect the approximately other 15% high-risk HPV types [131].

Proxy methods of HPV detection include immunohistochemistry with anti-E6-E7 antibodies, PCR ISH, and circulating antibodies against early HPV proteins. Antibody response to L1 is a poor test and not reliable, whereas antibodies to E antigens are very robust in OPC compared with cervical cancer [130]. Oncoproteins and antibodies to HPV oncoproteins can be detected (E1, E2, E6, and E7) in the serum, saliva, and plasma. HPV16 antibody to E6 protein has been shown to precede clinical manifestation by as much as 10 years and often by 2 years before clinical diagnosis [130, 132, 133]. HPV16 antibody E6 and the HPV sero-pattern for OPC had a high sensitivity (both $\geq$96%), specificity (both 98%), and a high diagnostic accuracy ($\geq$97%) [134]. A panel of HPV16 E antigens investigated in a case–control study also found a high sensitivity and specificity for HPV OPC which may be advantageous for risk stratification in future screening trials [89]. Considering that HPV antibodies can be detected over 10 years before the average time of OPC diagnosis [135], this study expands the possibility for an HPV antibody detection method to screen for OPC. An ongoing clinical trial, The HPV-related Oropharyngeal and Uncommon Cancers Screening Trial of Men (HOUSTON, identifier NCT02897427) will evaluate whether incorporation of serological HPV antibody testing in screening of HPV-associated cancer in men will be effective and what screening tools should be recommended [85].

Though these methodologies have great potential in reducing stage at diagnosis, the disadvantages include lack of validation or practical clinical use, burdensome technicalities for routine screening, lack of a curative early intervention, and lack of procedure agreement or screening standardization. A retrospective cohort study on saliva and plasma samples from OPC patients analyzed for HPV16 E6 and E7 DNA found that they were able to predict pretreatment prognosis. Sensitivity, specificity, positive predictive value, and negative predictive value were 76%, 100%, 42%, and 100%, respectively [136]. Salivary rinses [137], HPV antibodies [138], and HPV DNA in plasma [139] have been shown to be indicative of HPV-positive cancer, cancer recurrence or metastatic disease. Results from a nested case–control study showed that HPV16 E6 seropositivity was common in patients who later developed anal cancer, suggesting that patients who test positive for HPV16 E6 should be screened for anal and cervical cancers [140].

For cervical cytology screening, the false positivity of the highly sensitive HPV test is vetted by a highly specific Pap-test follow-up examination. The development of a 'Pap-test equivalent' for the oropharynx has been attempted and utilized but was limited in sampling the relevant tonsillar crypt epithelium where persistent HPV infection persists and leads to cellular changes [141]. This study found that OPC was detected using HPV16 alone (OR: 6.1, 95% CI 1.6–22.7) or in combination with abnormal cytology (OR: 20, 95% CI 4.2–95.4) with brush biopsy for patients presenting with oropharyngeal abnormalities [141]. Although salivary rinse or swab tests for oral HPV have been used in research settings, the sensitivity of saliva test is low. The specificity of the test is also affected by the origin of the HPV-positive cells, whether from tumor cells or any associated HPV infection [131].

Indirect tests correlating with HPV include immunohistochemistry to detect p16 expression and DNA/RNA microarray. The p16 protein is overexpressed in HPV-associated cancers and functions as a tumor suppressor by binding to the cyclin D1 CDK4/CDK6 complex, preventing phosphorylation of the Rb protein. ^{142}p16 immunohistochemistry has a high sensitivity. Approximately 5%–20% of p16 positive in non-OPC sites and 5% in OPC sites lack molecular evidence for HPV16 or other HR serotype DNA. This proportion varies between studies and ranges from 1.4% to 14% and may be a reflection of differences in HPV test sensitivities used or populations tested [142, 143]. A small minority of p16-positive OPC cases lack the virus, p16 can be overexpressed by other mechanisms, and a test for p16 lacks specificity for the presence of transcriptionally active HPV [144]. Although p16 may not have an ideal specificity to be used as a definitive test, it is good screening tool. The prognostic value of positive p6 immunochemistry in the PCR or RT negative tumor is unclear. For p16 expression in OPC where 85% of p16-positive tumors are PCR or RT positive, studies have consistently shown strong differences in overall, disease-free, recurrence-free, and disease-specific survival, depending on the respective outcome measures provided in the particular study [143, 145–149]. However, this insufficient diagnostic accuracy to warrant changes in therapy that would negatively impact HPV-negative patients or participation in HPV-specific experimental therapeutics.

