Health system and policy implications of changing epidemiology for oral cavity and oropharynx cancers in the United States 1995-2016

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The health system and policy implications of changing epidemiology for oral cavity and oropharynx cancers in the United States 1995-2016

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Cancers of the oral cavity (OCC) and oropharynx (OPC) are typically grouped under the general term "oral cancer". Yet, the incidence of OPC is increasing in the U.S. while the incidence of OCC has declined. These two, distinct but conflated groups of oral cancers are attributed to different risk factors. Incidence and survival trends were examined across U.S. population groups and by anatomical subsite. Disparities were identified in incidence and survival by gender, race/ethnicity, and subsite. Risk factors are complex, interactive and not fully identified. Cancer control research illustrates health disparities in access to care and patient outcomes. Database and supplemental searches yielded 433 articles published between 1995 and 2016 characterizing aspects of oral cancer epidemiology relating to incidence, survival, risk, disparities and cancer control. OCC survival in black men remains the most intractable burden. While understanding of oral cancer etiology is improving, application to policy is limited. Cancer control efforts are diverse, sporadic, limited in scope, generally lacking in success, and need stratification by OCC/OPC. Further intervention and epidemiologic research, improved workforce capacity, and integrated care delivery are identified as important directions for public health policy. Sustained, multi-level campaigns modeled on tobacco control success are suggested.

Keywords: Mouth neoplasms, oropharyngeal neoplasms, incidence, survival, healthcare disparities, alphapapillomavirus, risk behavior, early detection of cancer

Abbreviations: HPV, human papillomavirus; INHANCE, International Head and Neck Cancer Epidemiology; OC, oral cancers; OCC, oral cavity cancers; OPC, oropharynx cancers; OR, odds ratio; SEER Surveillance Epidemiology and End Results; US, United States

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Cancers of the oral cavity (OCC) and oropharynx (OPC) are typically grouped together under the general term “oral cancer” (OC). In this review the term OCC includes these subsites: anterior two-thirds of the tongue (oral tongue), gums, floor of mouth, hard palate, and buccal mucosa. OPC include the posterior one-third of the tongue (base of tongue), soft palate, tonsils, and “other” oropharynx.[1,2] Despite the usual conflation of these cancers as a single group, as demonstrated in this review, it is well established that the incidence of OPC is on the increase in the United States (U.S.) while the incidence of OC has declined. Moreover, these two, distinct groups of OC are generally attributed to different risk factors. While OPC tend to be associated with human papillomavirus (HPV), OCC are more likely to be associated with tobacco and heavy alcohol use.[3] These two groups of OC are also associated with different population groups. In the U.S., OCC are more common in older, male populations and particularly in black men. OPC are more common in younger, white and male populations.[1,2,4]

This review examines the epidemiological literature on OCC and OPC to assess U.S. trends in disease incidence and survival by oral subsite and to highlight disparities in disease burden. We describe both established and emerging risk factors for OC. The literature on incidence, survival, and risk is then considered in light of prevention and early detection strategies and sources of disparities to identify environmental, policy, and healthcare system factors that can influence outcomes and may offer opportunities for more effective interventions. Strategies for improvement in OC control are proposed.

Methods

A targeted literature review was undertaken through March 2016 to identify relevant epidemiological articles on OC. Searches were conducted in PubMed, Medline, and Cochrane. Search terms for the database searches, including Medical Subject Headings (MeSH) and other, relevant keywords, included “mouth neoplasms,” “oropharyngeal neoplasms,” “incidence,” “survival,” “costs and cost analysis,” “health care costs,” “health services accessibility,” “health status disparities,” “healthcare disparities,” “minority health,” “alphapapillomavirus,” “behavior, risk,” “risk reduction behavior,” “risk factors,” “risk assessment,” “preventive health services,” and “early detection of cancer.”

In addition to the literature searches, reference lists in identified articles were reviewed for additional articles. Finally, subject expert consultations were sought to ensure a comprehensive collection of articles.

Articles were included in the search if the publication date was between 1995-2016; if they were published in English; and, for clinical trials, if at least one trial location was in the U.S. The start date of 1995 was chosen to provide two decades of review and to work in conjunction with the emerging scholarly focus on HPV in head and neck cancer [5] and with the onset of the diverging trends of OCC and OPC.[6] Articles were excluded if they focused on nasopharynx, hypopharynx, lip, or salivary gland cancers which are etiologically distinct from most other OC. Editorials and non-systematic literature reviews were also excluded. A final list of 433 articles were selected for consideration by the authors.

Epidemiological Trends in Oral Cavity and Oropharynx Cancers

In the U.S., current estimates indicate that there are approximately 45,000 new cases and 8,500 deaths attributed to OCC and OPC annually.[7] When analyzing incidence, survival, prognosis, and associated trends for OCC and OPC, it is important to recognize that previous studies have shown different epidemiological trends for OCC and OPC.[1]

Chaturvedi, et al., reviewed the national data from the Surveillance, Epidemiology, and End Results (SEER) program registries from 1973-2004 and found that U.S. incidence trends for OCC remained stable up until 1982 and then declined significantly from 1983 through 2004. This was in contrast to a significant increase in incidence for OPC during the same time period.[2] Several other U.S. epidemiological studies, including those using more recent SEER time periods, have continued to observe the decline in OCC along with the rise in incidence in OPC.[4,6,8–12] These trends have been consistent across study populations and can be explained by their distinct etiology.[13–18]

