Head and Neck Cancer: Changing Epidemiology and Public Health Implications

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Characterizing the epidemiology of head and neck cancers is challenging and has received limited attention in the medical literature. Traditionally, 80%-90% of head and neck squamous cell carcinomas (HNSCCs) have been attributed to tobacco and alcohol use, but with growing public awareness and tobacco control efforts over the past few decades, there has been a downward trend in smoking prevalence in the US. There is also emerging evidence that human papillomavirus (HPV) is responsible for inconsistencies in HNSCC trends, with oncogenic HPV DNA found in approximately half of oropharyngeal cancers and in a high proportion of oropharyngeal cancers in nonsmokers and nondrinkers. The risk to HNSCC epidemiology is that whatever gains continue to be made in tobacco control may become lost in the increasing numbers of oropharyngeal cancers due to HPV. The purpose of this review is to explore the changing epidemiology of HNSCC, focusing on how it has been shaped by health policy and advocacy interventions and how it will continue to have public health implications in the future, particularly in considering preventive strategies against HPV. Given that the majority of HNSCCs are the result of exposure to preventable public health risks, more focus should be given to this area.

Head and neck cancer encompasses malignant tumors arising within the upper aerodigestive tract. The number of new cases of head and neck cancer in the United States was 48 in 2009, accounting for 3.2% of all new cancers and 2.0% (11,260) of all cancer deaths.[1] Worldwide, an estimated 644,000 new cases are diagnosed each year, with two-thirds of these occurring in developing countries.[2] The median age at diagnosis is in the sixth decade of life, and the incidence is three-fold higher in men. Despite this overall burden, the epidemiology of head and neck cancers receives limited attention in the medical literature.

Every tissue type is represented in the head and neck: from skin to bony paranasal sinuses, salivary glands to lymphoid tonsils, and laryngeal cartilage and joints to pharyngeal epithelium. More than 90% of head and neck cancers are squamous cell carcinomas, which originate from the mucosal surfaces of the lip and oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. These are a heterogeneous group of cancers with unique epidemiologic, histopathologic, and treatment considerations. As most patients with HNSCC present with advanced-stage locoregional disease, its treatment requires a multidisciplinary approach involving otolaryngologists, medical oncologists, radiation oncologists, speech therapists, pathologists, dentists, oral surgeons, and radiologists. While surgical resection with or without adjuvant radiotherapy had been the mainstay of HNSCC treatment, the concept of organ and function preservation has developed over the past two decades. This involves sparing as much of an organ as possible so that it remains functional, while maintaining or exceeding survival rates of non–organ-preserving strategies.[3,4] Although the majority of patients rank being cured as their top priority, up to 25% of HNSCC patients place a greater emphasis on issues related to quality of life.[5] The treatment strategies that have been developed to accomplish this organ and function preservation include concomitant chemoradiotherapy, intensity-modulated radiation therapy, improved surgical techniques with innovative reconstruction strategies, and molecular-targeted biological agents.

Major Risk Factors for HNSCC

Owing to the vast heterogeneity of cancers arising in the head and neck, characterizing the epidemiology of HNSCC is challenging. Traditionally, 80%-90% of HNSCC have been attributed to tobacco and alcohol use.[6] The risk for developing HNSCC for cigarette smokers is 5- to 25-fold greater than that for nonsmokers, with the risk increasing in a dose-response fashion with frequency, duration, and extent of smoking.[2,6-8] The risk substantially decreases with time from smoking cessation, although this risk never reaches the level of a never-smoker.[9,10] One Italian study found that the cumulative risk at 75 years of age for all upper aerodigestive tract cancers was 6.3% for
men who continued to smoke any type of tobacco, 3.1% for men who stopped smoking at around 50 years of age, 1.2% for men who stopped smoking at around 30 years of age, and 0.8% among lifelong nonsmokers.[10] Although active tobacco smoking is the major risk factor for HNSCC, involuntary or secondhand smoking has also been associated with an increased cancer risk. In an international pooled analysis, long exposure to involuntary smoking, described as occurring over a period of more than 15 years, both at home and work, was associated with an increased risk of HNSCC, particularly pharyngeal and laryngeal cancers.[11]

