Trends in Head and Neck Cancer Incidence in Relation to Smoking Prevalence

An Emerging Epidemic of Human Papillomavirus-Associated Cancers?

Erich M. Sturgis, MD, MPH[1,2]
Paul M. Cinciripini, MD[3]

[1] Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[2] Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[3] Department of Behavioral Science, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Dr. Cinciripini has acted as a consultant for Sanofi-Aventis, Glaxo-SmithKline, Xenova, and Pfizer.

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Address for reprints: Erich M. Sturgis, MD, MPH, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Unit 441, 1515 Holcombe Blvd., Houston, TX 77030; Fax: (713) 794-4662; E-mail: esturgis@mdanderson.org

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The trends in head and neck cancer incidence and smoking prevalence are reviewed, discussing where such trends parallel but also how and why they may not. In the U.S., public health efforts at tobacco control and education have successfully reduced the prevalence of cigarette smoking, resulting in a lower incidence of head and neck cancer. Vigilance at preventing tobacco use and encouraging cessation should continue, and expanded efforts should target particular ethnic and socioeconomic groups. However, an unfortunate stagnation has been observed in oropharyngeal cancer incidence and likely reflects a rising attribution of this disease to oncogenic human papillomavirus, in particular type 16 (HPV-16). For the foreseeable future, this trend in oropharyngeal cancer incidence may continue, but with time the effects of vaccination of the adolescent and young adult female population should result in a lower viral prevalence and hopefully a reduced incidence of oropharyngeal cancer. To hasten the reduction of HPV-16 prevalence in the population, widespread vaccination of adolescent and young adult males should also be considered. ***Cancer*** **2007;110:1429–35.**

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Excluding skin and thyroid cancers, virtually all carcinomas that occur in the head and neck region arise within the upper aerodigestive tract and connected adenexal structures. Taken together, carcinomas of the upper aerodigestive tract, also termed head and neck cancer, will account for only 45,660 new cancers in 2007 or only 3.2% of all incident malignancies in the U.S.[1] The overwhelming majority of these head and neck cancers are squamous cell carcinomas (SCCHN) with most of the remainder being salivary gland carcinomas. To better understand etiologic associations and clinical management/outcomes, head and neck cancers are subcategorized by their site of origin and annually account for approximately 17,000 cancers of the oral cavity, 10,000 of the larynx, 10,000 of the oropharynx, and 2500 of the hypopharynx.[1–3] In this article, we explore trends in head and neck cancer incidence in the U.S., the association with smoking trends or lack thereof, and the explanations and public health implications for these relations.

SCCHN and Tobacco

Strong basic carcinogenic and epidemiologic data have established tobacco as the carcinogenic factor in the overwhelming majority of SCCHN, and the classic criteria of disease causality have been well

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documented.[4] The risk for SCCHN for cigarette smokers is estimated to be approximately 10-fold over that of never-smokers. This risk increases in a dose-response type manner with duration and extent of smoking. In addition, the risk decreases with time from cessation of exposure, although that risk never reaches the level of a never-smoker.[5] The association between smoking and head and neck cancer risk is strongest for laryngeal cancer. Alcohol use appears to enhance the risk of SCCHN associated with smoking, particularly for heavy drinkers, and heavy alcohol use is also an independent risk factor for SCCHN.[4] The association with alcohol use appears to be strongest for hypopharyngeal cancer. Historically, approximately 80% to 90% of SCCHN in the U.S. is attributed to tobacco use and alcohol abuse.[4]

Tobacco Use and Control

Cigarette smoking is a 20th century phenomenon, with its pervasion in the U.S. occurring in the first half of the century and its control happening in the latter half (Fig. 1).[6,7] Industrialization in the U.S. around the turn of the 20th century also impacted the tobacco industry, with improvements in curing, mass production, transportation, and mass media.[8] In 1881 the cigarette machine was invented, in 1910 the safety match was patented, and in 1913 the first modern cigarette brand (Camel) was introduced by R.J. Reynolds.[8,9] During both World War I and the economic expansion and prosperity of the 1920s, growth in use mirrored the expansive, emerging consciousness of the country as a world power, and with women's liberation came social acceptance of female smoking and increased use by women. After a brief delay during the height of the Great Depression, the prevalence of cigarette use continued to climb in the later half of the 1930s before nearly doubling in use during World War II. Although much has been written about the glamorization of cigarette smoking through film and advertising, including even the sanctioning of use by segments of the medical establishment, the strategy of providing cigarettes as part of rations to American troops was central to building a solid foundation of male users for most of the rest of the century.

