A Patient-Centered Approach to Counseling Patients With Head and Neck Cancer Undergoing Human Papillomavirus Testing: A Clinician's Guide

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ABSTRACT

The International Agency for Research on Cancer and the National Cancer Institute have acknowledged human papillomavirus (HPV)-16 as an independent risk factor for oropharyngeal cancer (OPC). HPV-positive oropharyngeal cancer (HPVOPC) is a sexually transmitted entity that is on the rise; within the next 10 years, the annual number of HPV-associated OPC cases is projected to exceed the annual number of cervical cancer cases in the United States. Recognition of HPV status in OPC has broad implications beyond the traditional oncological concerns of timely diagnosis, accurate staging, and appropriate treatment of cancer patients. The National Comprehensive Cancer Network recommends testing the tumor site for HPV-status during OPC management; it is likely this will become a standard component of care for patients with high-probability tumors of the oropharynx.

As the practice of HPV testing becomes more common, it behooves providers to be able to adequately address the concerns of patients with HPVOPC. Although there are currently few relevant studies focusing on this population, existing literature on HPV-infected women and patients with cervical cancer strongly supports the concept that patients with HPVOPC need education to optimally address concerns such as self-blame, guilt, intimacy, and interpersonal relationships. When HPV testing is done, it should be accompanied by evidence-driven and patient-centered counseling to best minimize negative psychosocial outcomes and ensure optimum health promotion. Based on the current state of the literature, this article is intended to be a reference for physicians to effectively manage psychosocial outcomes when diagnosing patients with HPV-associated OPC. *The Oncologist* 2013;18:180–189

Implications for Practice: HPV testing for individuals with high-probability tumors of the tonsil and base of tongue is an emerging standard of care. This article provides physicians with guidelines on how to provide optimal patient-centered counseling for individuals receiving the concurrent diagnoses of a sexually transmitted cancer, with the understanding that with HPV testing brings the responsibility for physicians to provide education, address patient concerns in an evidence-driven manner, screen for emotional distress, and make referrals to psychosocial care when needed.

INTRODUCTION

Before the era of human papillomavirus (HPV), the typical patient with head and neck cancer was 50–60 years of age; presented with a long-standing history of tobacco use, alcohol consumption, or betel nut chewing; and was likely to be diagnosed with cancer of the oral cavity, larynx, or hypopharynx. However, beginning in the late 1980s, this “typical” patient started to become less common because of a steady decline in smoking rates in the United States [1,2]. In contrast to this trend, however, clinicians observed increasing numbers of patients with cancer of the tonsil and tongue base (i.e., oropharyngeal cancer [OPC]). These patients presented at much younger ages with a distinct profile of risk factors: nonsmokers and infrequent smokers with a high number of lifetime sexual

partners and extensive history of unprotected sex [3–5]. Based on epidemiological and molecular data, both the International Agency for Research on Cancer and the National Cancer Institute acknowledged the rise of a new and etiologically distinct form of head and neck cancer by recognizing HPV-16 as an independent risk factor for OPC [4, 6–8].

Recognition of HPV-positive OPC (HPVOPC) as a sexually transmitted disease has broad implications that extend beyond the traditional oncological concerns of timely diagnosis, accurate staging, and appropriate treatment of patients with cancer. In the absence of specific data regarding patients with HPVOPC, it is reasonable to apply existing information about the psychosocial impact of HPV infection on patients with cer-

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vical cancer to patients with HPVOPC. This diagnosis may bring a unique set of anxieties and stresses on patients and their interpersonal relationships. Therefore, health care providers should be prepared to address issues related to both the clinical and personal consequences of HPV infection in patients with OPC. Using the success of diagnostic counseling in human immunodeficiency virus (HIV) and BRCA genetic testing as models, we provide a rationale for consistent and effective patient counseling to allow diagnosing physicians to effectively manage psychosocial outcomes for patients with HPV-associated OPC.

Epidemiological and Molecular Evidence of the Causative Role of HPV in OPC

The changing demographics of head and neck cancer are attributed to HPV, the most commonly diagnosed sexually transmitted infection. It is well established that HPV is required for the development of cervical cancer. The currently approved vaccine targets both low-risk HPV types 6 and 11 and high-risk types 16 and 18 [9]. The role of HPV in the development of head and neck cancers—the sixth most common type of cancer in the world [10]—is now the focus of a rapidly growing body of literature. Approximately 25%–35% of all head and neck squamous cell carcinomas (HNSCCs) are associated with HPV genomic DNA, with the majority of these cancers occurring in the oropharynx [11]. Indeed, oral infection with high-risk type HPV increases the odds ratio for developing OPC [12]; individuals who are seropositive for HPV-16 have a 14-fold increased risk of developing OPC at a later time [7], thus strongly supporting the requirement for HPV exposure preceding disease development.

A recent review of the literature reported that HPV-16 accounts for more than 90%–95% of all HPV-associated oropharyngeal squamous cell carcinomas [13, 14]. It is unclear what makes HPV-16 so carcinogenic or the location of the oropharynx more susceptible to HPV transformation. It has been theorized that genetic features of HPV-16 facilitate survival in oral keratinocytes and that the deep invaginations of the mucosal surface of the tonsil may favor the capture and maintenance of virus, thus enhancing access of the virus to basal cells (the only dividing cells in the epithelium).

Pathogenesis

The viral proteins E6 and E7 are responsible for HPV-induced malignant transformation; they act by degrading and destabilizing the p53 and retinoblastoma (pRb) tumor suppressor proteins, respectively [15, 16]. Inactivation of these vital checkpoints allows HPV-transformed epithelium to acquire the classical hallmarks of cancer cells: unchecked cell proliferation, resistance to apoptosis, and immortalization [17]. Interestingly, there are differences in gene integrity and expression between HPV-positive and negative HNSCCs. In the typical HPV-negative squamous cell carcinoma, epigenetic or genetic alterations lead to mutations in p53, along with mutated and decreased p16 and increased levels of pRB. This contrasts with HPV-positive tumors in which the p53 is wild-type, p16 is upregulated, and pRb is downregulated [18]. These differing molecular profiles further support the etiologically distinct nature of HPV-positive and HPV-negative cancers.

