

The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States : Implications for dentistry

Jennifer L. Cleveland, Michele L. Junger, Mona Saraiya, Lauri E. Markowitz, Eileen F. Dunne and Joel B. Epstein
JADA 2011;142;915-924

The following resources related to this article are available online at jada.ada.org (this information is current as of March 22, 2012):

Updated information and services including high-resolution figures, can be found in the online version of this article at:
<http://jada.ada.org/content/142/8/915>

This article cites **78 articles**, 23 of which can be accessed free:
<http://jada.ada.org/content/142/8/915/#BIBL>

Information about obtaining **reprints** of this article or about permission to reproduce this article in whole or in part can be found at: <http://www.ada.org/990.aspx>

The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States

Implications for dentistry

Jennifer L. Cleveland, DDS, MPH; Michele L. Junger, DDS, MPH; Mona Saraiya, MD, MPH; Lauri E. Markowitz, MD; Eileen F. Dunne, MD, MPH; Joel B. Epstein, DMD, MSD, FRCD(C), FDS RCS(Edin)

Oral and pharyngeal squamous cell carcinomas traditionally have been associated with tobacco and alcohol use. Results from recent studies suggest that some of these cancers, primarily those of the oropharynx (and, more specifically, those of the base of the tongue and the tonsils), are associated with infection with high-risk human papillomavirus (HPV) types. Surveillance data indicate that incidence rates of tongue and tonsillar cancers increased steadily between 1973 and 2007, whereas rates of cancers at other oral and pharyngeal sites decreased.¹⁻¹⁰ Compared

Dr. Cleveland is a dental officer and epidemiologist, Division of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, MS F-10, 4770 Buford Highway, Atlanta, Ga. 30341, e-mail "JLCleveland@cdc.gov". Address reprint requests to Dr. Cleveland. Dr. Junger is a dental public health resident, Division of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta. Dr. Saraiya is a medical epidemiologist, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta. Dr. Markowitz is a medical epidemiologist, Division of Sexually Transmitted Disease Prevention, National Center for Hepatitis, HIV/AIDS, Sexually Transmitted Diseases, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Atlanta. Dr. Dunne is a medical epidemiologist, Division of Sexually Transmitted Disease Prevention, National Center for Hepatitis, HIV/AIDS, Sexually Transmitted Diseases, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Atlanta. Dr. Epstein is a professor, Department of Oral Medicine and Diagnostic Sciences, College of Dentistry; a professor, Department of Otolaryngology—Head and Neck Surgery, College of Medicine; and a professor, Cancer Center, College of Medicine, University of Illinois at Chicago.

ABSTRACT

Background. Results from studies conducted in the past several years suggest that some oropharyngeal cancers, those of the base of the tongue and the tonsils, are associated with high-risk types of human papillomavirus (HPV). In this article, the authors summarize the available evidence regarding the epidemiology of HPV-associated oropharyngeal cancers in the United States, the available HPV vaccines and the implications of these for dentistry. They also examine the differences in HPV prevalence between cancers of the oral cavity and those of the oropharynx.

Types of Studies Reviewed. The authors searched PubMed, Web of Science, The Cochrane Library and the National Guideline Clearinghouse to identify English-language systematic reviews and meta-analyses focused on HPV-associated oropharyngeal squamous cell cancers published from January 2005 through May 2011.

Results. Molecular and epidemiologic evidence suggest a strong etiologic association of HPV with oropharyngeal cancers. The incidence of oropharyngeal cancers in the United States has increased between 1973 and 2007, whereas that of cancers at other head and neck sites has decreased steadily. Compared with HPV-negative cancers, HPV-positive oropharyngeal cancers are associated with certain sexual behaviors, occur more often among white men and people who do not use tobacco or alcohol, and may occur in a population younger by about four years (median ages, 52-56 years). Despite often having a later stage of diagnosis, people with HPV-positive oropharyngeal cancers have a lower risk of dying or recurrence than do those with HPV-negative cancers. The effectiveness of the HPV vaccine in preventing oropharyngeal cancers is unknown.

Clinical Implications. Dental health care personnel (DHCP) should be knowledgeable about the role of HPV in carcinogenesis, the association of HPV with oropharyngeal cancers and HPV vaccines, and they should be prompt in referring patients with suggestive symptoms for evaluation. DHCP can play an important role in increasing patients' knowledge about HPV and oropharyngeal cancers.

Key Words. Human papillomavirus; oropharyngeal cancer; dentistry; epidemiology; risk factors; vaccines.

JADA 2011;142(8):915-924.



with HPV-negative oropharyngeal cancers, HPV-positive oropharyngeal cancers are more likely to occur among people who practice certain sexual behaviors, white men, those without the traditional risk factors of tobacco or alcohol use and younger patients (median ages 58-60 years versus 52-56 years).¹¹⁻¹⁸ In oral cancer screening guidelines published in 2010, an expert panel of the American Dental Association (ADA) recognized HPV as a risk factor for oropharyngeal cancers but questioned whether HPV also may be responsible for some oral cavity cancers.¹⁹

Two HPV vaccines are licensed in the United States, one bivalent and one quadrivalent.^{20,21} Data for both vaccines have shown their efficacy in prevention of cervical cancer²²; data for the quadrivalent vaccine showed its efficacy in prevention of other HPV-associated genital cancers.²³ However, it may be decades before the effectiveness of these vaccines in preventing HPV-positive oropharyngeal cancers is known. In addition, there is little information about the effectiveness of traditional visual and tactile screening examinations in early detection of oropharyngeal cancers. Because of apparent increases in oropharyngeal cancer and, specifically, cancers of the base of the tongue and the tonsils; these cancers' association with HPV; the release of the ADA guidelines; and heightened public awareness about HPV vaccines, dental health care personnel (DHCP) should be knowledgeable about HPV and its role in the development of oropharyngeal cancers.

The purpose of this article is to summarize available evidence regarding the epidemiology of HPV-associated oropharyngeal cancers, differences in HPV prevalence between cancers of the oral cavity and oropharynx, the available HPV vaccines and the implications of these for dentistry.