Public health efforts that have resulted in the decreased prevalence of tobacco use along with decreased consumption of alcohol have been cited as strong contributing factors to the decline in OCC incidence.[2,19] Meanwhile, it has been hypothesized that an increase in sexual practices associated with oral HPV infection among more recent birth cohorts may explain the rise in OPC over time.[2]

Disparities in OC incidence

There are distinct epidemiological trends based on demographic factors such as race/ethnicity, gender, and age. A study examining OCC and OPC national incidence trends in SEER from 1975-2008 found that blacks experienced a significant decline in both OCC and OPC beginning in 1985, with the decline being most pronounced in males. Additionally, all other racial/ethnic-gender groups experienced a decline in OCC over the time periods observed. The same study also found that incidence rates for OPC increased 88% in white males from 1975-1979 to 2004-2008.[11]

Studies have consistently demonstrated an increase in OPC, particularly at base-of-tongue and tonsil sites, among white males since the 1990s in contrast to stable or declining rates for these cancers in other race/ethnicity-gender groups.[2,4,13,14,20–22] A study examining SEER incidence data from 2000-2010, found that whites had the highest age-standardized cumulative incidence rate for OCC during the time period, with white males experiencing the highest rates of all racial/ethnic-gender groups. This study found a decline in OCC in both black and white males during the same time period, but in accordance with other studies, noted a rise in OPC in white males in contrast to stable or declining trend patterns for these cancers in other racial/ethnic-gender groups.[12]

Interestingly, studies have noted an increase in cancers of the oral tongue, that are not HPV related, among white women less than 45 years of age over time.[11,20,23] The cause of the increase of these cancers in this specific group is not known. Studies examining these

epidemiological trends have also been consistent in their finding that OPC are more frequently diagnosed in younger individuals when compared to OCC.[1,11,12,22,24–27]

Disparities in OC survival

Differences in survival have been observed based on race/ethnicity and anatomic location of OC. A study analyzing SEER data from the mid-1970's to the early-1990's found that the overall, relative 5-year survival rate for OPC was close to 50 percent, without much improvement over time. However, this study also found that, for blacks, the survival rate was closer to 30 percent, and this disparity in survival persisted even when stratified by stage of diagnosis. Black males, specifically, were shown to have the poorest survival of all of the race/ethnicity-gender groups analyzed during the time period in this study.[28] The results of this study were consistent with another investigation examining oral cancer survival statistics during a similar time period.[29]

A more recent analysis of SEER data from 1973-2008 found that the 5-year relative survival after diagnosis of cancers of the tongue and tonsils (OPC) did not differ by gender; however, a stark difference by race/ethnicity was noted with whites displaying a survival rate of close to 60 percent and blacks displaying a survival rate close to 30 percent.[20] A study analyzing OC survival data in Michigan from 1993-2002 also found blacks in the state to have substantially lower 5-year relative survival than their white counterparts. This study also found that, over the later time period, there was a trend of poorer survival among blacks in the state.[30] More recent

estimates indicate that there has been a slight improvement in 5-year relative survival for OC, however, blacks continue to experience much poorer survival than their counterparts.[31]

Notable differences in survival have been observed based upon whether an OPC is HPV-positive or HPV-negative.[2,32,33] HPV-positive OPC have been consistently shown to display significantly higher survival than HPV-negative OPC, despite the fact that these HPV-positive cancers are typically detected at later stages.[2,33] It has been hypothesized that the improved survival of HPV-positive OPC can be attributed to a better response of these cancers to radiation treatment and chemotherapy.[2,32,33]

OC Risk Factors

Tobacco and alcohol have long been identified as primary risk factors for OC.[34,35] Various other agents have been investigated, though often without clear associations. Given the wide diversity of, and undersized/underpowered efforts seeking to elucidate risk factors, our review focused on meta-analyses conducted during the study time frame (1995-2016) that yielded statistically significant observations. Separately, an assessment of the publications by the International Head and Neck Cancer Epidemiology (INHANCE) Consortium was made. INHANCE uses pooled data from consortium members, including investigations conducted in the U.S.

Meta-analyses of OCC risk factors

Among these 1995-2016 meta-analyses on OCC risk factors, none have a primary focus on tobacco smoking (Table 1). However, tobacco smoking is often included as an adjustment

factor.[36–44] Among the twelve meta-analyses identified that focused on OCC risk factors and yielded statically significant findings (Table 1), most frequently assessed, with two each, were HPV,[45,46] alcohol,[37,38] diet[40,41] and smokeless tobacco.[44,47] Strong elevated associations (odds ratio [OR]>4.0) were found for heavy drinking,[37,38] HPV[45] and smokeless tobacco.[47] Additional noteworthy associations (OR>1.5) were shown for moderate drinking,[38] processed meats[40] and socio-economic status measured by education, occupation and income.[36] The strongest inverse associations (OR<0.4) were found with fruits and vegetables.[41]