As the incidence rate for HPV-related OPC increases, particularly for individuals $<$45 years old [144], screening tests are needed for age- and management-specific risk stratification. However, the harmful and beneficial effects of screening must be defined and understood. Unavoidable harms include physiological and psychological consequences of tests with high false-

positivity, detection of advanced, late-stage, or metastatic OPC that leads to invasive treatment and higher morbidity, and unnecessary treatment of lesions that would have not progressed (overdiagnosis) [150].

Strengths and weaknesses of tests must also be considered. A combination of positive p16 immunohistochemistry staining and HPV PCR are the most sensitive tests, whereas ISH is the most specific. Similar to cervical cancer testing, a combination of a sensitive and specific test is needed to accurately administer a risk-based screening protocol for HPV OPC. Low HNC prevalence in some populations may result in low true-positive results for any screening test used, regardless of high sensitivity and specificity, and this must therefore also be considered in any OPC screening program. Further, the screening population must be well defined. Incidence trends for HPV-associated OPC are hypothesized to be a result of changes in sexual behaviors over time that vary by sex and race [89]. Risk factors have changed in recent years, as younger individuals are more exposed to HPV and have an increasing incidence of OPC in high-income countries. In this changing risk factor landscape affects a more diverse population, and all adults should be screened.

Discussion

Conclusions

The pattern and distribution of the incidence of these cancers by HNC subsite differ markedly across and within regions, largely due to etiological differences. These differences highlight the difficulties in reducing HNC incidence and, subsequently, mortality. The cornerstones of risk reduction will be prevention (through the control of tobacco use and alcohol consumption, as well as through HPV vaccination for OPC prevention) and earlier diagnosis holds promise but logistical, technological, and biomarker hurdles must be overcome.

It is important to note that although high-income countries currently have the highest incidence of HNCs overall, mortality is highest in lower income countries. Many countries (in particular those undergoing economic and social transitions) lack both population-based cancer registries and the interoperability of health information systems to capture HNC incidence and mortality data. Further, there is a need for public information dissemination on the dangers of tobacco use, alcohol consumption, and HPV infections. An expansion and improvement of surveillance systems for disease-driven databases, e.g., for incidence, mortality, and survival data are also needed. This requires a country-specific approach for preventative measures and leveraging resources to reduce the global burden of HNCs.

Public health policy regarding tobacco must be comprehensive, covering all forms of tobacco use, as well as betel quid use and smokeless tobacco in endemic areas or subpopulations. Clinicians gathering past medical history should also ask patients about tobacco use and alcohol consumption, with the aim of assessing whether intervention is needed and/or advising for smoking cessation (in the case of tobacco). Incidence declines have been observed for oral cavity cancer in some parts of the world, consistent with decreases in tobacco and betel quid use [22]. However, the incidence of OPC has been increasing, particularly in developed countries [22]. The increasing HPV vaccination coverage against the commonest HPV types and sexual education programs for both men and women should eventually decrease or stabilize OPC incidence but this reduction may take decades [151, 152].

Early diagnosis offers an opportunity to achieve better survival through earlier diagnosis. When early diagnosis is not possible, access to a multidisciplinary team for treatment is crucial. HNC continues to have poor late-stage survival rates and access to multidisciplinary management is an obstacle for many populations, the mainstay of HNC prevention lies in identifying risk factors, minimizing tobacco and alcohol exposure, HPV vaccination, and further development of accurate and available screening.

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