UNIQUE RISK FACTORS FOR HPVOPC

The sexual revolution—the social movement that challenged traditional norms of sexual behavior and interpersonal relationships—began in the 1960s and continued well into the 1980s [19]. Over the past few decades, age at first intercourse has been decreasing with a simultaneous increase in lifetime number of sexual partners [20]. A recent large U.S. study of nearly 6,000 men and women assessed lifetime prevalence of sexual behaviors; positive responses for “ever having performed oral sex” for men ages 30–49 years, 50–69 years, and 70 years or older were 86%, 74%, and 62%, respectively, with a similar trend found among women [21]. During the same period, the proportion of HPV DNA-positive tonsil tumors increased from 28% in the 1970s to 68% in the 2000s [22]; thus, it is reasonable to expect that the more than doubling of HPV-positive head and neck cancer rates between 1970 and 2007 [23] is a consequence of changing trends in sexual activity and oral sex practices. The normalization of frequent intercourse with multiple partners and accompanying sexual risks may have been the driving force behind the increase in HPV exposure and infection rates, leading to the replacement of traditional risk factors such as tobacco use and alcohol consumption with practices such as oral sex, greater number of oral and vaginal sex partners, and a younger age at first intercourse [3, 24]. Other modes of transmission have been proposed, including kissing, other mouth-to-mouth contact, autoinfection, and perinatal contact [25].

Given our current understanding of risk factors for HPVOPC, the profile of a typical HPV-positive patient with OPC is a married man who has in the past participated in casual sex, has had inconsistent use of barrier protection during vaginal or oral sex, and who has a history of a non-HPV sexually transmitted infection [3, 26–28]. A diagnosis of cancer caused by a sexually transmitted infection may impact the patient in ways many providers have not previously considered—for example, feelings of anxiety and self-blame may be augmented in the context of a relationship or marriage, in which the patient is perceived by his or her partner as being at fault for the disease and for potentially placing the partner’s health in harm. For some patients with HPVOPC, these concerns may arise even if not brought up by the partner/spouse. HPVOPC also has a relatively favorable prognosis when compared to classic head and neck cancer. It is increasingly clear that the epidemic of HPV-associated OPC occurs in a population with unique demographics, behavioral characteristics, and prognosis. Each of these factors has the potential to affect a patient’s well-being, relationships between patients and partners, and (in the context of well-designed clinical trials) the approach to treatment.

Therefore, we propose that when HPV testing is performed for patients with high-probability tumors of the tonsil and base of tongue, it is accompanied by evidence-driven and patient-centered pretest and posttest counseling so as to minimize negative psychosocial outcomes and ensure optimum health promotion. Although few relevant studies on the HPVOPC population currently exist, it is well established that emotional distress in patients with head and neck squamous cell carcinoma is common [29, 30]. When a sample of newly diagnosed patients was screened for emotional distress, a sig-

Table 1. Potential domains that may benefit from diagnostic counseling in patients with HPV-positive oropharyngeal cancer

Self	Interpersonal	Educational
Guilt, depression, lowered self-esteem	Fears of rejection or infidelity	Confusion
Changes in body image	Concerns for disease transmission	Misconceptions
Fears of cancer	Loss of interest in sex or diminished intimacy	Stigma
Feelings of powerlessness	Concerns over decreased reproductive capacity	Reliance on internet for information

Abbreviation: HPV, human papillomavirus.

nificant proportion reported high anxiety levels. Despite this, no referrals to psychosocial care were made; at the time of follow-up, high levels of distress doubled [31]. This further highlights the need for patient-centered counseling at the time of diagnosis.

Given that no such studies have been conducted for HPVOPC, we turn to existing literature focusing on HPV-infected women and patients with cervical cancer. This is appropriate given that emotional distress in patients with head and neck cancer exists regardless of age or sex [31]. Strong evidence supports the need for counseling at the time of diagnosis for the HPV-positive patient with OPC. Such counseling serves as both an opportunity for the physician to determine who would benefit from psychosocial care while addressing patient concerns over sexual activity, intimacy, interpersonal relationships, partner status, and potential reproductive impairment.

IMPACT OF HPV-POSITIVE STATUS ON PATIENTS WITH OPC AND THE NEED FOR COUNSELING

The psychosocial burden of an HPV diagnosis has been well documented among women. In fact, the HPV Impact Profile (HIP) is a questionnaire with demonstrated reliability and validity that assesses the psychosocial impact of HPV-related health conditions in women. It provides a total burden score over several scales related to emotional impact, sexual impact, self-image, partner issues and transmission, interactions with doctors, and impact on daily living [32]. Although possible modifications can and should be made to evaluate psychosocial burden in patients with head and neck cancer, to date, there has been no study measuring the impact of HPV-positive status of patients with OPC. However, HPV infection and the ensuing risk of neoplasia is the common link between women with atypical squamous cells of undetermined significance, patients with cervical cancer, and individuals with HPV-induced OPC; furthermore, patients within these populations all share the same risk factors of high number of sexual partners and casual or unprotected sex [33]. Therefore, until data acquired from the OPC community are available, it is necessary to extrapolate from the wealth of available data on women with HPV-induced cellular lesions (Table 1).

Significant emotional distress is a prominent feature among women recently diagnosed with HPV. They report negative feelings such as guilt, depression, confusion, and lowered self-esteem [34, 35] and grapple with relationship and intimacy issues; fear of rejection and decreased interest in sex may arise over disease transmission concerns [36]. In a prospective study, women with precancerous cervical dysplasia underwent reflex HPV testing; compared to the HPV-negative group, women with HPV experienced a significantly higher

state of initial distress and psychosocial burden, as measured by HIP [37]. Another study found pregnancy complications and impaired reproductive capacity among the chief concerns. In-depth interviews performed by Daley et al. highlighted powerful emotional themes that these women grapple with—fear, stigma, self-blame, powerlessness, stress, confusion, and isolation [38].