Meta-analyses of OPC risk factors

The search of risks associated with OPC yielded only seven meta-analyses (Table 2).[38,40,46–50] Only alcohol has two meta-analyses.[38,48] Very strong associations (OR >7.0) are shown for heavy drinkers and OPC,[38] HPV and tonsils,[46] smoking with drinking for OPC,[50] smokeless tobacco and combined cancers of the oral cavity, pharynx and larynx.[47] Elevated associations (OR>1.5) are seen for heavy drinkers and cancers of the pharynx,[38] tonsils[38] and oral cavity/pharynx;[48] processed meat with cancers of the oral cavity/pharynx;[40] HPV with oropharynx cancers;[46] tobacco smoking in a variety of intensities of exposure with oropharynx cancers;[50] and smokeless tobacco across assessments of sites and materials.[47]Among the OPC meta-analyses, reduced odds were found only with coffee.[49]

INHANCE for Head and Neck Cancer, OC and OPC risk factors

A multifaceted series of evaluations of OC risk factors via pooled analyses from the INHANCE Consortium supplements the previous OCC and OPC meta-analyses. This consortium has sought improved insight into risks for head and neck cancers, with more than 25 papers since 2004 when they were initiated following an inquiry into alcohol and aldehyde dehydrogenase genotypes in relation to head and neck cancer risks.[51] Web Table 1 emphasizes where head and neck subsites of oral cavity, oral cavity/pharynx, oral tongue/tongue, oropharynx and pharynx cancers are reported with statistically significant associations.

Tobacco is included as a major focus in at least 10 INHANCE studies including two studies not presented on Web Table 1 due to the complexity of reporting their results.[52–61] It is in essentially all other studies as an adjustment factor.[62–80] They provide improved understanding of the nuances of tobacco[55–59] and tobacco and alcohol interactions.[55,57,59] Encouraging reduction in cancer risk with tobacco cessation is demonstrated.[57]

The level of detail enabled by the INHANCE studies allows for comparison of associations with OC for specific exposures and subsites. The highest increased ORs seen were for OCC associated with beer and wine, followed by cancer of the pharynx in association with wine and beer.[69] Many tobacco associations were found with increased odds of three-fold or higher. These included ever tobacco use for both females and males over age 45,[52] involuntary smoke exposure for cancer of the pharynx[56] and numerous combinations of smoked tobacco.[58]

Also particularly noteworthy are associations with four or more oral sex partners with oropharynx and tongue cancers.[62]

Curiously, marijuana was shown to be either preventative or harmful based on the anatomical subsite.[64] Being underweight emerged as a risk factor while higher weights have shown a protective effect.[53,68] Recreational physical activity;[73] healthy diet with increased intake of fruits,[74] vegetables,[72,79] various supplements[77] and aspects of dietary intakes[66,71,74,75,80] as well as coffee[70] merit further attention for potentially promising effects on oral cancer risk.

INHANCE provided assessments for several risk factors included in Tables 1 and 2. Most frequently studied, with eight publications, was diet,[66,71,72,74,75,77,79,80] followed by directly/indirectly smoking tobacco with five analyses.[55–59] Alcohol,[69] coffee,[70] diabetes,[76] and socioeconomic status[78] were each evaluated by one analysis.

Additionally, INHANCE identified significant risk factors not seen in the above OC meta-analyses (Tables 1 and 2) such as age,[52] alcohol and tobacco interaction[55,59] and cessation,[57] family history,[63] height and body mass index,[53,54,65,68] marijuana,[64] recreational activity,[73] mouthwash[67] and sex behaviors.[62]

INHANCE recently provided a review of their work.[81] Improved understanding of genetic interactions with etiologic agents appears to be a promising means for further improvement of early detection and prevention. These studies may improve our ability to identify high-risk individuals for increased surveillance. However, it is not yet feasible to assess patient or population risk on the basis of genetic interactions with etiologic agents. Genetics, therefore, is

not reviewed in this paper, save for the extent there may be genetic implications regarding family history of cancer.[63]

HPV as a distinct risk factor for OPC

Because HPV-positive OCC and OPC are etiologically distinct, we discuss risk associated with HPV infections separately. These cancers have received much attention in the literature over the past decade.

HPV are a heterogeneous group of DNA viruses that are classified as either high-risk (oncogenic) strains associated with cancer, or low-risk strains associated with benign disease.[26] HPV is a well-established etiologic factor for a subset of OPC,[82,83] specifically those found in the base of the tongue and tonsil.[84–86] To a lesser extent, oncogenic HPV sub-types have also been detected in some OCC,[87] in particular cancers in the gingiva and oral mucosa.[88] A multicenter study conducted for the International Agency for Research on Cancer detected HPV DNA in 18.3% and 3.9% of tumor specimens from patients with OPC and OCC, respectively.[89]

HPV oncogenic sub-type 16 (HPV16) is the most prevalent HPV subtype associated with OC.[82,83,90–92] In addition, oncogenic subtypes other than HPV16 have also been detected in some OC.[82,88,93]

As noted above, the incidence of HPV-related OPC is highest among white males at younger ages.[2,6,88,90,92,94–97] Several studies have described a strong "age cohort effect," [2,85,86,98] which is likely due to changes in sexual practices.[96] Several collinear sexual behaviors represent primary risk factors for oral HPV infection,[98,99] including increased oral sexual contact, younger

age at sexual debut,[98] and a higher number of lifetime sexual partners.[91,92,97] This last association may be due to a higher number of lifetime partners engaging in oral sexual behaviors (i.e., oral sex, open-mouth kissing, oral-anal) rather than vaginal sex partners.[94,97,99] In addition to these risk factors, poor oral health has been associated with oral HPV infection, possibly through loss of epithelial barrier function resulting from ulcers, mucosal disruption, and inflammation,[94] and some studies suggest an increased risk of oral HPV infection in current smokers.[91,97]