In the 1950s the tide began to turn, with Dr. Ernst Wynder publishing landmark case-control studies linking tobacco smoking to lung cancer[10] and to cancer of the mouth in a study published in this journal.[11] In addition, Drs. E. Cuyler Hammond and Daniel Horn in the U.S. and Sir Richard Doll and Sir A. Bradford Hill in the U.K. published large cohort studies prospectively demonstrating a 10-fold risk for lung cancer and 5-fold risk for SCCHN associated with smoking.[12–14] However, after a short pause in the 1950s, the use of cigarettes rose steadily until the scientific/medical consciousness of the problem culminated in the Surgeon General's Report of 1964.[15] Although this report was a watershed event in reducing cigarette use in the U.S., numerous other governmental and nongovernmental efforts have contributed to the nearly uninterrupted annual reductions in the per capita use of cigarettes since that time.

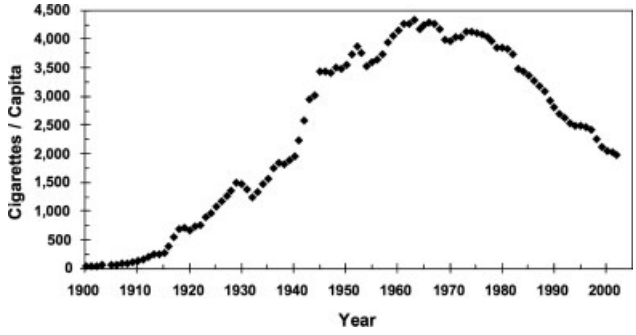

FIGURE 1. Per capita yearly consumption of cigarettes in the U.S.[6,7]

In recent years, the growing public awareness and support of tobacco control efforts have had a substantial impact in reducing cigarette consumption as well as the social acceptability of smoking behavior.[8,16] Tobacco control measures have included clean indoor air laws in worksites, restaurants, bars, and public buildings, ballot initiatives to raise cigarette excise taxes, and product disclosure laws requiring manufacturers to disclose nicotine yield and additives, and in 1998 the landmark Master Settlement Agreement between the tobacco companies and the attorneys general of 46 states provided the states with 206 billion of industry dollars to promote tobacco use prevention and control.[8] The importance of such measures on smoking prevalence is underscored by examining the declining smoking prevalence trends in California and Massachusetts, 2 states that have had publicly supported strong tobacco control programs.[17–19]

Nevertheless, the absolute number of Americans who classify themselves as current smokers has changed very little in the past 40 years; however, in 2005 more Americans classified themselves as never-smokers (smoked fewer than 100 cigarettes in their lifetime) than ever before (Fig. 2).[7,20] In addition, although the growth in the number of quitters or former smokers (smokers who had quit for at least the previous 12 months) slowed over the last decade, more American smokers for each of the last 4 years

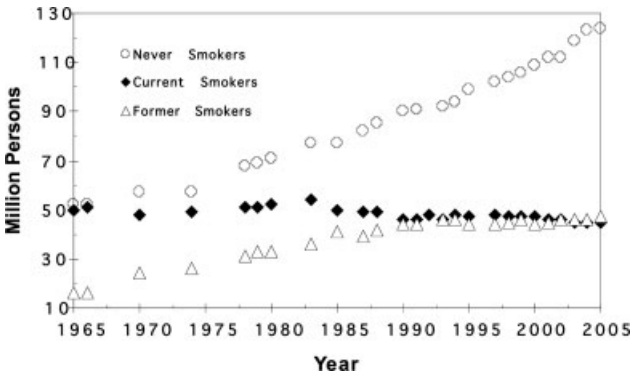

FIGURE 2. Yearly number of current, former (not smoking for the preceding 12 months), and never (never smoked or smoked fewer than 100 cigarettes in their lifetime) smokers in the U.S.[7,20]