METHODS

Literature review. We searched PubMed, Web of Science (now known as "Web of Knowledge"), The Cochrane Library and the National Guideline Clearinghouse to identify systematic reviews, meta-analyses, clinical trials, and molecular and epidemiologic studies focused on HPV-associated oropharyngeal squamous cell cancers published in the English language from January 2005 through May 2011. The MEDLINE Medical Subject Headings and general search terms we used included the following: "human papillomavirus," "head and neck neoplasm," "oral cancer," "mouth cancer," "pharyngeal cancer," "oropharyngeal cancer," "tonsil

cancer," "tongue cancer," "meta-analysis" and "review." We obtained pertinent articles and checked references for additional information when applicable.

Definitions and terminology. Head and neck squamous cell carcinoma (HNSCC) is a comprehensive term for squamous cell cancers of the nasal cavity, the paranasal sinuses, the oral cavity, the pharynx and the larynx (Table 1). The pharynx is further divided into the nasopharynx, the oropharynx and the hypopharynx. Although HPV has been detected in cancers throughout the head and neck, it appears to have a preference for tissues of the oropharynx (Figure 1), most notably the base of the tongue and the lingual and palatine tonsils. Cancers at these sites may be referred to as "HPV associated." (Note that surveillance data from population-based cancer registries typically do not include the HPV status of tumors. The term "HPV associated" refers to cancers that have been shown in the literature to be most strongly associated with HPV infection. Therefore, not all HPV-associated cases reflect actual HPV infections. In contrast, tumors identified as HPV positive or HPV negative actually have been tested for the presence of HPV DNA.) Sites generally not associated with HPV include cancers of the oral cavity, including those of the anterior two-thirds of the tongue, the gingiva, the floor of the mouth, the palate, and other or unspecified parts of the mouth and larynx.

HUMAN PAPILOMAVIRUSES

HPVs are DNA viruses that infect the stratified epithelium (basal cells) of the skin or mucous membranes. There are more than 100 types of HPVs, which are categorized according to the type of cells they infect and their ability to induce cellular changes.²⁴⁻²⁶ Widespread HPV types such as HPV-1 infect cutaneous epithelia and cause the common wart.²⁵ HPV types that infect mucosal epithelia are classified as low risk or high risk. Low-risk types of HPV cause benign oral hyperplasias that usually are painless and nonulcerated.²⁶ *Verruca vulgaris* (caused by HPV-2, HPV-4 and other HPV types) usually occur on the lips, hard palate and gingiva (Figure 2A, page 918). Condyloma acumi-

ABBREVIATION KEY. **ADA:** American Dental Association. **APC:** Annual percentage change. **DHCP:** Dental health care personnel. **FDA:** Food and Drug Administration. **HNSCC:** Head and neck squamous cell carcinoma. **HPV:** Human papillomavirus. **NPCR:** National Program of Cancer Registries. **SEER:** Surveillance, Epidemiology, and End Results.

nata, or genital warts (caused by HPV-6 and HPV-11), also may affect the oral mucosa and are found more commonly on keratinized mucosa. High-risk types HPV-16 and HPV-18 are associated with approximately 70 percent of cervical cancers, whereas HPV-16 alone is associated with about 85 to 95 percent of HPV-positive oropharyngeal cancers (Figure 2B).^{11,16,27-33} Among the sites of HPV-associated cancers occurring annually in the United States, the oropharynx is the second most common after the cervix (Figure 3).³⁴⁻³⁶

HPV appears to have a preference for the lymphoepithelial tissue of the Waldeyer ring, most notably the lingual and palatine tonsils.^{37,38} In these areas there are deep invaginations, the tonsillar crypts, in which immature basal cells may be more exposed to HPV.³⁸ Once inside the host cell, the virus typically integrates into the host cell genome to replicate. Malignant transformation occurs through the expression of two HPV viral oncogenes, E6 and E7.³⁹ These oncogenes encode for oncoproteins that bind to and inactivate host cell proteins that normally regulate cell division. This inactivation allows proliferation of malignant cells.⁴⁰ Detection of HPV DNA in oropharyngeal cancers, however, is not sufficient evidence to prove a causal relationship.^{1,24,35,39} Data demonstrating viral integration of HPV into the host DNA and expression of E6 and E7 oncogenes are evidence that HPV likely is a causal factor in a substantial proportion of oropharyngeal cancers.^{35,41,42}

Results from natural history studies of cervical HPV infection have shown that most cervical HPV infections are asymptomatic, are transient and clear within one to two years; if the infection with carcinogenic types is persistent, the risk of cervical cancer increases substantially.⁴³⁻⁴⁵ In contrast, natural history studies of oral HPV infection are limited, and circumstances in which oral HPV infection may lead to cancer are uncertain.^{46,47} Questions remain about the natural history of oral HPV infection.⁴⁸ What is the clearance rate of an oral HPV infection? How long is the latency between infection and carcinogenesis? Is per-

TABLE 1

Definitions of terms.	
TERM	DEFINITION
Site	
Head and Neck	Includes the nasal cavity, the paranasal sinuses, the oral cavity, the pharynx and the larynx
Oral Cavity	Includes the lips, the labial and buccal mucosa, the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingiva and the hard palate
Pharynx	Includes the hollow tube inside the neck that begins behind the nose and ends at the top of the trachea and esophagus; is about 5 inches long, depending on body size, and is divided into three sections: nasopharynx, oropharynx and hypopharynx
Oropharynx	Includes the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate and the posterior pharyngeal wall
Epidemiology	
Incidence	The number of new cases of disease occurring in a defined population during a specified interval, usually expressed as the number of cases per 100,000 people at risk per year
Prevalence	The total number of cases of a disease in a given population at a specific time
Other	
Natural History Study	A study that follows across time a group of people who have, or are at risk of developing, a specific medical condition or disease; collects health information to increase understanding of how the medical condition or disease develops and how to treat it
Screening	The process by which a practitioner evaluates a patient without symptoms to determine whether he or she is "likely" or "unlikely" to have a potentially malignant or malignant lesion
Annual Percentage Change (APC)	The average rate of change in a cancer rate per year in a given time frame (that is, how quickly or slowly a cancer rate has increased or decreased each year across a period of years); the number is given as a percentage (for example, "an approximate 1 percent per year decrease"); a negative APC describes a decreasing trend and a positive APC describes an increasing trend.