In June 2006, the Food and Drug administration approved the use of the HPV vaccine. Despite the vaccine's ample media coverage and the subsequent "normalization" of HPV infection, it is clear that considerable gaps in knowledge still exist among individuals for whom the vaccine is recommended. One recent study looking at men and women between the ages of 18 and 25 years found that 95% of the women and 80% of the men knew that there was a vaccine against cervical cancer, but only 50% of the women and 25% of men had heard of HPV [39]. Similarly, female college students reported very high levels of awareness of HPV (96%), although significant misconceptions existed: more than a third reported that men cannot contract HPV and over 40% believed that HPV and HIV have similar effects in the human body [40]. Even beyond the college campus, these trends have been observed; a 2007 statewide survey of nearly 17,000 women in California found that less than half of respondents could correctly answer three or more HPV knowledge questions [41]. Studies of men are scarce; however, existing studies showed striking gender differences. Men displayed significantly poorer knowledge about HPV than women, especially concerning the long-term consequences and modes of HPV transmission [39]; they may even interpret their partner's HPV diagnosis as an indication of infidelity [42].

Clearly, despite widespread interest in and media coverage of HPV and HPV-related cancer, considerable confusion, ignorance, and misinformation still exists. Confusion tends to lead to poorer understanding of one's prognosis; women who felt confused over their HPV diagnosis were less likely to understand the different consequences of high-risk and low-risk HPV types; furthermore, those who reported confusion were often less compliant with follow-up treatment and were less likely to disclose their HPV status to partners [38]. These findings likely occur within the context of sexually transmitted infection (STI)-related stigma, which has been shown to impede information seeking and treatment-related behaviors [43, 44] and therefore may produce detrimental health outcomes.

An HPV diagnosis may provoke a range of psychological reactions in patients, in addition to concerns about partner rejection and future transmission of the virus. This places HPV-positive patients with OPC in a uniquely vulnerable position in

which they must adjust to a cancer diagnosis while struggling with the stigma that their cancer is caused by an STI. These observations urgently warrant a counseling paradigm in which health care providers play a critical role in providing accurate information and moderating the psychosocial impact of the concurrent diagnoses in HPV-positive patients with OPC.

COUNSELING: GENERAL CONSIDERATIONS

Currently, OPC management does not require HPV status testing at the tumor site. Counseling is only suggested by guidelines from the National Comprehensive Cancer Network. Although our goal here is not to provide a rationale for mandatory HPV testing, it is likely to become increasingly widespread and play an essential role in management of OPC. Therefore, we propose a counseling paradigm that physicians can refer to and implement as HPV testing becomes more routine. We acknowledge that the ideal approach to determining the educational and counseling needs of patients with HPVOPC would be based on data gathered directly from these patients (e.g., from surveys and focus groups administered to the HPVOPC population). However, in the absence of such studies, we have adapted a counseling paradigm from the informational needs of patients with cervical cancer, which we consider to be appropriate for patients with HPVOPC. There is a great wealth of empirical evidence about topics of information desired by the general public and more specifically from the cervical cancer population, as well as the mode of delivery of such information based on surveys of patient satisfaction and dissatisfaction at the time of their diagnosis [35, 45, 46]. Anxiety and distress about being HPV positive can diminish when a patient's information needs are met [45]; when probed about ways to improve satisfaction surrounding their diagnosing experience, patients expressed the desire for openness to discussion of relevant psychosocial issues, improved communication regarding sexual health, referral to other sources of information, and provision of written information about HPV [35].

Based on this evidence, we suggest counseling strategies for physicians to implement when testing patients with OPC for HPV status. Ideally, this process will be modeled after established guidelines for test-related counseling in genetic testing and HIV testing—both of which share strong similarities with HPV testing—as well as key differences. Like genetic testing in breast cancer and other cancers, testing for HPV has the potential to identify a disease etiology with distinct implications for prognosis and treatment; similarly, the results of HPV testing have similar potential implications for cancer risk in others—although in the case of HPV testing the affected others are current or former sexual partners rather than blood relatives. As in genetic counseling, the medical implications of a positive or a negative test result are not always clear. A test for the autosomal dominant mutation that causes Huntington disease exists despite the fact that there is no definitive treatment; similarly, an HPV-positive test today provides prognostic information without altering disease management. However, this is likely to change as the results of HPVOPC-specific clinical trial information become available.

HIV testing is preceded and followed by in-depth counseling of the test and the implications of either result [47]. Like HIV testing, testing for HPV involves a sexually transmitted vi-

rus with potential for shame and stigmatization, as well as practical concerns about its current and future health implications and potential transmissibility. Pretest and posttest counseling is an essential component of both genetic and HIV testing, and both of these existing paradigms provide good

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models that can inform the development of counseling strategies for patients with OPC who undergo HPV testing. These models suggest that discussions about the appropriateness of testing, the psychological risks and benefits of knowing test results, the specific test(s) that might be used, and the technical accuracy of the test(s) should take place prior to testing. The results of testing must be placed into context by providing factual information about HPV and its transmission, the implications of test results for patient prognosis and treatment, and an opportunity for patients to identify their areas of greatest concern by asking open-ended questions.

Our counseling paradigm addresses HPV transmission and prevention, prognosis and treatment, and likelihood of cancer development in sexual partners. Unfortunately, answers to questions about HPV can be complex and in some cases unanswerable because of a lack of existing studies or equivocal results. It can also be difficult for providers and patients to share information regarding STIs. Therefore, it is imperative for the physician to provide accurate and up-to-date information in a supportive and comprehensible manner. It is equally important to acknowledge gaps in the information about these topics, even if that means conveying the uncertainty of elements of disease and risk management. Finally, providers should strive to foster open lines of communication and frame HPV in a neutral and nonstigmatizing context to minimize anxieties and promote effective coping strategies.

COUNSELING: INCORPORATING UP-TO-DATE ANSWERS TO FREQUENTLY ASKED QUESTIONS REGARDING HPV

Definitive determination of a patient's HPV status is important in order to provide appropriate education about the virus and the implications of a positive diagnosis. The challenge of HPV testing is to differentiate the presence of an incidental virus from one with oncogenic activity. Detection of E6 and E7 oncoprotein mRNA expression is the gold standard against which the sensitivity and specificity of all other tests are evaluated. However, it is costly, requires technical expertise, and has practical limitations within the routine diagnostic setting. Immunohistochemical staining for overexpression of cellular protein p16, HPV DNA in situ hybridization (ISH), and polymerase chain reaction (PCR) are other molecular biology techniques with their own unique strengths and limitations.