We have noted that HPV-positive OC are recognized as distinct from HPV-negative OC.[10,96] They are more likely to occur in non-smokers, non-drinkers, and males[100] and also tend to have better prognoses than HPV-negative OC.[96] HPV-positive tumors are associated with longer survival time,[2] reduced mortality,[6,101] and increased sensitivity to chemotherapy and radiation therapy.[96]

Despite more favorable outcomes in HPV-related OPC, their increasing incidence shows no sign of tapering off. Incident cases are expected to exceed newly diagnosed cervical cancer cases by 2020.[6] Focusing on head and neck cancers, Sanders et al. estimated the population attributable risk for oncogenic HPV to be 4.7%,[26] and in an analysis of data from three SEER registries, the presence of HPV DNA detected in OPC tumors increased from 16.3% during the period from 1984-1989 to 72.7% during the period from 2000-2004.[6]

Prevention and early detection

Prevention and early detection are basic components of cancer control programs.[102] These are the primary and secondary phases of disease prevention: 1) altering risk to avoid disease onset and 2) detecting early-stage disease processes and stopping their progression.[103] The literature on OC control pays a great deal of attention to these phases, sometimes separately, but, more typically, together.

Because several different risk factors have been identified, prevention strategies can be highly variable. Interventions can also be undertaken at various levels: communities, high-risk populations, professions and professional associations, clinical practices, and individuals at risk. Strategies have been implemented by a variety of change agents, including public health agencies, scientific investigators, community coalitions, community organizations, and clinicians and clinician organizations.[104]

Because OC can appear in multiple and differentially accessible anatomical subsites of the head and neck, and because early signs and symptoms are highly variable,[105] early detection can be challenging. Although precancerous lesions can be detected through visualization and palpation in the oral cavity, there are no known precancerous lesions for OPC. Moreover, there remains a great deal of controversy over whether early detection through screening programs is an appropriate strategy.[106–110] In 2013 the U.S. Preventive Services Task Force again found the evidence base for screening in asymptomatic adults insufficient.[111] Similarly, a recent Cochrane review concluded that the available evidence is not sufficient to

warrant population-based screening programs.[112] Nevertheless, some argue that targeted screening should be conducted based on weaker evidence of potential benefit.[109,110]

As described above, primary prevention for OCC appears to have received a large boost from decades of public health efforts to discourage tobacco use.[113] Epidemiologic studies point to the coincidence of tobacco use reductions achieved over decades of multifaceted interventions across the country and a lagged and sustained reduction in OC incidence rates.[11,114] The tobacco campaigns were generally not directed toward reducing OCC, but were apparently quite successful in doing so nevertheless. Some studies have focused on assessing and improving the role of healthcare providers in promoting tobacco cessation specifically to reduce OC incidence further.[115–124]

Similar contributions to OC incidence reduction may also have occurred in association with broad campaigns to reduce alcohol abuse and improve physical activity and nutrition, campaigns not directed specifically at OC, but possibly affecting them nevertheless. To examine these broad campaigns is beyond the scope of the current review.

Several studies have investigated public awareness of OC and means of improving prevention and early detection practice, either generally[125–128] or in specific, at-risk populations including smokers,[129,130] blacks,[131–133] Latinos[134,135] and rural populations.[136–138] Studies consistently find that public knowledge of OC and receipt of early detection examinations has been, and continues to be, limited. Although some studies have suggested racial and ethnic differences, with Hispanics and blacks being less aware and having more limited early detection

services,[115,128] studies have also concluded that the differences are ultimately attributable to health literacy, education and income disparities rather than race or ethnicity.[127,137,139] Tobacco-use status, an indicator of elevated risk, does not appear to increase the likelihood of having an exam.[124,129,130,140] Fear of cancer may be negatively associated with having an exam in some high-risk populations[132,133] although being concerned about cancer has also been shown to be positively associated with getting an exam.[140]

Some studies have investigated the educational materials to which the public has access. Most have found sources of information inadequate, even misleading.[141–145] Some have specifically linked awareness to preventive behaviors[127,129,135] although causal paths remain uncertain. Health behavior theories typically do not link knowledge directly to behavior,[146] but knowledge is a necessary first step, and a need for improved health information dissemination is recognized.[147,148]

A variety of strategies have been reported for improving public awareness of and access to early detection services.[104] Mass media campaigns have shown some success in increasing awareness and demand for screening services.[149,150] Success in increasing public awareness generally, however, has been limited.[151,152] Billboards have not shown promise as a message delivery mechanism for improving OC awareness in populations at risk.[153]

Clinician awareness of OC and behavior directed at risk reduction in patients have also been investigated.[154,155] Many of these studies are limited to specific states or even regions of states. Investigators have examined dentists;[121,122,147,148,156–162] dental hygienists;[116,118,162–167]

physicians;[158,159,168] and other primary care providers.[168–170] Generally, studies have found provider knowledge and behavior not to be optimal. Much need for improvement has been identified across these many investigations and a need for training programs has been emphasized.[154,160] However, studies of provider training programs' oral cancer content do not suggest that much improvement is coming.[167,171,172]