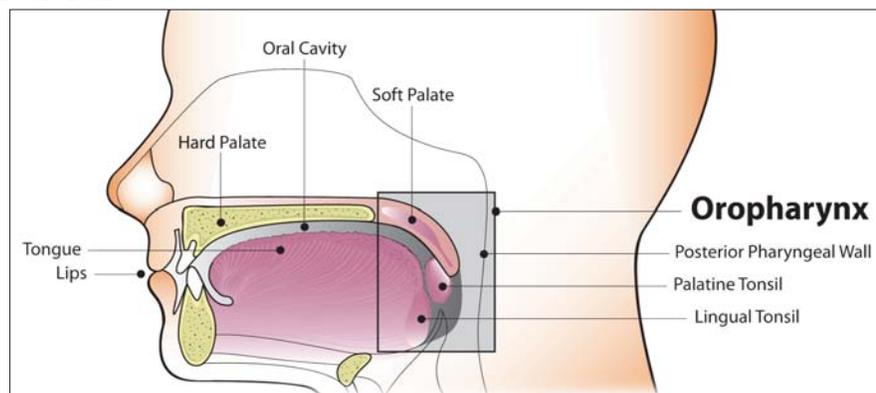


Figure 1. The oral cavity and oropharynx.

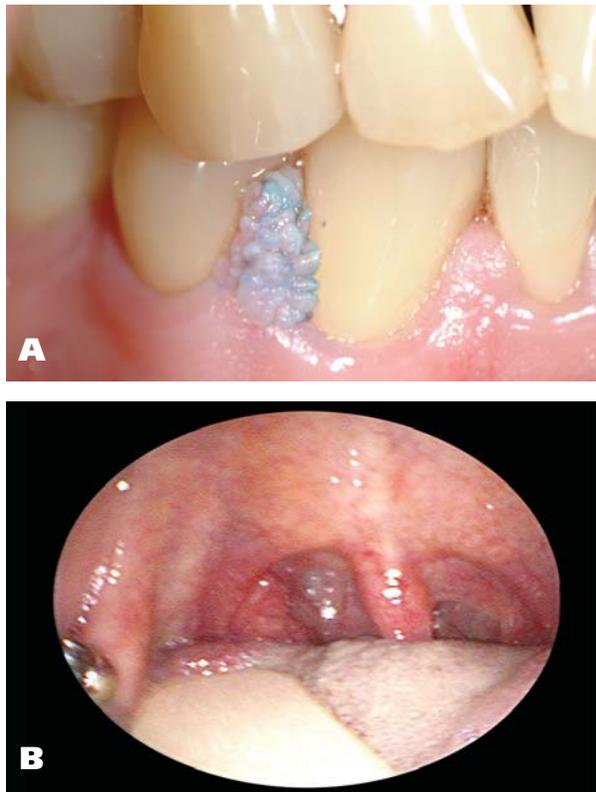


Figure 2. A. Pedunculated lesion clinically consistent with verruca vulgaris (wart). Image provided courtesy of Dr. Joel Epstein, College of Dentistry, University of Illinois at Chicago. **B.** Endoscopic view of human papilloma virus–positive squamous cell carcinoma of the palatine tonsil. Image provided courtesy of Dr. Susan Muller, Winship Cancer Institute, School of Medicine, Emory University, Atlanta.

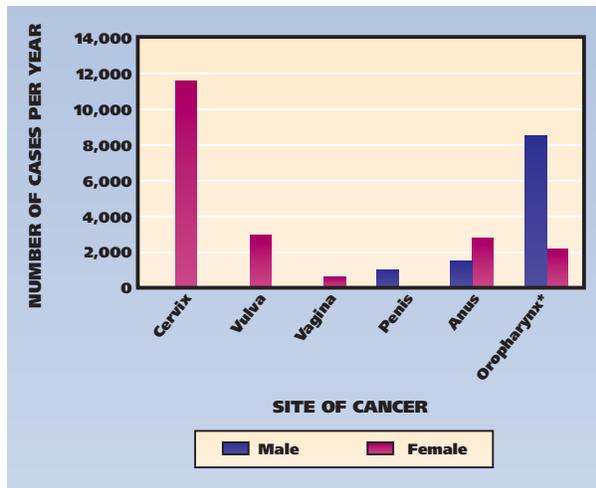


Figure 3. Yearly incidence counts of human papillomavirus–associated cancers in the United States, 2003-2007. *Cancers of the oropharynx include cancers of the tonsils, base of the tongue and other oropharynx. Sources: Centers for Disease Control and Prevention²⁶; National Program of Cancer Registries, unpublished data, 2009; Surveillance, Epidemiology, and End Results program, unpublished data, 2009.

sistence of HPV necessary for carcinogenesis to occur? What is a person's risk of developing cancer once infected? How much do other factors, such as tobacco use, contribute to the development of HPV-positive cancers? Well-designed, prospective studies of sufficient sample size will be required to provide answers to these questions.

EPIDEMIOLOGIC CHARACTERISTICS

Incidence of HPV-associated and HPV-positive oropharyngeal cancer. Incidence rates of base-of-tongue and tonsillar cancers have increased substantially in the United States during the past three decades, whereas cancers at other head and neck sites, including the oral cavity, have been decreasing steadily.¹⁻¹⁰ The decrease in oral cavity cancer rates has been attributed to a decrease in smoking, whereas the increase in oropharyngeal cancer rates has been attributed to a growing incidence of HPV-associated cancers.⁴

Incidence rates of the base-of-tongue and tonsillar cancers have varied considerably by age, sex, and race or ethnicity. For example, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of cancer registries for 1973 to 2001 indicate that age-adjusted incidence of cancer at the base of the tongue and in the palatine tonsils increased by almost 2 and 4 percent annually, respectively, among white adults aged 20 to 44 years, whereas incidence of cancers at other oral and pharyngeal sites remained constant or decreased.³ More comprehensive data from SEER and the Centers for Disease Control and Prevention's National Program of Cancer Registries from 1999 through 2007 indicate that incidence rates of HPV-associated oropharyngeal cancers increased significantly among white males (annual percentage change [APC] 3.6; $P < .05$) and decreased for black males (APC = -2.0)¹⁰ (Figure 4). Among females, rates remained stable across all races and ethnicities. Most recently, results from a study in which investigators examined the HPV status of 271 oropharyngeal cancer specimens from three SEER sites showed that the incidence of HPV-positive cancers increased by 225 percent during 1988 through 2004, whereas the incidence of HPV-negative cancers decreased by 50 percent during the same period.⁹ The authors speculated that should these trends continue, the annual number of HPV-positive oropharyngeal cancers among males in the United States would exceed that of cervical cancers among females by the year 2020.