Table 2. Frequently asked questions regarding HPV-positive oropharyngeal cancer

Topic	Question	Answer
Transmission	How, when, or from whom did I get HPV?	HPV is a sexually transmitted virus. Most sexually active people will get HPV in their lifetimes. It is impossible to know with certainty from whom or when you acquired HPV because most people do not know they have it.
Prevention	How can I avoid transmitting HPV to others?	Lifetime mutual monogamy or abstinence are the best ways to prevent transmission. Condom use and fewer sexual partners are considered the mainstay of prevention. Experts are still determining what risks, if any, sexual partners of patients with HPVOPC have in developing cancer.
Duration of infection and progression to cancer	Will I always have HPV?	A healthy immune system suppresses the virus in most infected people. Experts are still determining whether HPV remains in the body, when HPV is no longer contagious, and how long it takes between HPV infection and development of oropharyngeal cancer.
Treatment	What are the best treatment options for HPVOPC?	There is currently no method for detecting the cancer in a precancerous stage, such as with the Pap test in cervical cancer. However, studies show that patients with HPVOPC who are also nonsmokers respond better to cancer treatment and have better overall survival than patients with HPV-negative oropharyngeal cancer.
Information for partners	What should I tell my partner about my HPV status?	Most infected people control HPV and do not develop signs or symptoms. If you decide to tell your partner about your HPV testing result, it is best to talk openly and honestly. Partners who have been together often share HPV, but it is impossible to know the direction of transmission. HPV is a common virus. It does not imply infidelity or promiscuity. There should be no shame or blame associated with an HPV diagnosis.

Abbreviations: HPV, human papillomavirus; HPVOPC, HPV-positive oropharyngeal cancer.

Although there is no current standard approach, most HPV detection in clinical samples for diagnostic purposes uses techniques that detect the presence of genomic HPV material. PCR is both highly sensitive and specific; it requires very close attention to tissue handling to avoid false-positive results. ISH is notable for high specificity (except at low viral load) and is optimized for fixed tissue samples; however, it is less sensitive than PCR [48]. Immunohistochemistry staining for p16 has been increasing in popularity because it is low in cost, a validated independent prognostic biomarker, and correlates strongly with positive high-risk HPV status [49–51]. However, given the high sensitivity and limited specificity of p16 staining, it is recommended that interpretation of results be informed by other data such as staining pattern, histology, anatomy of tumor, and clinical characteristics of the patient [48]. Additional types of HPV-related testing that patients may be aware of are serological testing for HPV antibodies in the blood [52, 53] and testing for presence of HPV in oral swabs or saliva [54, 55]. Although these are potentially useful epidemiologic tools that someday may play a role in assessing risk of HPV-related tumors, they are not validated and are not currently used to determine HPV status for clinical purposes.

When a patient with OPC undergoes HPV testing, this should be preceded by discussion of the implications of a positive or negative result for transmissibility, prognosis, treatment, and recurrence risk. Information about HPV can be complex, controversial, and/or limited, and it is constantly changing as new information becomes available; thus, it is important for the provider to provide the most up-to-date information possible, as well as to convey uncertainty when appropriate.

When a patient has been identified as HPV positive, it is essential to address their questions systematically, with an emphasis on clear patient-provider communication to ensure that all questions are answered. Conversely, patients whose tumors test negatively for the virus may be disappointed that they have the “worse kind of tumor” and experience feelings of pessimism. In both cases, patients will require a clear explanation of their expected prognosis and treatment plan, as well

as the opportunity to ask questions. To help guide this discussion, we have developed a set of questions and answers based on relevant information from both the Centers for Disease Control and Prevention HPV guidelines [56] and a set of empirically determined questions answered by a panel of experts from the American Social Health Association [57]. In addition, we have included supporting and relevant empirical data where appropriate. Although not intended to be comprehensive—and subject to change as additional research becomes available—these questions and answers (Table 2) can serve as a starting point for providers to develop their own counseling scripts.

HPV Transmission: “How, When, or From Whom Did I Get HPV?”

HPV is primarily a sexually transmitted virus. It is impossible to know for certain from whom or when one initially acquired HPV because most people do not know they have it. The patient may have been exposed in another relationship months, years, or decades earlier, and the infection may have been dormant (“hidden”) in the meantime. HPV is very common and can be transmitted through vaginal and anal sex. However, oral sex, kissing, and genital-to-genital contact or genital-to-hand-to-oral contact can also allow for transmission to occur.

Human papillomaviruses can either be of the mucosa or cutaneous type. HPV has been reported to have selectivity for the anogenital tract, urethra, skin, larynx, and mucosa of the trachea, bronchi, and oropharynx [58]. Furthermore, HPV is classified into high-risk types (primarily types 16 and 18) with oncogenic potential and low-risk types associated with genital condylomas. Mechanisms of oropharyngeal HPV transmission remain unclear. Concordance has been reported between maternal and newborn HPV genotypes, suggesting perinatal transmission of infection that can subsequently remain subclinical for an extended period of time [59]. The evidence on type-specific concordance between couples is mixed owing to variations in recruitment, detection, and specimens tested. However, in a re-

cent study, hygiene habits such as sharing towels or razors was not found to contribute to concordance [60, 61].

Hand-to-oral and hand-genital transmission has also been reported in earlier studies [62, 63] but recent evidence for oral autoinoculation of the virus from anogenital sites is mixed. A recent study found an individual's genital HPV infection to be highly correlated with subclinical oral HPV infection [64], whereas others have not found concordance within the same patient [65, 66].

Risk factors such as oral sex and open-mouthed kissing are associated with oral HPV infection. The odds of contracting oral HPV infection are substantially increased with progressively higher numbers of oral sexual and open-mouthed kissing partners [67]. However, a recent study called into question whether oral sex is the main transmission mode of oral HPV infection. Between spouses, oral sex was not associated with asymptomatic oral HPV infection; rather, persistent oral HPV infection in one partner was a significant risk factor for oral infection in the other [68], suggesting that the oral-to-oral route is an important mode of HPV transmission.