The literature finds clinicians lack early detection skills and do not sufficiently engage in risk counseling. Clinicians are generally more likely to discuss tobacco with their patients than alcohol. They are even less likely to discuss sexual practices.[166,173,174]

Studies have reported efforts to improve clinician practice through continuing education[122,175] and other interventions. Internet-based support for tobacco cessation counseling in dental offices showed modest success in a randomized trial.[123] Online training improved intent to counsel and perceived self-efficacy for alcohol counseling also. There is some evidence that more recently trained clinicians may be more aware and vigilant in primary and secondary prevention practice.[120,157]

Having a dental visit improves likelihood of having an OC exam.[129,130] Dentists are much more likely than medical physicians to perform OC examinations.[159] Nevertheless, clinical diagnosis is very difficult and histologic confirmation is required.[175,176] Clinical diagnostic adjuncts being promoted in dentistry have limited value.[107,177]

With the rising incidence of OPC, the literature has reflected limited interest in promoting awareness of HPV, its link to OPC, the need for safe sexual practices and, where appropriate, vaccination. In fact, there is an extensive literature regarding promotion of HPV vaccination. However, the focus of that literature is primarily on cervical cancer rather than OPC, putting it outside the scope of this review. The work by Daley and colleagues represents a notable exception. Their investigations determined that dentists and dental hygienists are not adequately prepared to counsel patients about HPV and that interventions are needed.[161,173]

Disparities and cost of care

Disparities in OC across different population groups, particularly between whites and blacks, are persistent challenges that have defied efforts at intervention. The literature suggests that the underlying reasons are complex, involving risk behavior patterns, genetic differences, differential access to care and variable quality of care. The extent to which race is a primary factor in health disparities is an important empirical question that remains to be resolved.[178]

OC are among the most expensive cancers to treat. A 2012 paper estimates that OPC alone have an annual direct medical cost of $300 million in the U.S.[179] One study estimated that the lifetime cost for each OPC and OCC case ranges from $15,340 to $46,800, with an average cost of $33,020.[180] Lee et al., using 2008 Nationwide Inpatient Sample data (N=17,632 hospitalizations), estimated a total hospitalization cost for OCC (including lip and salivary gland) and OPC at $1.08 billion, or $62,885 per hospitalization.[181] These costs account only for direct, in-patient costs of care. The cost of OCC and OPC in both years of life and lost productivity is

also high. One study estimated the years of potential life lost at 63,587.[182] Late-stage cancers have been estimated to cost 36 percent more than localized disease in the first year after diagnosis.[183]

Cost drivers identified in the Medicare population include demographics, comorbidities, and treatment selection.[184] Complications and adjuvant therapies increase cost of care dramatically.[181,185] Treatments confined to surgery are least expensive.[186]

OPC are generally more expensive to treat than OCC.[184] Privately insured patients' cancers cost far more than Medicaid and Medicare covered patients' cancers, in that order.[187] There is evidence that out-of-pocket costs may lead some OC patients to abandon their medications.[188]

Racial and ethnic disparities in incidence and survival are numerous, as described elsewhere in this review. Black Americans, particularly black men,[189] have poorer outcomes than whites.[190] They have historically had poorer survival rates.[90,191–194] One study, however, did not find self-reported race or degree of West African ancestry to be associated with survival suggesting that other factors such as stage at diagnosis may be underlying causes of apparent racial differences.[195] Colevas et al., for example, found the highest incidence rates for OPC to be in low socioeconomic status groups.[13] Riley et al. found that apparent racial and ethnic disparities in receiving early detection services were actually attributable to differences in health literacy and socioeconomic status.[137] High rates of tobacco and alcohol use are also

associated with poorer survival.[196] Tobacco use and other health limiting behaviors are associated with racial/ethnic minority status and socioeconomic disparities.[197,198]

Disadvantages are not confined to blacks versus whites. The U.S.-born population, for example, has been shown to have better survival rates than citizens born outside the U.S.[199] Suarez et al**.**, found that Puerto Rican men have higher incidence and mortality rates than men on the U.S. mainland including Hispanic men, non-Hispanic black men, and non-Hispanic white men. This may be a consequence of quality of care or access to care, the authors conclude.[200] Morse and colleagues found that a lower percentage of in situ cancers are detected in Puerto Rico versus mainland U.S. and suggested that limited access to care is the underlying cause of late diagnosis.[201]

Lack of access to quality care may be contributing to greater adverse outcomes in blacks as well.[192] Treatment at academic centers, lack of need for adjuvant therapy, and private insurance all have been associated with improved outcomes.[202] In the case of OC, access to oral health care is particularly important. Late-stage disease and larger tumors have been linked to less than annual dental visits.[203,204] Regular dental visits are associated with having an OC examination.[129,130,138] Dentists, of all primary care providers, are the most likely to perform these exams.[159] However, if blacks do receive an exam, it is more likely to be from someone other than a dentist.[205]

Lower incidence rates of HPV-positive cancers have been attributed to poorer survival in blacks.[90,193] HPV positivity is generally associated with improved survival.[206] A recent study with

a small sample has found, though, that HPV positive tumors in blacks disproportionately lacked the tumor suppressor gene P16, which may suggest yet another mechanism underlying the observed racial disparity in survival.[207]

The quality of healthcare received by blacks has been found to be lacking compared to whites. Blacks have been shown, for example, to be less frequently recommended for surgery even when controlling for factors like tumor stage and patient age.[90,191,208] Nevertheless, their treatment may actually cost more overall than that of whites, likely a consequence of comorbidities confounding treatment.[184] Blacks have also been shown to lack health insurance and have poorer overall health compared to whites,[209] which may also account for poorer cancer-specific survival.