HPV infection. HPV infection can be identified through several measures, including detection of HPV DNA in biopsy specimens, of HPV DNA in oral specimens and of serum antibodies to HPV proteins (HPV seroprevalence).

HPV DNA in biopsy specimens. The prevalence of HPV DNA in cancer specimens varies widely depending on factors such as tumor site (oral cavity or oropharynx) and geographic variability in risk factors.^{28,29,31,49} In a worldwide systematic review and meta-analysis published in 2005, investigators detected HPV-16 in 16.0 percent of oral cavity cancers (35 studies) and in 30.9 percent of oropharyngeal cancers (27 studies).²⁹ When they limited their review to studies conducted in North America, however, the investigators detected HPV-16 in 10.1 percent (95 percent confidence interval [CI], 7.7-12.8 percent) of oral cavity cancers (eight studies) and in 42.1 percent (95 percent CI, 36.3-48.1 percent) of oropharyngeal cancers (seven studies).²⁹ Investigators in more recent studies who used data from North America detected even lower percentages of HPV-16 in oral cavity cancers (0 to 2 percent)^{15,50,51} and higher percentages in oropharyngeal cancers (50 to 87 percent).^{8,11,15,17,50-52} International researchers also have detected

similar trends in the distributions of HPV in oral cavity and oropharyngeal cancers.^{5,7,32,53} Although several of the recent studies have small sample sizes, these findings suggest that HPV is more likely to be detected in oropharyngeal than in oral cavity cancers. These differences could reflect the use of more accurate HPV DNA assays or true changes in HPV prevalence.¹⁶

HPV DNA in oral specimens. Detection of HPV DNA in oral specimens indicates current oral HPV infection. Methods for collecting oral exfoliated cells, such as by means of direct swab sampling or of collection of saliva or oral rinse specimens, however, have not been standardized, nor can oral rinses be used to identify the origin of HPV infection.^{42,54} Other factors, such as the time between specimen collection and

eating, may affect detection of HPV DNA in exfoliated oral cells.^{42,47} Nonetheless, investigators have estimated that 2 percent of children and adolescents and 3 to 10 percent of adults have oral HPV infection.⁴⁵⁻⁵⁸ Authors of a recent meta-analysis of 18 studies reported pooled worldwide prevalence estimates for HPV-16 of 1.3 percent (95 percent CI, 1.0-1.7 percent); for all carcinogenic types of HPV, 3.5 percent (95 percent CI, 3.0-4.1 percent); and for any type of oral HPV infection, 4.5 percent (95 percent CI, 3.9-5.1 percent).⁵⁹ The authors concluded that a small but substantial proportion of healthy people had oral HPV infection of types known to cause cancer.

HPV seroprevalence. Serum antibodies have been used as a marker of cumulative exposure to HPV. Results from numerous seropreva-

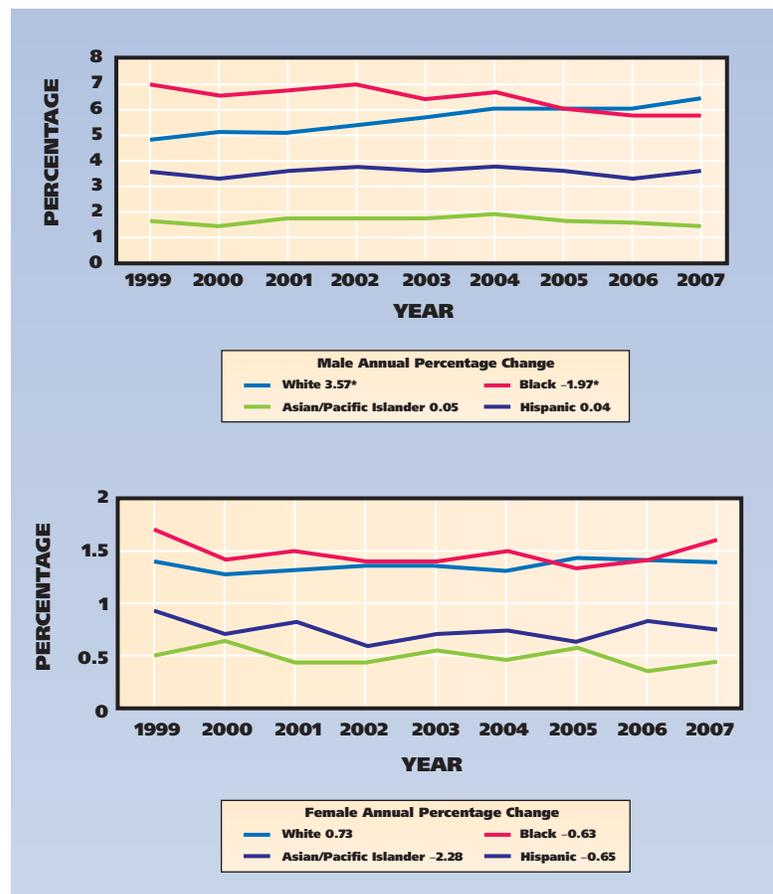


Figure 4. Annual percentage change (APC) in human papilloma virus-associated oropharyngeal cancer according to sex and race or ethnicity, 1999-2007. Hispanic ethnicity is not mutually exclusive from race categories. Rates were calculated per 100,000 people and adjusted by means of direct standardization to the 2000 U.S. population. * Indicates an APC significantly different from zero ($P < .05$). Sources: Centers for Disease Control and Prevention³⁶; National Program of Cancer Registries, unpublished data, 2009; Surveillance, Epidemiology, and End Results program, unpublished data, 2009.

lence studies showed strong associations between serum HPV antibodies and oropharyngeal cancer and weak associations with controls or cancers at other head and neck sites, such as the oral cavity and larynx.^{12,58,60-62} Results from a large study in Sweden demonstrated a 14-fold increase in the risk of developing oropharyngeal cancer among people who were HPV-16 seropositive.³⁰ To date, this, to our knowledge, is the only study providing evidence that HPV infection precedes development of oropharyngeal cancer. Although HPV seroprevalence provides evidence of HPV exposure, seroprevalence studies are limited because they cannot be used to specify the mucosal site of HPV infection.^{32,54} Seroprevalence may reflect cumulative exposure to the virus; however, not all people exposed to HPV develop antibodies, and HPV antibodies may decrease across time.^{32,41} Therefore, the usefulness of HPV antibodies in predicting the development of cancer has not been established.