HPV Prevention: "How Can I Avoid Transmitting HPV to Others?"

Lifetime mutual monogamy or abstinence are the best possibilities for prevention. This does not mean abstinence from the patient's partner, with whom this infection has likely been shared for a considerable period of time. Most sexually active people will get HPV early in their lifetimes. Condoms prevent many bacterial and viral infections, but if HPV is present on uncovered skin or nongenital mucosal sites such as the oropharynx, transmission is possible. As with all other sexual behaviors, safer sexual practices and fewer sexual partners may be considered the mainstay of prevention. Simple transmission may not be sufficient to lead to cancer and other factors related to genetics, immune function, other STIs and infections, promiscuity, and multiple sexual partners may come into play in progression from infection to cancer.

Clearance of HPV and regression of HPV-associated penile lesions and cervical intraepithelial neoplasia has been reported with consistent condom use [69, 70]. However, this recommendation may not be practical for individuals in long-

Patients and their partners should be made aware that the oncogenic nature of the disease is not in and of itself contagious. Earlier evidence based on a small study shows specific HPV genetic markers identified among couples in which both members contracted tonsil cancer, associating direct viral transmission with cancer in both exposed parties. This, however, appears to be the exception, not the norm; the vast majority of partners of patients with HPVOPC never develop either oropharyngeal or cervical cancer.

term, monogamous relationships or relevant to HPV infection in the oropharynx.

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HPV genetic markers identified among couples in which both members contracted tonsil cancer, associating direct viral transmission with cancer in both exposed parties [71]. This, however, appears to be the exception, not the norm; the vast majority of partners of patients with HPVOPC never develop either oropharyngeal or cervical cancer. Currently, a multicenter study is being conducted by D'Souza et al. to determine a partner's risk for developing cancer [72]. For now, the existence and frequency of viral transmission among sexual partners and subsequent cancer development continues to be an active area of investigation. In the meantime, there is little medical justification for counseling HPV-positive patients with OPC on changing their sexual practices and intimate behaviors to modify risk of malignancy in partners.

Duration of HPV Infection and Progression to Cancer: "Will I Always Have HPV?"

A healthy immune system suppresses the virus in most infected persons. It is difficult to predict when HPV is no longer contagious. Experts disagree on whether the virus is eventually eliminated from the body or whether it is reduced to undetectable levels. There are treatments for cancer caused by HPV (discussed below) but not for the presence of the virus itself.

Substantial data exist regarding the outcomes of genital HPV infections among women; however, the natural history of oral HPV infection in men and women is just beginning to be explored. Thus, when answering patient questions related to the timing of infection relative to cancer onset, providers can offer information available from the data on genital HPV infection and cervical cancer. Women are infected soon after their sexual debut, with the highest prevalence seen in women younger than 25 years of age [73]. Evidence from genital HPV infections show that 90% of women have undetectable levels within 2 years and that those with persisting infections have a higher risk of progression to precancerous cervical lesions that, if left untreated, will progress to invasive cervical cancer within 10–20 years [74]. Based on the evidence of genital HPV infections at an early age and the late onset of oropharyngeal cancer [75], it is likely that there is considerable latency between HPV oral infection and the development of OPC, suggesting that in the majority of patients previous exposure—rather than a current partner—is the source of disease.

A recent population-based cross-sectional study examining the epidemiology of oral HPV-16 detected HPV in the saliva of 3% of men and 1% women, corresponding to an estimated 2 million individuals in the U.S. with active salivary expression at any single time [76]. It is unknown what the absolute risk of OPC is for this small but significant population. There is also a lack of known risk factor modifiers or therapies that can help to prevent persistence of oral HPV, which is believed to be necessary for inducing OPC. Few prospective studies have addressed the natural history of oral HPV infections. However, of these studies, one arbitrarily defined "persistent" HPV infection as present 6 months after baseline [77], whereas another showed clearance of infection 12 months after the start of the study [68], suggesting that the time-to-clearance for infected persons can be quite variable. Furthermore, the length of time from initial infection to the start of the study

was not available for either study. Thus, further prospective studies are needed to clarify the timing and natural history of persistent oral HPV infection and risk of subsequent head and neck cancer.

Prognosis, Treatment, and Risk of Recurrence for HPV-Positive OPC: “What Are the Best Treatment Options for HPVOPC?”

HPV itself is not directly treated in HPVOPC. The precancerous condition, known as dysplasia, can be detected in the cervix with the Papanicolaou (Pap) test, treated, and monitored accordingly. Although there is currently no method for detecting and treating precancerous lesions in the oral cavity or pharynx, numerous studies have shown that patients with head and neck cancer and HPV respond better to cancer treatment and have significantly better overall survival than HPV-negative patients with OPC. Importantly, as the results of clinical trials focused on HPVOPC become available, it may be possible to treat HPV-positive tumors with less intense treatment regimens. Patients should discuss all treatment options with their provider before deciding on a plan of treatment.

Accumulating evidence suggests that HPV status is an important prognostic factor and HPV positivity predicts favorable outcomes in head and neck cancers treated with surgery, radiation alone, or chemoradiation. A retrospective clinical trial demonstrated that patients with HPV-positive OPC tumors have better 3-year rates of overall survival and a 58% reduction in risk of death after adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment [78]. An earlier prospective clinical trial confirmed the favorable prognostic factor of positive HPV status that could not be explained by differences in treatment regimen or tumor site. HPV positivity conferred an improved response to either chemoradiation (84% vs. 57%) or induction therapy (82% vs. 55%) [79]. More recently, overall survival and progression-free survival rates in patients with HPVOPC were found to be 79% and 73%, respectively, compared with 31% and 29% in HPV-negative patients with OPC [80]. However, risk of cancer progression or death increases directly as a function of total pack-years of smoking, regardless of HPV status. Furthermore, smoking during radiation independently increases the risk of death [81]. Therefore, when counseling patients it is important to consider their current and previous smoking status and implement smoking cessation when appropriate.