Alcohol has also been shown to synergistically increase the HNSCC risk attributable to tobacco use.[7] Heavy alcohol consumption alone is an independent risk factor for HNSCC. High-frequency use, defined as three or more drinks per day, was independently associated with an increased risk of cancers of the oropharynx, hypopharynx, and larynx.[12] No evidence thus far has established risk differences for various types of alcoholic beverages.[13]

Other risk factors that have been associated with HNSCC include dietary patterns, viruses, and occupational exposures. Numerous studies have associated HNSCC with vitamin A deficiency, whereas other studies describe an inverse association with high fruit and vegetable intake.[2,8] Viruses that have been implicated include Epstein-Barr virus (EBV) and human papillomavirus (HPV), and occupational exposures such as chromium, nickel, and radium have also been linked particularly to sinonasal carcinomas.[2]

**Twentieth Century Trends**

Throughout the early part of the 20th century, newly diagnosed cases of HNSCC have continued to rise annually, due in part to increasing incidence and improved methods of detection. Over the last two decades, however, there has been a downward trend in HNSCC incidence and mortality, with variability based on anatomic sites. The decline in HNSCC incidence rates has benefited both men and women, as well as all ethnicities, although disparities still remain; African-American males continue to have a higher incidence of oral and oropharyngeal cancers than do white males.[14] Additionally, studies in both high- and low-income countries have demonstrated that patients with low socioeconomic status and low educational attainment had a greater risk for HNSCC, particularly oral cancer.[15]

The overall 5-year survival rate from HNSCC is less than 50%. Although this survival rate has remained unchanged during the past few decades,[7] there is evidence supporting a decrease in HNSCC mortality rates over the last 20 years.[6] Reasons for this downward trend include changes in tumor biology and risk factors, and decreasing HNSCC incidence rates.[6,16] Nevertheless, disparities in survival also remain, with mortality rates among African-American males being approximately twice as high as compared to their white male counterparts.[7] The decline in overall HNSCC incidence and mortality in the United States over the past two decades is likely related to changes in tobacco consumption over the latter half of the 20th century.[6,8]

**The Rise and Fall of Big Tobacco—and of Head and Neck Cancer?**

Although the tobacco plant is thought to have been growing in the Americas since 6,000 B.C.E., cigarette smoking is largely a 20th century phenomenon.[17,18] From the beginning of the 20th century, cigarettes were widely popular and socially acceptable; by the mid 20th century, however, reports linking cigarette smoking to cancer, heart disease, and other serious health problems led to public efforts to control tobacco smoking.