Discussion

Reducing the incidence of OC, improving clinical outcomes, and eliminating disparities pose significant public health challenges. OC are common in medically and dentally underserved populations, difficult to detect and diagnose at early stages of disease, and population risk profiles are complex and shifting which makes it hard to target high-risk populations with focused and sustained campaigns.

Although we have documented a decline in incidence of OCC over time, that appears to be an indirect outcome of intensive, multi-faceted and sustained tobacco control efforts not directed toward OC prevention. Despite some twenty years of cancer control activity directed

at improving public awareness of OC, increasing demand for early detection services, and preparing the health workforce for engaging in prevention and early detection practices, there is no evidence that any of that has made any substantial difference. Intervention opportunities and promising mechanisms for intervention have been demonstrated, but much work is still needed to build on that base and extend the programming to all high-risk populations, those currently identified and those yet to be discovered.

Improvements are needed in all phases of cancer control from prevention to early detection to disease management. The information generated by this review can inform practice and policy for environmental and systems changes that can reduce the burden of OC.

Among the challenges identified are a normative environment in which oral health is not a priority. There is a demonstrated need for intensive health promotion campaigns aimed at changing attitudes toward oral health and increasing demand for oral health services which can be contribute both to risk reduction and earlier diagnosis.

With an educated and motivated public demanding oral health services, a need for expanded access to care would be required. Every patient should have a medical home and a dental home, preferably in a single setting, where the range of preventive and diagnostic services can be offered with all required expertise.

Primary care providers from diverse professional backgrounds can play roles in OC control by educating patients about risk and delivering competent diagnostic services.[210]

However, before that can be accomplished on a meaningful scale, clinicians need to be empowered with the required clinical skills, and OC control must become a clinical priority. This review has identified a number of deficiencies as well as promising strategies for improving workforce performance. These investigations should be continued as a matter of public policy.

In addition, the workforce needs to be expanded in order to provide more and better services to underserved populations which are most at risk for OC and poor outcomes. One strategy for improving access to oral health care has been to authorize midlevel providers, such as dental therapists. Dental therapists have been providing services to tribal populations in Alaska for nearly a decade. Therapists have also been expanding access to oral health care in Minnesota since 2011. Just this year both Maine and Vermont have enacted statutes authorizing alternative providers. These model programs are being evaluated positively, although not specifically for their contributions to prevention and detection of OC.[211–213] Nevertheless, this is one promising alternative for improving access to oral health services with potential for extending OC prevention and early detection services which other states should consider testing and evaluating.

There are a number of policy options for inducing clinicians to provide care to underserved populations.[214] Among these policies are financial incentives, such as loan forgiveness programs, which governments at all levels can explore and adopt to their specific area needs in order to expand access to care in underserved populations. Further investigation is needed, however, to identify successful strategies.[215,216]

Risk reduction can also be accomplished through policies aimed at limiting tobacco use and promoting HPV vaccination. Tobacco remains the single most important OC risk factor and even limited smoking and passive smoking can contribute to the disease burden. Tobacco control programs have been effective in reducing smoking rates in the U.S., but more remains to be done, particularly in preventing youth uptake. Tobacco 21 policies, which require purchasers of tobacco products to be at least 21 years of age, should be enacted by states and local governments to limit access to tobacco products by youth. In addition, the Food and Drug Administration now has expanded authority to regulate tobacco products and that authority can and should be directed toward youth uptake prevention. Healthy People 2020 offers a number of strategies for tobacco control and state and local governments should assess their alternatives and adopt programs to meet their local needs.[217]

HPV vaccination could possibly prevent a majority of OPC. Vaccines are available and authorized, but uptake and course completion remain challenges.[218] States should consider mandatory vaccination programs which have been adopted in a small number of jurisdictions.[219] The programs of these early adopters should be evaluated and the results disseminated to inform policy makers elsewhere. There are a number of health promotion resources available for public education and for adaptation to clinical practice which may be used to encourage both uptake and course completion.[220]

Finally, we need to promote inter-professional healthcare models which coordinate care across disciplines. Progress in risk reduction and early detection could be greatly enhanced if

oral health was regarded as systematic health, and care between dentists and physicians was integrated.[221] Collaborative care with all the needed expertise (internal medicine, oral medicine, otolaryngology, oral surgery, general dentistry, oncology) should be a national priority. One approach would be to amend the Affordable Care Act to require oral healthcare to be fully integrated into accountable care organizations.

Dissemination of medical and dental research findings across disciplines also requires specific efforts to ensure evidence based practice. Keeping the healthcare workforce abreast of the evolving evidence base should be a priority. Inter-professional continuing education programs should be promoted. Such programs should enable providers to have current understanding of population risk profiles. Clinicians must be attentive to changing population characteristics in the increasingly diversifying U.S. populace.