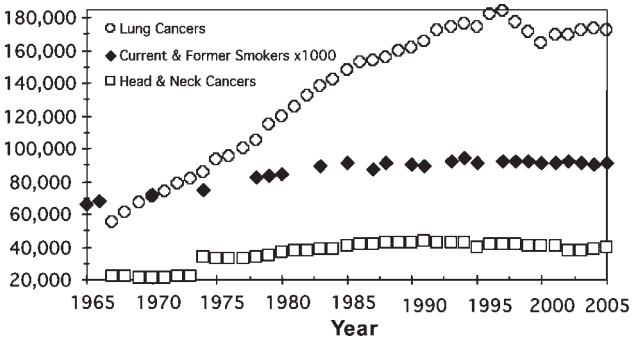

FIGURE 3. Yearly number of current and former (not smoking for the preceding 12 months) smokers and annual estimated number of incident cases of lung as well as head and neck cancers in the U.S.[7,20,23]

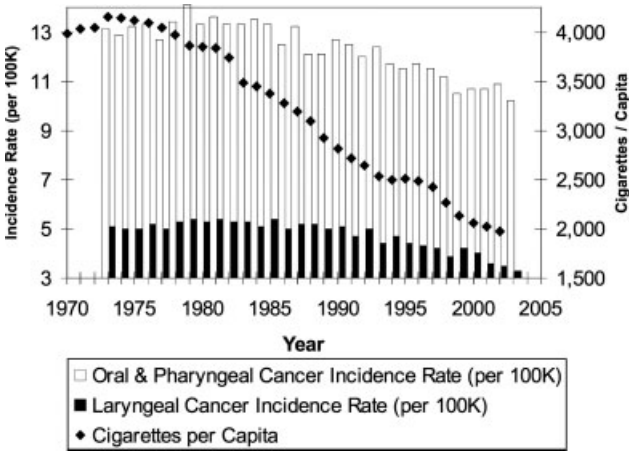

FIGURE 4. Per capita yearly consumption of cigarettes and annual age-adjusted (to U.S. 2000 standard) incidence rates of oral/pharyngeal and laryngeal cancers per 100 thousand persons in the U.S.[6,25]

have classified themselves as former smokers than current smokers (Fig. 2).[7,20] Of U.S. adults in 2005, 20.9% (45 million) were current smokers (down from a high of 42.5% in 1965), 21.6% (47 million) were former smokers (up from 13.5% in 1965), and 57.5% (124 million) had never smoked (up from 44.0% in 1965) (Fig. 2).[7,20] These public health advances over the last 4 decades are impressive, but major geographic, sex, as well as ethnic and socioeconomic disparities remain.[18–22]

Where SCCHN Trends Follow Smoking Trends

After many years of annually increasing numbers of newly diagnosed cancers, the nation experienced a break in that growth in 1998, and it was not until 2006 that estimates again reached 1997 levels. When plotted against the absolute number of current and former smokers in the U.S., the foundation of these trends are clear. As the total number smokers (current and former) in the U.S. stabilized, the nation experienced a plateau in the number of newly diagnosed tobacco-associated cancers and this is true for head and neck cancers in particular (Fig. 3).[7,20,23]