When Dr. Ernst L. Wynder and others started publishing landmark epidemiologic studies at the turn of the 20th century, linking tobacco smoking to lung cancer and to cancer of the head and neck,[6,17-21] nearly half of all adult Americans—over half of all men and about one-third of all women—were cigarette smokers.[6,17,18] Tobacco companies responded to these initial public health concerns by filtering their cigarettes, to decrease the amount of tar inhaled in the smoke, but in doing so they touted the change as conferring not only a health benefit, but also improving the taste of their cigarettes. In 1961, as a result of growing evidence of the health hazards of smoking, the presidents of the American Cancer Society, American Heart Association, National Tuberculosis Association, and the American Public Health Association submitted a joint letter to President Kennedy, urging him to establish a commission to study the impact of smoking on health.[17] This resulted in the Surgeon General’s Report of 1964, which, based on approximately 7,000 articles related to smoking and disease, reported that cigarette smoking is a cause of lung and laryngeal cancer and concluded that these findings warranted appropriate remedial action.[17,18] Significant public health efforts to reduce the prevalence of tobacco use began shortly after this
In the late 1960s and early 1970s, health warnings on cigarette packs were instituted, there was a nationwide ban on tobacco advertising on television and radio, and antismoking groups responded with antismoking advertisements. For the first time in the 20th century, yearly cigarette consumption began to decline.[17,18] In more recent years, the growing public awareness and support of tobacco control efforts has had substantial influence in reducing the social acceptability of smoking behavior and continuing the downward trend in tobacco consumption.[6] In the 1990s, tobacco control measures included clean-indoor-air laws, restrictions on tobacco sales to minors, cigarette excise tax increases, and product disclosure laws that require manufacturers to disclose nicotine yield and additives.[17,18] In the midst of multiple litigations, the Master Settlement Agreement in November 1998, between big tobacco companies and the attorneys general of 46 states, provided the states with an unprecedented $206 billion industry dollars to promote prevention and control of tobacco use.[6,17] Although the public health advances over the past few decades that have curbed tobacco consumption in the United States are impressive, major disparities such as age, sex, ethnicity, and socioeconomic status still remain, with highest smoking prevalence among younger adults, men, American Indians and Alaskan Natives, and those of lower socioeconomic status.[22]

The decrease in smoking prevalence since the 1970s has been mirrored by a decline in the number of newly diagnosed tobacco-associated cancers.[6,18] This is particularly true for HNSCCs, which have seen an overall decrease in incidence rates that appears to trail the decline in smoking prevalence by 10 to 15 years.[6] Age-adjusted incidence rates for cancers of the larynx, oral cavity, and hypopharynx have all shown significant decline over the past three decades, but oropharyngeal cancers have not shown a similar decline.[6] Cancers of the oropharynx have been on the rise, now accounting for almost as many cases as the traditional principal sites of HNSCC: the oral cavity and larynx. The increase in oropharyngeal cancer is most dramatic in adults younger than 45 years of age, particularly for cancers of two oropharynx subsites: base of tongue and tonsil.[1,23,24] One recent analysis of Surveillance Epidemiology and End Results (SEER) data from 1973–2001 showed an annual increase in the incidence of oral tongue, base of tongue, and tonsil cancers, by 2.1%, 1.7%, and 3.9%, respectively, in 20- to 44-year-old white patients, while the incidence of HNSCC at other head and neck sites declined.[24] There is emerging evidence that HPV is responsible for these inconsistencies in HNSCC trends.