HPV transmission. Mucosal HPV spreads through direct skin-to-skin contact, primarily by means of vaginal, anal and oral sex. Vertical transmission between mother and infant^{63,64} and autoinoculation are less common methods of transmission.⁶⁵ Although epidemiologic studies involving direct evaluation of oral transmission of HPV are not available, study findings have linked oral HPV infection with a history of open-mouthed kissing and oral sex.^{13,18,55,66,67} In addition, authors of two case reports identified concurrent development of HPV-positive tonsillar cancers in husband-wife pairs, which suggests the potential for oral HPV transmission within couples.^{48,68} Although case reports cannot control for other potential risk factors, such as tobacco and alcohol use, the findings of these case reports suggest that sexual contact may lead to HPV transmission.

HPV risk factors. Risk of developing HPV-positive oropharyngeal cancer increases with increasing number of self-reported lifetime sexual partners (oral and vaginal), younger age at first sexual activity, and history of having a same-sex partner; in addition, the level of risk can vary according to tumor site.^{11-15,69} Although HPV-positive oropharyngeal cancers occur among both users and nonusers of tobacco, study results have been mixed regarding whether oral HPV infection interacts with these exposures to further increase the risk of developing cancer.^{11,12,15,32,58,60,70,71} For example, researchers conducting a study in which they stratified risk factors according to HPV-16 tumor status found that HPV-16-positive tumors were associated strongly with specific

sexual behaviors and marijuana smoking—but not with tobacco smoking, alcohol use or poor oral hygiene.¹² HPV-16-negative tumors were associated with tobacco smoking, alcohol use and poor oral hygiene but not with sexual behaviors and marijuana smoking. In contrast, investigators in other studies found similar increased risks of developing cancer associated with tobacco and alcohol use among patients who were HPV positive and negative.^{70,72} Larger, population-based studies will be necessary to determine the potential role of tobacco use, alcohol use and HPV in oropharyngeal cancers.

Survival and prognosis. HPV-positive oropharyngeal cancers typically are detected at later stages (involvement of regional lymph nodes and distant metastasis) than are HPV-negative cancers.^{1,34,52} Despite later stages of diagnosis, patients with HPV-positive oropharyngeal cancers have consistently higher survival rates and better response to radiation therapy and chemotherapy and are less likely to experience progression and recurrence of tumors.^{1,16,17,73-75} The differences in outcomes likely result from a variety of factors, including possible greater sensitivity of HPV-positive tumors to treatment with radiation and chemotherapy compared with that of HPV-negative tumors^{1,73,75,76} or an enhanced immune response after radiotherapy.⁷⁷ Improved prognosis also may reflect the fact that these patients are younger, have fewer comorbidities and may lack a history of tobacco and alcohol use.⁷⁸

HPV tumor status can be an important predictor of prognosis in oropharyngeal cancer.⁷⁶ Clinical trials involving larger samples and stratified according to HPV tumor status and tumor location are required to facilitate comparison of the effects of treatment protocols in and survival of patients with HPV-positive and HPV-negative cancers, as well as to determine reasons for any differences that might exist between the groups.⁷⁹ Although it is anticipated that HPV tumor status may drive important treatment decisions and may allow for less aggressive treatment for HPV-positive tumors, no clinical trials have been conducted to date to confirm this hypothesis.¹⁷ Investigators are designing clinical trials to evaluate whether modifying cancer therapy according to HPV status and other risk factors can improve patient outcomes.¹⁵

HUMAN PAPILLOMAVIRUS VACCINES

The U.S. Food and Drug Administration (FDA) has licensed two vaccines for use against HPV.^{20,21}

Quadrivalent vaccine. In 2006, the FDA licensed a quadrivalent vaccine that protects against two low-risk HPV types (6 and 11) and two high-risk HPV types (16 and 18) (Gardasil, Merck, Whitehouse Station, N.J.). The vaccines were developed for women and girls and were aimed at preventing cervical cancer, precancerous lesions and genital warts associated with the HPV types targeted by the vaccines. A year later, the FDA added prevention of vaccine-type-related vaginal and vulvar cancer as an indication for this particular vaccine. In 2009, the FDA licensed the quadrivalent vaccine for use in men and boys for prevention of genital warts.²⁰ When further data became available regarding the quadrivalent vaccine's efficacy in prevention of anal precancerous lesions, in 2010 the FDA approved the vaccine for prevention of vaccine-type-related anal cancer and precancerous lesions in both sexes.⁸⁰

Bivalent vaccine. In 2009, the FDA licensed a bivalent vaccine that protects against high-risk HPV types 16 and 18 (Cervarix, Glaxo-SmithKline, Brentford, England) for use in women and girls for prevention of HPV-16- and HPV-18-related cervical cancer and precancerous lesions.²¹ HPV vaccines are not therapeutic but are aimed at preventing HPV infection; therefore, these vaccines are most effective when received before exposure to HPV—ideally, before initial sexual contact.^{22,23}

Effectiveness of HPV vaccines. The effectiveness of HPV vaccines in preventing oral HPV infection and cancer is unknown. Because HPV-16 and HPV-18 have been identified in approximately 90 to 95 percent of HPV-positive oropharyngeal cancers,^{17,29} either of the licensed HPV vaccines could have a great effect on disease burden. Because most cancers have long latent periods and HPV-positive oropharyngeal cancers are relatively uncommon, it likely will be decades before the effect of HPV vaccines can be evaluated.²

TABLE 2

Examples of patients' questions about human papillomavirus (HPV) and possible responses from dental health care personnel.