These trends in absolute numbers do not account for an increasing population size or for an aging population. This past year the population of the U.S. reached 300 million, with a median age of 36 years, up from approximately 200 million in 1970 with a median age of 27 years.[24] When incidence rates are age-adjusted to the 2000 U.S. standard population, clear declines since the mid-1980s for both oral cavity/pharyngeal cancer and laryngeal cancer incidence rates can be found. These decreasing incidence rates trail by 10 to 15 years the declines in smoking prevalence, which began in the 1970s (Fig. 4).[6,25] These decreasing head and neck cancer incidence rates have benefited both men and women and all ethnicities, but major disparities remain, particularly for African-American men.[25,26] In addition, head and neck cancer mortality rates have decreased over the last 20 years.[25,27] The reasons for this drop in mortality are complex but are explained chiefly by the decreasing head and neck cancer incidence rates attributable to having fewer smokers.[25,27] Clearly, improvements in treatment reflected in higher survival rates would also lower mortality, but recent data suggest that whereas 5-year relative survival rates have improved for hypopharyngeal and oropharyngeal cancers, the survival rates for the majority of SCCHN cases (oral cavity and laryngeal cancers) are either stagnant or slightly worse.[2] Although we celebrate the treatment advances including more widespread adoption of multimodality care and organ preservation, it would appear that prevention (ie, reducing smoking prevalence) is impacting overall head and neck cancer

incidence and mortality rates to a much greater degree than any treatment advance.

Where Smoking Prevalence and SCCHN Incidence Trends Are Not Parallel

Although the public health benefits of tobacco control to the head and neck cancer problem are clear, the reductions in incidence are not consistent across all age groups or for all sites within the head and neck region, and we suspect that human papillomavirus type 16 (HPV-16) is responsible for many of these inconsistencies. Anecdotal series of oral tongue cancers in young adults have been reported for some time, and multiple researchers have documented this phenomenon.[28–33] Most recently in *Cancer*, Shiboski et al.[34] confirmed an increase in the national incidence rates of oral tongue cancer in young adults, but found a more dramatic rise in the incidence rates of oropharyngeal cancer in adults younger than 45 years of age. This increase in incidence rates over the last 30 years among young adults was particularly striking for tonsil cancer (approximately 4% per year) and base of tongue cancer (approximately 2% per year).[34] In addition, although the age-adjusted incidence rates for larynx, oral cavity, and hypopharynx cancer have all shown significant declining trends over the last 30 years, oropharyngeal cancer is not demonstrating a similar decline.[2] Further complicating the interpretation of these trends are reported significant increases in the incidence of "tongue" cancers.[2] However, although this is in part explained by the increasing incidence rates of oral tongue cancer in young adults, this may overlook a likely contribution of an increase in base of tongue cancers, which are often grouped together with oral tongue cancers. Finally, as a site of origin, the oropharynx continues to account for a higher proportion of head and neck cancers, and now accounts for almost as many cases as the traditional principal sites of head and neck cancer—the oral cavity and the larynx.[1,2] Figure 5 shows the annual estimates of new head and neck cancers in the U.S. by subsite for the last 20 years and highlights some of the issues discussed above.[3,23] However, it should be noted that any rise in the numbers of oropharyngeal cancers is less apparent because the American Cancer Society "pharynx" cancer estimates[3,23] group hypopharyngeal cancers (a cancer that appears to be declining in incidence[2]) with oropharyngeal cancers and because many oropharyngeal cancers (chiefly base of tongue cancers) are listed under "tongue" rather than "pharynx" cancer (Fig. 5).[3,23]

At a population level, the majority of SCCHN remain attributable to smoking, but the reasons for a rising proportion of SCCHN in the oropharynx and for more of these cancers being diagnosed in a younger population are less clear. The attributable fraction of SCCHN due to smoking is higher in countries with higher smoking prevalence, such as many areas of Europe; however, other factors likely contribute to the etiology of SCCHN and to the rise in relative incidence of oropharyngeal cancer.[4,35,36] Certainly, in south-central Asia it is well understood that use of smokeless oral tobacco products (particularly when combined with the betel leaf, lime, catechu, or areca nut) has lead to SCCHN (particularly oral cavity cancer) becoming the most common cancer in men and the third most common in women.[36] However, in the U.S., the use of these products or of smokeless tobacco alone is quite rare and has actually been in greater relative decline than smoking rates.[37,38] In addition, although secondhand tobacco smoke has been labeled as a lung carcinogen and case-control studies have linked such environmental tobacco smoke exposures to SCCHN,[35] the exposure to environmental tobacco smoke also appears to be in dramatic decline in the U.S. thanks to public health actions of the 1990s.[39]