These efforts can be informed by high quality, powerful research designs such as the collaborative work of the INHANCE Consortium. Much is gained, for example, from the attention given by INHANCE to tobacco exposures and cessation. Findings from INHANCE include the relationships of OC with involuntary smoking,[56] low levels of smoking[59] and different smoked tobacco products.[58] These observations suggest inclusion of OC in prevention efforts for other cancers, such as lung cancer. Assessment of combinations of tobacco products suggests that cigarettes conceal the independent risks of cigars and pipes.[58] The Consortium also provides insight into the relative contributions to OC risk by tobacco and alcohol alone and together, clarifying the independence of high alcohol exposure and OC risk[55,69] and differential responses to cessation of tobacco smoking (risk reduction in 1-4 years)

or alcohol (risk reduction at 20 or more years).[57] The detailed work provided by INHANCE on tobacco exposure is an example of evidence that has potential for policy development and evidence based practice.

Risk patterns and epidemiological trends are subject to much variability over time. Yet, public-health and scholarly focus cannot be allowed to shift solely to the rising trends in HPV-related OCs. Efforts to promote tobacco control, alcohol use reduction, improved dietary practices and physical activity still need to be continued with vigor. As demographic variation is associated with variable risk profiles, it is important to monitor and adapt to these changing demographics and associated risks as health policy moves into the future.[167] Surveillance mechanisms need to be in place and clinicians need current surveillance data on which to base clinical decisions. Future assessments of OC risk factors in the U.S. are likely to include factors currently seen at the global level, but have not been examined in U.S. studies. The U.S. is a diverse country with high levels of immigration. As the immigrant population swells, new risk factors can be expected to emerge and require public health attention. [222] Anticipated factors include such exposures as betel,[223–225] bidi[226] and mate.[227]

Finally, improved capacity to detect early stage disease is needed. Targeting high-risk populations remains a blunt instrument because of a lack of refinement in our knowledge of risk factor interactions. Genetic predispositions to disease progression in both OCC and OPC need to be more fully understood in order to target risk-reduction and early detection interventions more precisely.

This review has significant limitations that should be acknowledged. We confined the study to a limited time frame. This temporal limitation caused us to exclude literature that might have enabled a more comprehensive discussion of OC. We also elected to confine the study to the U.S. population, thus disallowing an exploration of the rich literature produced from other countries, particularly with respect to risk factors. The choice to restrict the study was necessary, however, to allow us to focus on the contrasts between OCC and OPC and the current understanding of underlying risks which appear to be responsible for the observed trends. As OC are extremely heterogeneous with many risk factors that vary in relevance across different regions of the world, it was not considered possible to take a broader view.

Conclusion

OC present a significant and difficult public health challenge. Although frequently regarded as a homogeneous group of cancers, it is clear that their complexity is subtle and in part driven by anatomical site differences. Although it is clear that HPV-positive OC are etiologically distinct from HPV-negative OC, these distinct etiologies are not fully understood. Additional research is needed to fully understand oral cancers and also to inform effective interventions targeting at-risk populations and the healthcare workforce that serves them.

Promising strategies include health education and improved access to better informed and organized care. Clinical practice needs to be improved and the healthcare workforce needs to be trained, encouraged, and enabled to address the continuing and ever changing challenges

these cancers present. Extensive, multi-level campaigns modeled on the successes of tobacco control are recommended.

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Table 1. Statistically Significant Risk Factors for Oral Cavity Cancers: Meta-analyses Published Between January 1, 1995 and March 22, 2016.

First Author, Year[Reference #]	Study Period	No. of Studies	Sample Size		Findings			Comments
			No. cases	No. controls	Cancer Site (Exposure)	OR	95% CI	
					Alcohol			
Turati, 2010[38]	Up to September 2009	9	534	1,471	OCC (Light drinkers)	1.17[a,c]	1.01, 1.35	Increased odds by site
		17	1,706	847	OCC (Heavy drinkers)	4.64[a,c]	3.78, 5.70	
Bagnardi, 2015[37]	Before September 2012	52	13,895	4,942	OCPC (Light drinkers)	1.13[a,c]	1.00, 1.26	Increased odds: dose response
					OCPC (Moderate drinkers)	1.83[a,c]	1.62, 2.07	
					OCPC (Heavy drinkers)	5.13[a,c]	4.31, 6.10	
					Diabetes			
Gong, 2015[42]	January 1, 1966 – May 31, 2014	13	1,806	N/A	OCPC	1.15[b,c]	1.02, 1.29	Increased odds with Type 2 DM
					Diet			
Pavia, 2006[41]	Up to September 2005	16	65,802	N/A	OCC (Fruit)	0.51[a]	0.40, 0.65	Reduced odds
			57,993	N/A	OCC (Vegetables)	0.50[a]	0.38, 0.65	
Xu, 2014[40]	January 1966 – May 2013	13	4,104	N/A	OCPC (Processed meat)	1.91[a,c]	1.19, 3.06	Increased odds
					HPV			
Miller, 2001[45]	December 1982 – April 1997	19	N/A	N/A	OSCC	5.37[a]	2.49, 11.55	Increased odds: HPV detection in OSCC vs. normal tissue
Hobbs, 2006[46]	Inception to February 2004	8	1,641	2,277	OCC	2.0[b]	1.2, 3.4	Increased odds
					Periodontal disease			
Yao, 2014[43]	2005-2010	5	1,191	1,992	OCC	3.53[a]	1.52, 8.23	Increased odds
					Smokeless tobacco			
Rodu, 2002[47]	1957-1998[d]	4	581	798	OCC (SLT-unspecified)	2.8[b,c]	1.9, 4.1	Increased odds: site and SLT material specific
		8	3,145	5,245	ALL SITES (CT)	1.2[b,c]	1.0, 1.4	
		4	391	1,340	ALL SITES (DS)	5.9[b,c]	1.7, 20	