The data on recurrence and secondary primary tumor in HPV-positive OPC are mixed; however patients with HPV-positive second primary tumors—although much more rare than HPV-negative second primary tumors—also have improved survival rates. HPV-positive patients who are also tobacco users are at significantly higher risk of disease recurrence than never-tobacco users. Therefore, in order to avoid disease relapse, HPV-positive patients who use tobacco should be counseled on the benefits of cessation [82, 83]. Furthermore, men with HPVOPC who have never been married may benefit from regular screenings for anal cancer, as this demographic has been shown to have an increased risk for developing primary anogenital cancer within 4–5 years of OPC diagnosis [84].

In genetic testing, inheritance or mutation resulting in genetic abnormality predisposes an individual to disease; for many genetic diseases, the outcome determines subsequent interventions or intensified screening practices. For others (e.g., Huntington disease), testing provides prognostic information only. At the time of this article, therapeutic guidelines do not take into account a patient's tumor HPV status [85], nor does the current staging system reflect the different treatment response and survival of HPV-positive and HPV-negative patients with OPC [86]. Nonetheless, when deciding between different treatment options, it is important that patients understand how their HPV and smoking status modify prognosis and likely response to therapy.

Partner Notification: “What Should I Tell My Partner About My HPV Status?”

Most sexually active people will eventually be infected with HPV. The majority of infected persons do not develop signs or symptoms; therefore, they do not know they are infected. If the patient decides to tell his or her partner about HPV testing results, it is best for them to talk openly and honestly. Partners who have been together tend to share HPV. This means that the partner likely has HPV already. There is no way to know if the partner gave the patient HPV or vice versa. Because HPV is a common virus and is usually acquired early in life, having an HPV infection does not imply infidelity. It is important to remember that there should be no shame or blame associated with a diagnosis of HPV.

When a patient has suspected OPC and testing for HPV occurs either at the time of biopsy or after, they should be counseled regarding the sexually transmitted nature of the virus. However, it is equally important for the provider to convey any uncertainties about the transmissibility associated with particular sexual behaviors. In the case of HIV, where there are more concrete facts and less uncertainty, the patient is interviewed to elicit information about their partners, who can then be confidentially notified of their possible exposure or potential risk. Infected individuals and their partners are offered a range of medical, prevention, and psychosocial services that can facilitate prevention of transmission, such as positive behavior modification to reduce transmission [54, 86]. Unlike HIV, there is no evidence to support partner notification of HPV-positive patients or referral for clinical evaluation of their partners. The current ethically acceptable approach to STI testing supports this notion, as notification of partners may cause unnecessary and unethical distress given the absence of clinical standards of treatment [87]. However, patients may benefit from having an informed discussion with their partner about their diagnosis, which can foster partner support. However, physicians should be aware that partner disclosure may have repercussions for some patients, such as partner rejection or even abuse. Therefore, it is important to support the patient's decision whether or not they choose to notify. If the patient elects to disclose their HPV status, physician should be prepared to provide medical information should the partner seek it.

HPV is neither a necessary nor a sufficient cause of OPC. However, persistent oral HPV infection in partners may increase the risk of developing oral cancer. It is recommended that these individuals use regular dental appointments as im-

portant tools for detecting any high-risk HPV-related changes in the oral and oropharyngeal mucosa. Behavioral modifications, such as cessation of alcohol and tobacco use, should be encouraged because they are not only health-enhancing strategies but have been found to significantly decrease the odds of oral HPV persistence [77]. The available HPV vaccines cover the HPV genotypes found most commonly in the oral mucosa, but their protective effect against oral/oropharyngeal cancer, especially in individuals who have already been exposed to HPV, remains to be demonstrated.

Exposed partners may be considered a high-risk population for developing oropharyngeal cancer. Therefore, screening methods similar to the Pap test for cervical cancer, would be desirable in this population; however, as yet these tests do not exist, and it is not clear that an HPV-induced oropharyngeal precancerous lesion analogous to cervical dysplasia exists [88]. Furthermore, until there is more data on the natural history of oral HPV infection and how best to prevent the progression of precancer, screening may have limited utility.

CONCLUSION

Within the next 10 years, the annual number of HPV-associated oropharyngeal cancers is projected to exceed the annual number of cervical cancers in the U.S. [5]. Thus, screening and prevention will become increasingly important; however, because no HPV-induced oropharyngeal precancerous lesion has yet been identified, oral HPV infection remains the only currently available indicator of future oropharyngeal cancer risk. However, further research is needed to improve

the testing and quantify the magnitude of risk before this is incorporated into routine practice. Risk of recurrence of primary HPV-associated tumors must also be clarified. Thus, research efforts should focus on understanding the natural history of HPV infection and the factors that modify progression to oncogenesis; identifying host immune and other factors that determine whether oropharyngeal HPV infection leads to clearance versus persistence; and developing behavioral strategies to modify risk of progression to malignancy once persistent HPV infection has been established. Also, given the success of primary prevention of cervical cancer and genital warts with HPV vaccines, efforts should be made to understand the ability of these vaccines to prevent OPC and to encourage vaccination of male and female children.

As more definitive information becomes available, health care providers of patients with HPVOPC will continue to play an important role in making this information accessible and helping patients navigate the complex decisions arising during diagnosis and treatment of their disease. A consistent and evidence-based strategy for pre- and post-HPV testing counseling will help providers ensure that this is done in a supportive and patient-centered manner.