The Case for HPV

HPV is a DNA virus comprising more than 100 genotypes that specifically target the basal layer of squamous epithelial cells. Almost all invasive cancers of the cervix and most other anogenital tract cancers contain oncogenic HPV viruses. The basic molecular mechanisms by which oncogenic HPV proteins E6 and E7 disrupt cell-cycle control and stimulate viral replication through their respective effects on p53 and Rb tumor suppressor genes have been well-studied and accepted in the carcinogenesis of cervical and other anogenital tract cancers.[6-8] The involvement of HPV in oral and oropharyngeal carcinogenesis was first proposed in 1983, based on characteristic HPV morphological and immunohistochemical properties seen on oral squamous cell carcinoma biopsies.[7,25] HPV, particularly HPV 16, is now regarded as an independent risk factor for a subset of HNSCCs. There is consistent evidence that oncogenic HPV DNA is contained in approximately 50% of oropharyngeal cancers and in a high proportion of oropharyngeal cancers in nonsmokers and nondrinkers.[2,6,8,26,27] Although HPV DNA in HNSCC is not exclusively found in nonsmokers, many studies have shown that HPV-positive tumors in nonsmokers tend to be localized to the oropharynx.[7] At the molecular level, there is further support for the claim that HPV increases the risk for HNSCC, independent of and in a manner different from the carcinogenic effects of tobacco and alcohol. The genetic and transcriptional development of HNSCC related to tobacco and alcohol has been well studied and established. In HNSCC caused by these two traditionally major risk factors, p53 is commonly mutated and the chromosome band 9p21-22 is lost early in carcinogenesis, resulting in loss of the tumor suppressor gene, p16.[26] In contrast, HPV-positive HNSCC has decreased expression of wild-type p53, due to inactivation/degradation by HPV viral protein E6, and these tumors do not show p16 depletion. In fact, p16 overexpression has been identified as a marker for transcriptionally active HPV, which the cervical cancer literature has established as being necessary for HPV to induce carcinogenesis. There is a correlation between HPV-associated anogenital cancers and HNSCC. Several studies have
examined the incidence of second cancers after an initial diagnosis of cervical or other anogenital cancers, and have subsequently demonstrated an increased risk of HNSCC, as well as additional anogenital cancers.[28] A population-based SEER study found that the lifetime risk of second primary cancer in the head and neck in patients with cervical cancer was higher than in the general population, with a standardized incidence ratio (SIR) of 1.7, suggesting a role of HPV.[29] The Swedish Family Cancer Database followed 135,386 women from 1958 to 1996 who were initially diagnosed with cervical carcinoma, for the occurrence of second primary cancers in the upper aerodigestive tract, as well as first primary cancers among their husbands.[30] This study revealed that female patients with cervical cancer had elevated risks for second cancers in the upper aerodigestive tract; for patients with in situ disease, the overall SIR was 1.68 (1.10–2.43), compared with females with invasive cervical cancer, who had an overall SIR of 2.45 (1.05–4.98). Husbands of cervical cancer patients also had elevated SIRs of cancers of the upper aerodigestive tract,[30] suggesting an association with HPV.

When considering the distinct risk factors for HPV-positive HNSCC, HPV seems to meet most of the criteria for disease causation: strength and consistency; numerous basic scientific and epidemiologic data supporting HPV as a cause of HNSCC; biological plausibility, with the model of HPV tumorigenesis in the head and neck derived from well-established models of cervical cancer; and a temporal relationship.

Unlike HPV-negative HNSCC, the major risk factors for HPV-positive cancers are not tobacco and alcohol; risk appears to be related to sexual history.[31] The risk for HPV-positive HNSCC has been shown by numerous studies to increase with increasing numbers of oral and vaginal sexual partners, multiple simultaneous partners, earlier age of first intercourse, a history of genital warts, and in men a history of same-sex contact.[31-33] In an international pooled analysis, risk for base of tongue cancer was greater among men who ever had oral sex, (odds ratio [OR] = 4.32), had two simultaneous partners in comparison to only one (OR = 2.02), and had a history of same-sex contact (OR = 8.89).[34] Consequently, changing sexual practices, such as more frequent oral sex among adolescents and young adults, may be contributing to this upward trend in HPV-associated oropharyngeal cancers.[35]

One of the most significant clinical implications of distinguishing HPV-positive HNSCC is that it appears to be associated with a better prognosis and have distinct molecular characteristics. These cases are also associated with unique risk factor profiles, when compared with HPV-negative cancers. Studies have shown that patients with HPV-positive oropharyngeal cancer are more responsive to treatment and have better rates of survival than those with HPV-negative oropharyngeal cancer.[7,26]

In a study by Weinberger et al., p16 overexpression in oropharyngeal SCC was associated with a 5-year overall survival (OS) rate of 79% compared with a 5-year OS of 20% in patients with HPV-negative tumors and 18% in patients with HPV-positive tumors but normal expression of p16.[36] A second study found that, compared with patients who had HPV-negative tumors, patients with HPV-positive tumors had higher response rates to induction chemotherapy and combined concomitant chemoradiotherapy. Patients with HPV-positive tumors had improved survival, with a 2-year OS of 95%, compared with 62% for their HPV-negative counterparts.[37] While the mechanism of improved survival in HPV-associated HNSCC is still unclear and needs further research,[26] the ability to distinguish patients with HPV-positive tumors appears to have significant clinical implications, in terms of better tailoring their treatments and informing them of their prognosis.