		7	1,428	3,681	ALL SITES (SLT-unspecified)	1.9[b,c]	1.5, 2.3	
Weitkunat, 2007[44]	1920-2005	32	13,669	297,134	OCC (All types of SLT)	1.87[a,e]	1.40, 2.48	Increased odds: summing all SLT types
					Socioeconomic Status			
Conway, 2008[36]	1950 -	41	15,344	33,852	All Countries Contributing Studies			Increased odds
	September	37			OCPC (Low Education)	1.85[a]	1.60, 2.15	
	2006	14			OCPC (Low Occupation)	1.84[a]	1.47, 2.31	
		5			OCPC (Low Income)	2.41[a]	1.59, 3.65	
					North America			
		13			OCPC (Low Education)	1.62[a]	1.34, 1.96	
		6			OCPC (Low Occupation)	1.63[a]	1.31, 2.04	
		2			OCPC (Low Income)	3.41[a]	2.14, 5.44	
					Tea			
Wang, 2014[39]	Up to June	19	4,675	N/A	OCC (All teas studied)	0.85[a,c]	0.78, 0.93	Reduced risk
	2013	5	1,313	N/A	OCC (Green tea)	0.80[a,c]	0.67, 0.95	

Abbreviations: OCC, oral cavity; OCPC, oral cavity/pharynx; N/A, not available from published report; DM, Diabetes Mellitus; HPV, Human Papilloma Virus; OSCC, oral squamous cell carcinoma; SLT, smokeless tobacco; CT, chewing tobacco; DS, dry snuff; SES, socioeconomic status;

[a] adjusted

[b] adjustment unclear

[c] relative risk

[d] years of publications of used studies

[e] odds ratio or relative risk random-effects estimate

Table 2. Significant Risk Factors for Oropharyngeal Cancers: Meta-analyses Published Between January 1, 1995 and March 22, 2016.

First Author, Year[Reference #]	Study Period	No. of Studies	Sample Size		Findings			Comments
			No. cases	No. controls	Cancer Site (Exposure)	OR	95% CI	
					Alcohol			
Turati, 2010[38]	Up to September 2009	17	1,491	N/A	P (Heavy drinkers)	6.62[a,c]	4.72, 9.29	Increased odds by site
		6	293	N/A	T (Heavy drinkers)	4.11[a,c]	2.46, 6.87	
		4	280	N/A	OPC (Heavy drinkers)	7.76[a,c]	4.77, 12.62	
Tramacere, 2010[48]	Up to September 2009	45	17,085	N/A	OCPC (Light drinkers)	1.21[b,c]	1.10, 1.33	Increased odds
					OCPC (Heavy drinkers)	5.24[b,c]	4.36, 6.30	
					Coffee			
Turati, 2011[49]	Up to October 2009	9	2,633	N/A	OCP	0.64[a,c]	0.51, 0.80	Reduced odds
					Diet			
Xu, 2014[40]	January 1966- May 2013	13	4,104	N/A	OCPC (Processed meat)	1.91[a,c]	1.19, 3.06	Increased odds
					HPV			
Hobbs, 2006[46]	Inception to February 2004	5	383	1,816	OPC	4.3[b]	2.1, 8.9	Increased odds by site
		8	217	163	T	15.1[b]	6.8, 33.7	
					Smoking Tobacco			
Ansary-Moghaddam, 2009[50]	By January 2007	24	14,934	N/A	OPC (Smoking)	3.41[a,c]	2.74, 4.24	Increased odds with intensity of exposure and alcohol
					OPC (<20 CPD)	1.61[a,c]	0.90, 2.88	
					OPC (≥20 CPD)	3.12[a,c]	1.78, 5.47	
					OPC (Smoking nondrinkers)	2.62[a,c]	2.01, 3.41	
					OPC (Smoking drinkers)	8.07[a,c]	5.28, 12.40	
					Smokeless Tobacco			
Rodu, 2002[47]	1957-1998[d]	3	169	472	P (SLT-unspecified)	2.3[b,c]	1.2, 4.4	Increased odds: site and SLT material specific
		3	298	947	OPC (DS)	4.0[b,c]	2.7, 5.9	
		3	655	2,718	OPC (SLT-unspecified)	1.5[b,c]	1.1, 2.0	
		2	362	457	OPL (CT)	1.7[b,c]	1.2, 2.4	
		1	93	393	OPL (DS)	13.0[b,c]	8.0, 20.0	

Abbreviations: N/A, not available from published report; P, pharynx; T, tonsil; OPC, oropharyngeal; OCPC, oral cavity/pharynx; HPV, Human Papilloma Virus; CPD, cigarettes per day; SLT, smokeless tobacco; DS, dry snuff; OPL, oral cavity, pharynx, larynx; CT, chewing tobacco;
[a] adjusted [b] adjustments unclear [c] relative risks [d] years of publications of used studies