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REFERENCES

1. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: Is it time to change our treatment paradigms? *J Natl Compr Canc Netw* 2011;9:665–673.
2. Centers for Disease Control and Prevention. Tobacco use among middle and high school students—United States, 2000–2009. *MMWR* 2010;59:1063–1068.
3. 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;100:407–420.
4. D'Souza G, Kreimer AR, Viscidi R et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356:1944–1956.
5. Chaturvedi AK, Engels EA, Pfeiffer RM et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294–4301.
6. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. *Lancet* 2004;363:1488–1489.
7. 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;344:1125–1131.
8. 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;92:709–720.
9. Centers for Disease Control and Prevention. Human papillomavirus vaccine. Available at <http://www.cdc.gov/vaccinesafety/Vaccines/HPV>. Accessed October 12, 2011.
10. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
11. Kreimer AR, Clifford GM, Boyle P et al. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;14:467–475.
12. 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;125:1337–1344.
13. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 2008;113:3036–3046.
14. Herrero A, Castellsagué X, Pawlita M et al. Human papillomavirus and oral cancer: The International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 2003;95:1772–1783.
15. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 1990;248:76–79.
16. Dyson N, Howley PM, Münger K et al. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989;243:934–937.
17. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70.
18. Marur S, D'Souza G, Westra WH et al. HPV-associated head and neck cancer: A virus-related cancer epidemic. *Lancet Oncol* 2010;11:781–789.
19. Allyn D. The sexual revolution: An unfettered history. Boston, MA: Little, Brown, 2000:1–367.
20. Bajos N, Bozon M, Beltzer N et al. Changes in sexual behaviours: From secular trends to public health policies. *AIDS* 2010;24:1185–1191.
21. Herbenick D, Reece M, Schick V et al. Sexual behavior in the United States: Results from a national probability sample of men and women ages 14–94. *J Sex Med* 2010;7:255–265.
22. Hammarstedt L, Lindquist D, Dahlstrand H et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer* 2006;119:2620–2623.
23. 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;125:362–366.
24. 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;110:1429–1435.
25. Gillison ML. Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. *J Adolesc Health* 2008;43:S52–S60.
26. Chaturvedi AK, Engels EA, Anderson WF et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612–619.