Future Public Health Implications and Conclusions

Despite the impressive public health advances in tobacco control made over the last 30 years, the overwhelming majority of HNSCCs are still attributed to tobacco and alcohol use. Efforts must also be devoted to targeting the disparities in HNSCC: persons with lower socioeconomic status and lower levels of education, and racial and ethnic groups such as African-Americans, Native Americans, and Alaskan Natives, are particularly at risk for HNSCC, largely because of their greater consumption of tobacco and alcohol. It appears, however, that there is an emerging epidemic of HNSCC which is largely affecting younger persons who are nonsmokers and nondrinkers. The risk to HNSCC epidemiology is that whatever gains are made in preventing individuals from becoming new smokers, or in helping current smokers to quit, may become lost in the increasing numbers of oropharyngeal cancers caused by HPV.[6]

Some preventive strategies against HPV-associated HNSCC can be modeled after those used against
cervical cancer, the incidence of which has long been in decline in the United States.[38] In terms of primary disease prevention, in 2006, the Food and Drug Administration approved a vaccine against HPV types 6, 11, 16, and 18 for adolescent girls and young women 9–26 years old. In late 2009 the vaccine was also approved for boys and men 9–26 years of age, for the prevention of genital warts.[39,40] Although the vaccination will undeniably decrease the incidence of cervical carcinoma in females, its impact on oropharyngeal cancer incidence is unclear. The vaccine was also only recently approved for males, a population which some studies suggest has a greater proportion of nonsmokers with oropharyngeal cancers, compared with females, and therefore carries more of the HPV burden than females.[6,41] Although the vaccination appears promising, especially given that it targets HPV 16, it remains to be seen whether its use will have an effect on the incidence of HNSCC, particularly in the younger adult population.

Although oral sexual practices are on the rise among adolescents and young adults,[35] there is very little discourse in the medical literature regarding efforts to address sexual behavior as a form of primary prevention, therefore health education is warranted regarding risk factors for HPV contraction and ways to decrease transmission. In a recent US study by Cermak et al., women reported that their physicians were not educating them about HPV testing, risk factors for contracting HPV, and preventive measures against HPV.[42] Given the association between increasing oral sexual practices and increased risk for HNSCC, health education specialists should use appropriate strategies to not only to educate young people about HPV and its association with anogenital cancer, but also about HPV and the risk of HNSCC.

Success in reducing the incidence of cervical cancer in the United States has been primarily in secondary prevention of disease. Widespread use of the Papanicolau screening test has proven to be a cost-effective method of identifying and treating premalignant cervical lesions in the entire female population. In contrast, effective screening for oropharyngeal premalignancies is limited, although theoretically possible given the unique molecular markers associated with HPV infection. A recent study evaluated salivary rinsing as a potential screening test, not for primary detection, but rather for recurrence of HPV-positive tumors after treatment. In this study, polymerase chain reaction (PCR) detection of HPV E6/E7 viral protein numbers by PCR had a sensitivity of 50% and a specificity of 100% for detection of cancer recurrence.[43] While the study population was small, the findings suggest that quantitative measurement of salivary HPV-16 DNA may be promising for surveillance and early detection of recurrence, although its effectiveness in early detection of premalignant lesions remains to be seen.

Capturing the true epidemiology of head and neck cancers is difficult, owing to the relatively small number and heterogeneity of the cancers. This leads to limited medical literature. Unlike breast or colorectal cancers, however, a great majority of head and neck cancers are the result of exposures to important public health risks—tobacco, alcohol, and the human papillomavirus—and are thus preventable. Given that head and neck cancers can affect some of life’s most critical functions, including speech, communication, swallowing, eating, and cosmesis, more implications for prevention need to be addressed.

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