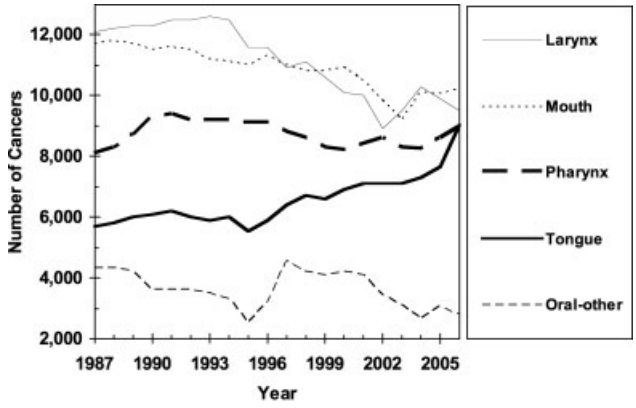

FIGURE 5. Annual estimated number of incident cases of head and neck cancers by subsite in the U.S.[3,23]

Although neither the use of smokeless tobacco nor secondhand tobacco exposures are likely to account for the evolving trends in SCCHN incidence, until recently significant effort at uncovering etiologic factors other than tobacco and alcohol in SCCHN has yielded limited results. For instance, moderately powered case-control studies and a cohort study have yielded conflicting data regarding the association between marijuana use and SCCHN.[40,41] Some data also suggest that marijuana use in the U.S. has been in decline over the past 20 years,[42] and consequently trends in marijuana use are also not a likely cause of the changing SCCHN incidence trends.

Other anecdotal evidence suggests that the reflux of gastric acid into the pharynx is a risk factor for laryngeal cancer, although very limited controlled data support such an association.[43,44]

However, an expert committee of the National Academy of Sciences has concluded that there is sufficient evidence to consider asbestos as a significant independent risk factor for laryngeal cancer,[45] and significant epidemiologic data support indoor air pollution from combustion of fossil fuels as an independent risk factor for SCCHN.[35] Given the regulations against asbestos in and the modern heating and cooking practices of the U.S., it is unlikely that the evolving trends in oropharyngeal cancer incidence can be attributed to these exposures.

The link between oncogenic HPV and oropharyngeal cancer is quite strong and the majority of the classic criteria of disease causality have been documented by numerous independent investigators.[46] First, the literature is both consistent and specific, with oncogenic HPV DNA being identified in approximately 50% of oropharyngeal cancers and a particularly high proportion of oropharyngeal cancers in nonsmokers, and consistently greater than 90% of HPV-positive oropharyngeal tumors having HPV-16. The association is also quite strong with a significant risk of oropharyngeal cancer reported in epidemiologic case-control studies by numerous independent investigators and after adjustment for smoking and alcohol exposures. Finally, basic molecular mechanisms by which the oncogenic HPV proteins E6 and E7 disrupt cell cycle control and apoptosis through their respective effects on p53 and Rb are well understood. Consequently, the similarities between oncogenic HPV-induced oropharyngeal cancer and cervical carcinogenesis and the biologic plausibility of the HPV carcinogenesis model all support HPV causality of a proportion of oropharyngeal cancers.