27. Vidal L, Gillison ML. Human papillomavirus in HNSCC: Recognition of a distinct disease type. *Hematol Oncol Clin North Am* 2008;22:1125–1142.
28. Forte T, Niu J, Lockwood GA et al. Incidence trends in head and neck cancers and human papillomavirus (HPV)-associated oropharyngeal cancer in Canada. *Cancer Causes Control* 2012;23:1343–1348.
29. De Boer MF, McCormick LK, Pruyn JF et al. Physical and psychosocial correlates of head and neck cancer: A review of the literature. *Otolaryngol Head Neck Surg* 1999;120:427–436.
30. Kugaya A, Akechi T, Okuyama T et al. Prevalence, predictive factors, and screening for psychological distress in patients with newly diagnosed head and neck cancer. *Cancer* 2000;88:2817–2223.
31. Verdonick-de Leeuw IM, de Bree R, Keizer AL et al. Computerized prospective screening for high levels of emotional distress in head and neck cancer patients and referral rate to psychosocial care. *Oral Oncol* 2009;45:e129–e133.
32. Mast TC, Zhu X, Demuro-Mercon C et al. Development and psychometric properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV. *Curr Med Res Opin* 2009;25:2609–2619.
33. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: Collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer* 2007;120:885–891.
34. Maggino T, Casadei D, Panontin E et al. Impact of an HPV diagnosis on the quality of life in young women. *Gynecol Oncol* 2007;107:S175–S179.
35. Clarke P, Ebel C, Catotti DN et al. The psychosocial impact of human papillomavirus infection: Implications for health care providers. *Int J STD AIDS* 1996;7:197–200.
36. McCaffery K, Waller J, Nazroo J et al. Social and psychological impact of HPV testing in cervical screening: A qualitative study. *Sex Transm Infect* 2006;82:169–174.
37. Kwan TT, Cheung AN, Lo SS et al. Psychological burden of testing positive for high-risk human papillomavirus on women with atypical cervical cytology: A prospective study. *Acta Obstet Gynecol Scand* 2011;90:445–451.
38. Daley EM, Perrin KM, McDermott RJ et al. The psychosocial burden of HPV: A mixed-method study of knowledge, attitudes and behaviors among HPV+ women. *J Health Psychol* 2010;15:279–290.
39. Klug SJ, Hukelmann M, Blettner M. Knowledge about infection with human papillomavirus: A systematic review. *Prev Med* 2008;46:87–98.
40. Dillard JP, Spear ME. Knowledge of human papillomavirus and perceived barriers to vaccination in a sample of U.S. female college students. *J Am Coll Health* 2011;59:186–190.
41. Almeida CM, Tiro JA, Rodriguez MA et al. Evaluating associations between sources of information, knowledge of the human papillomavirus, and human papillomavirus vaccine uptake for adult women in California. *Vaccine* 2012;19:3003–3008.
42. Fernandez ME, McCurdy SA, Arvey SR et al. HPV knowledge, attitudes, and cultural beliefs among Hispanic men and women living on the Texas-Mexico border. *Ethn Health* 2009;14:607–624.
43. Fortenberry JD. The effects of stigma on genital herpes care-seeking behaviours. *Herpes* 2004;11:8–11.
44. Fortenberry JD, McFarlane M, Bleakley A et al. Relationships of stigma and shame to gonorrhea and HIV screening. *Am J Public Health* 2002;92:378–381.
45. Waller J, McCaffery K, Kitchener H et al. Women's experiences of repeated HPV testing in the context of cervical cancer screening: A qualitative study. *Psychooncology* 2007;16:196–204.
46. Anhang R, Goodman S, Goldie SJ. HPV communication: Review of existing research and recommendations for patient education. *CA Cancer J Clin* 2004;54:248–259.
47. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55:1–17.
48. Westra WH. Detection of human papillomavirus in clinical samples. *Otolaryngol Clin North Am* 2012;45:765–777.
49. Thomas J, Primeaux R. Is p16 immunohistochemistry a more cost-effective method for identification of human papilloma virus-associated head and neck squamous cell carcinoma? *Ann Diagn Pathol* 2012;16:91–99.
50. El-Naggar AM, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: A guide for interpretative relevance and consistency. *Head Neck* 2012;34:459–461.
51. Agoston ES, Robinson SJ, Mehra KK et al. Polymerase chain reaction detection of HPV in squamous carcinoma of the oropharynx. *Am J Clin Pathol* 2010;134:36–41.
52. Anderson KS, Wong J, D'Souza G et al. Serum antibodies to the HPV16 proteome as biomarkers for head and neck cancer. *Br J Cancer* 2011;104:1896–1905.
53. Waterboer T, Dondog B, Michael KM et al. Dried blood spot samples for seroepidemiology of infections with human papillomaviruses, *Helicobacter pylori*, Hepatitis C virus, and JC virus. *Cancer Epidemiol Biomarkers Prev* 2012;21:287–293.
54. Cameron JE, Snowwhite IV, Chaturvedi AK et al. Human papillomavirus-specific antibody status in oral fluids modestly reflects serum status in human immunodeficiency virus-positive individuals. *Clin Diagn Lab Immunol* 2003;10:431–438.
55. Turner DO, Williams-Cocks SJ, Bullen R et al. High-risk human papillomavirus (HPV) screening and detection in healthy patient saliva samples: A pilot study. *BMC Oral Health* 2011;11:28.
56. Dunne EF, Friedman A, Datta SD et al. Updates on human papillomavirus and genital warts and counseling messages from the 2010 Sexually Transmitted Diseases Treatment Guidelines. *Clin Infect Dis* 2011;53:S143–S152.
57. Gilbert LK, Alexander L, Grosshans JF et al. Answering frequently asked questions about HPV. *Sex Transm Dis* 2003;30:193–194.
58. Campisi G, Panzarella V, Giuliani M et al. Human papillomavirus: Its identity and controversial role in oral oncogenesis, premalignant and malignant lesions. *Int J Oncol* 2007;30:813–823.
59. Koskimaa HM, Waterboer T, Pawlita M et al. Human papillomavirus genotypes present in the oral mucosa of newborns and their concordance with maternal cervical human papillomavirus genotypes. *J Pediatr* 2011;160:837–843.
60. Kero K, Rautava J, Syrjänen K et al. Human papillomavirus genotypes in male genitalia and their concordance among pregnant spouses participating in the Finnish Family HPV study. *J Sex Med* 2011;8:2522–2531.
61. Widdice LE, Breland DJ, Jonte J et al. Human papillomavirus concordance in heterosexual couples. *J Adolesc Health* 2010;47:151–159.
62. Kellokoski JK, Syrjänen SM, Chang F et al. Southern blot hybridization and PCR in detection of oral human papillomavirus (HPV) infections in women with genital HPV infections. *J Oral Pathol Med* 1992;21:459–464.
63. Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. *Sex Transm Infect* 1999;75:317–319.
64. Peixoto AP, Campos GS, Queiroz LB et al. Asymptomatic oral human papillomavirus (HPV) infection in women with a histopathologic diagnosis of genital HPV. *J Oral Sci* 2011;53:451–459.
65. Xavier SD, Bussolati Filho I, de Carvalho JM et al. Prevalence of human papillomavirus (HPV) DNA in oral mucosa of men with anogenital HPV infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:732–737.
66. Castro TM, Bussolati Filho I, Nascimento VX et al. HPV detection in the oral and genital mucosa of women with positive histopathological exam for genital HPV, by means of the PCR. *Braz J Otorhinolaryngol* 2009;75:167–171.
67. D'Souza G, Agrawal Y, Halpern J et al. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis* 2009;199:1263–1269.
68. Rintala M, Grénman S, Puranen M et al. Natural history of oral papillomavirus infections in spouses: A prospective Finnish HPV Family Study. *J Clin Virol* 2006;35:89–94.
69. Tokudome S, Suzuki S, Ichikawa H et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: A randomized clinical trial. *Int J Cancer* 2004;112:164.
70. Bleeker MC, Hogewoning CJ, Voorhorst FJ et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. *Int J Cancer* 2003;107:804–810.
71. Andrews E, Shores C, Hayes DN et al. Concurrent human papillomavirus-associated tonsillar carcinoma in 2 couples. *J Infect Dis* 2009;200:882–887.
72. Human papillomavirus (HPV) oral transmission study in partners over time (HOTSPOT) (NCT01342978). Available at <http://clinicaltrials.gov/ct2/show/NCT01342978>. Accessed December 15, 2012.
73. Denis F, Hanz S, Alain S. Clearance, persistence and recurrence of HPV infection. *Gynecol Obstet Fertil* 2008;36:430–440.
74. Gravitt PE. The known unknowns of HPV natural history. *J Clin Invest* 2011;121:4593–4599.
75. Sudhoff HH, Schwarze HP, Winder D et al. Evidence for a causal association for HPV in head and neck cancers. *Eur Arch Otorhinolaryngol* 2011;268:1541–1547.
76. Gillison ML, Broutian T, Pickard RK et al. Prevalence of oral HPV infection in the United States, 2009–2010. *JAMA* 2012;307:693–703.
77. D'Souza G, Fakhry C, Sugar EA et al. Six-month natural history of oral versus cervical human papillomavirus infection. *Int J Cancer* 2007;121:143–150.
78. Ang KK, Harris J, Wheeler R et al. Human papil-

lomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35.

79. 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;100:261–269.

80. Posner MR, Lorch JH, Goloubeva O et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: A subset analysis from an international phase III trial. *Ann Oncol* 2011;22:1071–1077.

81. Gillison ML, Zhang Q, Jordan R et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-nega-

tive oropharyngeal cancer. *J Clin Oncol* 2012;30:2102–2111.

82. 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;16:1226–1235.

83. Hafkamp HC, Manni JJ, Haesevoets A et al. Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer* 2008;122:2656–2664.

84. Sikora AG, Morris LC, Sturgis EM. Bidirectional association of anogenital and oral cavity/pharyngeal carcinomas in men. *Arch Otolaryngol Head Neck Surgery* 2009;135:402–405.

85. Pfister D. Clinical practice guidelines in oncology, version 2.2011. Washington, DC: National Comprehensive Cancer Network, 2011.

86. Centers for Disease Control and Prevention. Recommendations for partner services program for HIV infection, syphilis, gonorrhea, and chlamydia infection. *MMWR* 2008;57:1–9.

87. Field N, Tanton C, Mercer CH et al. Testing for sexually transmitted infections in a population-based sexual health survey: Development of an acceptable ethical approach. *J Med Ethics* 2012;38:380–382.

88. Kreimer AR, Chaturvedi AK. HPV-associated oropharyngeal cancers: Are they preventable? *Cancer Prev Res* 2011;4:1346–1349.