QUESTION FROM PATIENT	RESPONSE FROM DENTAL HEALTH CARE PERSONNEL
What head and neck cancers can be caused by HPV?	Cancers in the back of the throat, especially the base of the tongue and the tonsils, are the most common head and neck cancers that are caused by HPV. This area of the head and neck is known as the "oropharynx."
Should I be tested for oral HPV infection?	Right now, there is no test approved by the U.S. Food and Drug Administration for detection of oral HPV infection. Results of future studies will show whether HPV tests might be effective screening tests for oropharyngeal cancers.
How do you get oral HPV infection?	The same types of HPV that infect the genitals also can infect the mouth and throat. These types generally are referred to as "oral HPV." Oral HPV is thought to be transmitted by skin-to-skin contact during oral sex (oral-genital and oral-anal). It also may be passed on during open-mouthed or "French" kissing. Only a few researchers have evaluated how people contract oral HPV. More information is needed.
Can HPV vaccines prevent oropharyngeal cancers?	The HPV vaccines on the market were developed to prevent cervical cancer. However, the same types of HPV that cause most cervical cancers can cause oropharyngeal cancers. It is possible that these vaccines also help prevent some of these cancers. However, preventing HPV infection will not eliminate other risk factors linked to these cancers, such as tobacco and alcohol use.

CLINICAL IMPLICATIONS

Little information exists about the effectiveness of traditional visual and tactile screening examinations in identifying oropharyngeal cancers. Cancers of the oropharynx are less visible^{81,82} and more likely to be detected at later stages than are those of the oral cavity.^{1,34,52} In addition, oropharyngeal cancer can share symptoms—such as sore throat, hoarseness, earaches and enlarged lymph nodes—with benign conditions such as pharyngitis or tonsillitis.⁸³ DHCP should be alert to patients' oral or written indications of these and other symptoms, such as dysphagia, hemoptysis and unexplained weight loss, and be vigilant about performing thorough intraoral and extraoral head and neck examinations that include lymph node examination.⁸⁴ DHCP should promptly refer for medical follow-up any patient who has persistent signs and symptoms of disease in the oropharynx.⁸³

Although standardized screening tests for early detection of precancerous and uterine cervical cancer (Papanicolaou test [Pap smear]) and for detection of cervical HPV infection exist, HPV tests are not approved or recommended for use in detecting oral HPV infection. There is no evidence that detection of high-risk HPV can be used to predict the development of oropharyngeal cancer or disease in the oral cavity accurately. Considerably more information is needed

about the natural history of oral HPV infection to determine potential interventions that may reduce oropharyngeal cancer incidence. In addition to an adequate understanding of natural history, researchers must evaluate several other criteria to determine whether a screening test is appropriate for general use, including whether it leads to reductions in mortality, whether it is accurate and whether it results in more harm than good.⁸⁵

About 75 percent of HNSCCs are related to tobacco and alcohol use. Although it is unclear whether these factors increase the risk of developing HPV-associated oropharyngeal cancers, smokers with HPV-positive cancers have a poorer prognosis and may be at increased risk of experiencing disease recurrence compared with HPV-positive patients with cancer who never smoked.⁸⁶ DHCP should ask patients about their tobacco and alcohol use and educate users about their potential risks of developing HNSCCs. Dentists should encourage tobacco-use cessation and provide appropriate counseling.⁸⁷ Alternatively, DHCP could provide brief counseling messages (such as informing the patient about adverse health effects of tobacco use and advising the patient to quit) and could promote use of the National Network of Tobacco Cessation Quitlines portal (1-800-QUIT-NOW); both have been effective in tobacco-use cessation.^{87,88} DHCP also should be aware that oropharyngeal cancers, particularly those of the tonsils and the base of the tongue, can affect a younger population regardless of the traditional risk factors of tobacco and alcohol use.¹¹⁻¹⁸

CONCLUSIONS

Molecular and epidemiologic evidence suggest a strong etiologic association of HPV with a large proportion of oropharyngeal cancers but seldom with cancers of the oral cavity in the United States. Preventing even a proportion of oropharyngeal cancers is important because of the increase in their incidence rates during the past three decades. Study results suggest that patients with HPV-positive oropharyngeal cancers are younger, more likely male and white, more likely to have a higher number of lifetime sexual and oral sexual partners, less likely to use tobacco and alcohol, and more likely to have better survival rates than are patients with HPV-negative oropharyngeal cancers. Although research regarding HPV and oropharyngeal cancer is growing rapidly, there are gaps in our knowledge about the natural history of oral HPV infection, appropriate management and treatment of these cancers and the effectiveness

of the HPV vaccine in preventing oral HPV infection. Further research is needed to improve our knowledge about the role of HPV in oropharyngeal cancer.

Understanding and communicating information about HPV and oropharyngeal cancer may be a challenge for DHCP and patients. As awareness about HPV-associated oropharyngeal cancer increases, patients are likely to approach dental care providers with a variety of concerns (Table 2). DHCP should be aware of HPV as an identified risk factor for oropharyngeal cancer that may affect people regardless of traditional risk factors such as tobacco use and alcohol use. As scientific evidence evolves and new technologies are developed, DHCP should prepare to assume an important role in communicating information about HPV to dental patients. ■

Disclosure. None of the authors reported any disclosures.

The authors thank Dr. Scott Tomar, College of Dentistry, University of Florida, Gainesville; Ms. Laurie Barker, Division of Oral Health, Centers for Disease Control and Prevention (CDC), Atlanta; Ms. Meg Watson, Division of Cancer Prevention and Control, CDC, Atlanta; Ms. Allison Friedman, Division of Sexually Transmitted Disease Prevention, CDC, Atlanta; Dr. Sara Gordon, College of Dentistry, University of Illinois at Chicago; and Dr. David Bordeaux, private practitioner, Atlanta for their comments and review of this article. In addition, they thank Dr. Susan Muller for providing the photograph in Figure 2B.

1. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008; 26(4):612-619.
2. Ryerson AB, Peters ES, Coughlin SS, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998-2003. *Cancer* 2008;113(10 suppl):2901-2909.
3. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years. *Cancer* 2005;103(9):1843-1849.
4. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer* 2007;110(7):1429-1435.
5. Näsman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? *Int J Cancer* 2009;125(2):362-366.
6. Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2006. Bethesda, Md.: National Cancer Institute; 2009. "http://seer.cancer.gov/csr/1975_2006/". Accessed May 21, 2011.
7. Attner P, Du J, Näsman A, et al. The role of human papillomavirus in the increased incidence of base of tongue cancer. *Int J Cancer* 2010;126(12):2879-2884.
8. Ernster JA, Sciotto CG, O'Brien MM, et al. Rising incidence of oropharyngeal cancer and the role of oncogenic human papillomavirus. *Laryngoscope* 2007;117(12):2115-2128.
9. Chaturvedi A, Engels E, Pfeiffer R, et al. Human papillomavirus (HPV) and rising oropharyngeal cancer incidence and survival in the United States. In: Program and Abstracts of the 2011 American Society of Clinical Oncology Annual Meeting; June 3-7, 2011; Chicago. Abstract 5529.
10. Cleveland J, Watson M, Wilson R, Saraiya M. Incidence of potentially human papillomavirus-associated cancers of the oropharynx in the U.S., 2004-2007. In: Program and Abstracts of the 2011 North American Central Cancer Registries Annual Meeting; June 21-24, 2011; Louisville, Ky. Abstract P-045.
11. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*

2007;356(19):1944-1956.

12. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst* 2008;100(6):407-420.

13. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol* 2010;39(1):166-181.

14. Smith EM, Ritchie JM, Summersgill KF, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer* 2004;108(5):766-772.

15. D'Souza G, Zhang HH, D'Souza WD, Meyer RR, Gillison ML. Moderate predictive value of demographic and behavioral characteristics for a diagnosis of HPV16-positive and HPV16-negative head and neck cancer. *Oral Oncol* 2010;46(2):100-104.

16. Dayyani F, Etzel CJ, Liu M, Ho CH, Lippman SM, Tsao AS. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). *Head Neck Oncol* 2010;2:15.

17. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100(4):261-269.

18. Kreimer AR, Alberg AJ, Daniel R, et al. Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus. *J Infect Dis* 2004;189(4):686-698.

19. Rethman MP, Carpenter W, Cohen EE, et al; American Dental Association Council on Scientific Affairs Expert Panel on Screening for Oral Squamous Cell Carcinomas. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *JADA* 2010;141(5):509-520.

20. Centers for Disease Control and Prevention. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59(20):630-632.

21. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59(20):626-629.

22. Paavonen J, Naud P, Salmerón J, et al; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374(9686):301-314.

23. Garland SM, Hernandez-Avila M, Wheeler CM, et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356(19):1928-1943.

24. Ragin CC, Modugno F, Gollin SM. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. *J Dent Res* 2007;86(2):104-114.

25. Vidal L, Gillison ML. Human papillomavirus in HNSCC: recognition of a distinct disease type. *Hematol Oncol Clin North Am* 2008;22(6):1125-1142.

26. Gordon SC, Ganatra S, Foong CF, Sroussi HY. Viral infections of the mouth. *Medscape Reference*. "http://emedicine.medscape.com/article/1079920-overview#showall". Accessed June 22, 2011.

27. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92(9):709-720.

28. Hobbs CG, Sterne JA, Bailey M, Heyderman RS, Birchall MA, Thomas SJ. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. *Clin Otolaryngol* 2006;31(4):259-266.

29. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;14(2):467-475.

30. Mork J, Lie AK, Glatte E, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2001;344(15):1125-1131.

31. Termine N, Panzarella V, Falaschini S, et al. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). *Ann Oncol* 2008;19(10):1681-1690.

32. Herrero R, Castellsagué X, Pawlita M, et al; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 2003;95(23):1772-1783.

33. de Sanjose S, Quint WG, Alemany L, et al; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;11(11):1048-1056.

34. Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. *Cancer* 2008;113(10 suppl):2841-2854.

35. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 2008;113(10 suppl):3036-3046.

36. Centers for Disease Control and Prevention. Human papillomavirus (HPV)-associated cancers: number of HPV-associated cancer cases per year. "www.cdc.gov/CANCER/hpv/statistics/cases.htm". Accessed June 22, 2011.

37. Paz IB, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP. Human papillomavirus (HPV) in head and neck cancer: an association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer* 1997;79(3):595-604.

38. Pai SI, Westra WH. Molecular pathology of head and neck cancer: implications for diagnosis, prognosis, and treatment. *Annu Rev Pathol* 2009;4:49-70.

39. Psyrri A, DiMaio D. Human papillomavirus in cervical and head-and-neck cancer. *Nat Clin Pract Oncol* 2008;5(1):24-31.

40. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Res* 2002;89(2):213-228.

41. World Health Organization, International Agency for Research on Cancer. Human Papillomaviruses. Lyon, France: World Health Organization; 2007. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 90.

42. D'Souza G. Epidemiology of oral HPV infection. In: Adelstein DJ, Ridge JA, Gillison ML, et al. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9-10, 2008, Washington, D.C. *Head Neck* 2009;31(11):1393-1422.

43. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338(7):423-428.

44. Jenson AB, Kurman RJ, Lancaster WD. Tissue effects of and host response to human papillomavirus infection. *Dermatol Clin* 1991;9(2):203-209.

45. Rodríguez AC, Schiffman M, Herrero R, et al; Proyecto Epidemiológico Guanacaste Group. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst* 2008;100(7):513-517.

46. Psyrri A, Gouveris P, Vermorcken JB. Human papillomavirus-related head and neck tumors: clinical and research implication. *Curr Opin Oncol* 2009;21(3):201-205.

47. Syrjänen S. Human papillomaviruses in head and neck carcinomas (published correction appears in *N Engl J Med* 2007;357[3]:313). *N Engl J Med* 2007;356(19):1993-1995.