Several lines of anecdotal evidence suggest that the emerging trends in oropharyngeal cancer incidence that have not paralleled the reduction in tobacco exposures in the U.S. are attributable to oncogenic HPV exposures. As discussed, HPV-associated SCCHN are classically oropharyngeal cancer with a younger age at presentation and less tobacco exposure than traditional SCCHN. Indeed, it is principally these subgroups of SCCHN patients (younger adults with oropharyngeal cancer) that are increasing in incidence.[34] The mode of transmission of oncogenic HPV to the upper aerodigestive tract is to our knowledge not fully understood, but risk factors such as multiple sexual partners and oral-genital sex are likely.[47–50] It has been reported that the sexual history of oncogenic HPV-positive oropharyngeal cancer patient populations is similar to that of women with cervical cancer.[48–50] Although trends in the prevalence of oncogenic HPV are unknown, the incidence of cervical cancer has long been in decline in the U.S.,[25] most likely due to widespread cervical screening practices allowing the effective identification and treatment of premalignant cervical lesions. In contrast, effective screening or treatment for oropharyngeal premalignancies is quite limited. Although speculative, more widespread use of condoms could also have contributed to the decline in the incidence rates of cervical cancer, but other changing sexual practices such as more frequent oral sex in adolescents and young adults[51] could contribute to an increase in oncogenic HPV-associated oropharyngeal cancers. In addition, survival rates for oropharyngeal cancer in the U.S. have increased dramatically in the past 10 years,[2] potentially reflecting the younger population affected and/or more aggressive/effective treatments.[52] However, this improvement in survival also may reflect a more favorable prognosis for oncogenic HPV-positive oropharyngeal cancers that has been reported by numerous authors.[53] Finally and notably, it has been recently reported that the prevalence of HPV-16 in 203 archival oropharyngeal cancer specimens from the Stockholm region of the Swedish Cancer Registry increased from 23% in the 1970s to 28% in the 1980s, 57% in the 1990s, and 68% in the 2000s.[54] During the same time period, smoking prevalence has dramatically declined in Sweden, leading the authors to suggest that an epidemic of oropharyngeal cancer associated with HPV-16 is possibly due to changing sexual practices, similar to those noted in the U.S.[51,54]

Future Public Health Burden

Because the absolute number of current and former smokers in the U.S. has changed little over the last 15 years, it would appear that for the foreseeable future the absolute number of SCCHN associated with cigarette smoking will continue at current levels. Of course, as our total population continues to grow (of whom never-smokers continue to comprise a greater proportion), the incidence of tobacco-associated SCCHN will continue to decrease. However, we might expect that whatever gains are made in preventing individuals from becoming new smokers or converting current smokers to former smokers may be overcome by an increasing number of oropharyngeal cancers associated with oncogenic HPV.

The Food and Drug Administration has recently approved a vaccine against HPV-16 and HPV-18 for adolescent girls and young women ages 9 to 26 years

and it is currently recommended that it be administered to girls at ages 11 to 12 years.[55] However, the vaccine has not been approved for young men or boys, although trials of efficacy in males are underway. Although vaccinating females will do much to control the public health impact of cervical dysplasia and carcinoma, the impact on oropharyngeal cancer incidence or the beneficial effects in males is less clear.[56] Although we might assume that the current vaccination strategy could prevent HPV-16/18-associated oropharyngeal cancers in women, some data suggest that the overwhelming majority of oropharyngeal cancers in nonsmokers (which are overwhelmingly associated with oncogenic HPV) occur in men.[49,57,58] The current vaccination strategy will only benefit men secondarily as the cohort of vaccinated women age and the incidence of chronic oncogenic HPV infection in the sexually active female population declines. It is possible that such an effect could take a generation to achieve.

Conclusions

The incidence of SCCHN in the U.S. has been in decline over the past 20 years, largely due to a decline in the prevalence of smoking, which began approximately 40 years ago. Although limited improvements (with the exception of pharyngeal cancers) have occurred in relative 5-year survival rates for SCCHN, the decrease in mortality rates are chiefly credited to the declines in incidence. These successes support continued vigilance at preventing and ceasing tobacco use, and expanded efforts should target the young and particular ethnic and socioeconomic groups. Of concern is the stagnation in the incidence of oropharyngeal cancer, which data suggest may be attributed to a growing incidence of oncogenic HPV-associated cancers. Although the cervical cancer and dysplasia prevention policy of the HPV-16/18 vaccination of young women and adolescent females are commended, we fear that vaccination programs limited to females will only delay the potential benefit in prevention of HPV-16/18-associated oropharyngeal cancers, which typically occur in men. We encourage the rapid study of the efficacy and safety of these vaccines in males and, if successful, the recommendation of vaccination in young adult and adolescent males.

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