48. Haddad R, Crum C, Chen Z, et al. HPV16 transmission between a couple with HPV-related head and neck cancer. *Oral Oncol* 2008;44(8):812-815.

49. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;118(12):3030-3044.

50. Machado J, Reis PP, Zhang T, et al. Low prevalence of human papillomavirus in oral cavity carcinomas. *Head Neck Oncol* 2010;2:6.

51. Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer* 2010;116(9):2166-2173.

52. Saraiya M, Unger ER, Cleveland JL, et al; HPV Typing of Cancers Workgroup. HPV prevalence in oropharyngeal (OP) cancers: seven cancer registries. In: Program and abstracts of the 2011 American Association of Dental Research, March 17, 2011; San Diego. Abstract 1493.

53. Scapoli L, Palmieri A, Rubini C, et al. Low prevalence of human papillomavirus in squamous-cell carcinoma limited to oral cavity proper. *Mod Pathol* 2009;22(3):366-372.

54. Gravitt PE. Laboratory diagnosis of human papillomavirus-associated head and neck squamous cell carcinomas, 1: overview of methods for HPV detection. In: Adelstein DJ, Ridge JA, Gillison ML,

- et al, eds. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9-10, 2008, Washington, D.C.; 2009: 1401-1404.
55. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis* 2009;199(9):1263-1269.
56. Smith EM, Swarnavel S, Ritchie JM, Wang D, Haugen TH, Turek LP. Prevalence of human papillomavirus in the oral cavity/oropharynx in a large population of children and adolescents. *Pediatr Infect Dis J* 2007;26(9):836-840.
57. Hansson BG, Rosenquist K, Antonsson A, et al. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005;125(12):1337-1344.
58. Schwartz SM, Daling JR, Doody DR, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 1998;90(21):1626-1636.
59. Kreimer AR, Bhatia RK, Messegue AL, González P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. *Sex Transm Dis* 2010;37(6):386-391.
60. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst* 2007;99(23):1801-1810.
61. Pintos J, Black MJ, Sadeghi N, et al. Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada. *Oral Oncol* 2008;44(3):242-250.
62. Smith EM, Ritchie JM, Pawlita M, et al. Human papillomavirus seropositivity and risks of head and neck cancer. *Int J Cancer* 2007;120(4):825-832.
63. Rintala MA, Grénman SE, Puranen MH, et al. Transmission of high-risk human papillomavirus (HPV) between parents and infant: a prospective study of HPV in families in Finland. *J Clin Microbiol* 2005;43(1):376-381.
64. Smith EM, Parker MA, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Evidence for vertical transmission of HPV from mothers to infants. *Infect Dis Obstet Gynecol* 2010;2010:326-369.
65. Hernandez BY, Wilkens LR, Zhu X, et al. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis* 2008;14(6):888-894.
66. Kreimer AR. Oral sexual behaviors and the prevalence of oral human papillomavirus infection. *J Infect Dis* 2009;199(9):1253-1254.
67. Rintala M, Grénman S, Puranen M, Syrjänen S. Natural history of oral papillomavirus infections in spouses: a prospective Finnish HPV Family Study. *J Clin Virol* 2006;35(1):89-94.
68. Andrews E, Shores C, Hayes DN, et al. Concurrent human papillomavirus-associated tonsillar carcinoma in 2 couples. *J Infect Dis* 2009;200(6):882-887.
69. Dahlstrom KR, Li G, Tortolero-Luna G, Wei Q, Sturgis EM. Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites. *Head Neck* 2011;33(6):847-855.
70. Smith EM, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Tobacco and alcohol use increases the risk of both HPV-associated and HPV-independent head and neck cancers. *Cancer Causes Control* 2010;21(9):1369-1378.
71. Ribeiro KB, Levi JE, Pawlita M, et al. Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. *Int J Epidemiol* 2011;40(2):489-502.
72. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. *Head Neck* 2008;30(1):75-84.
73. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J Cancer* 2007;121(8):1813-1820.
74. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev Res (Phila)* 2009;2(9):776-781.
75. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;336(1):24-35.
76. Gillison ML. HPV and prognosis for patients with oropharynx cancer. *Eur J Cancer* 2009;45(suppl 1):383-385.
77. Vu HL, Sikora AG, Fu S, Kao J. HPV-induced oropharyngeal cancer, immune response and response to therapy. *Cancer Lett* 2010;288(2):149-155.
78. Bleyer A. Cancer of the oral cavity and pharynx in young females: increasing incidence, role of human papilloma virus, and lack of survival improvement. *Semin Oncol* 2009;36(5):451-459.
79. Rischin D. Oropharyngeal cancer, human papilloma virus, and clinical trials. *J Clin Oncol* 2010;28(1):1-3.
80. U.S. Food and Drug Administration. FDA: Gardasil approved to prevent anal cancer. "www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237941.htm". Accessed May 22, 2011.
81. Gorsky M, Epstein JB, Oakley C, Le ND, Hay J, Stevenson-Moore P. Carcinoma of the tongue: a case series analysis of clinical presentation, risk factors, staging, and outcome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98(5):546-552.
82. Mashberg A, Merletti F, Boffetta P, et al. Appearance, site of occurrence, and physical and clinical characteristics of oral carcinoma in Torino, Italy. *Cancer* 1989;63(12):2522-2527.
83. Pitchers M, Martin C. Delay in referral of oropharyngeal squamous cell carcinoma to secondary care correlates with a more advanced stage at presentation, and is associated with poorer survival. *Br J Cancer* 2006;94(7):955-958.
84. Epstein JB, Sciubba JJ, Banasek TE, Hay LJ. Failure to diagnose and delayed diagnosis of cancer: medicolegal issues. *JADA* 2009;140(12):1494-1503.
85. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. *Semin Oncol* 2010;37(3):202-215.
86. Maxwell JH, Kumar B, Feng FY, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. *Clin Cancer Res* 2010;16(4):1226-1235.
87. Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update—Clinical Practice Guideline. Rockville, Md.: U.S. Department of Health and Human Services, Public Health Service; 2008.
88. Carr AB, Ebbert JO. Interventions for tobacco cessation in the dental setting: a systematic review. *Community Dent Health* 2007;24(2):70-74.