

Human Papillomavirus Status in Head and Neck Cancer

The Ethics of Disclosure

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Human papillomavirus (HPV) is an emerging causative factor for squamous carcinoma of the oropharynx and perhaps other head and neck cancers. There is a great deal of uncertainty regarding the clinical significance and implications of HPV status in this patient population. As a result, there is no established protocol for informing patients of the potential link between viral infection and their cancer. This paper discusses some of the ethical issues involved with informing head and neck cancer patients of their HPV status, recognizing the dilemma posed by unresolved clinical questions and the need to respect the autonomy of patients by disclosing relevant information. *Cancer* 2010;116:4221-6. © 2010 American Cancer Society.

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An increasing volume of data have linked infection with human papillomavirus (HPV), a sexually transmitted pathogen, with head and neck cancer.^{1,2} HPV infection may explain the increasing incidence and changing demographics of these cancers, particularly squamous cell carcinomas of the oropharynx.^{3,4} Patients with HPV-related tumors often lack the classic risk factors for these malignancies, such as a history of tobacco or alcohol abuse, and often present at younger ages.⁵ Currently, there are no conclusive data suggesting that treatment modalities or other aspects of care should differ for head and neck cancer patients based on their HPV status.

The issue of discussing the relationship of HPV status and the development of head and neck cancer poses a dilemma. Clinicians aspire to keep their patients duly informed, but may not know which patients might have HPV-related infections, nor can they make further definitive statements regarding etiology or outcome based on the limited knowledge of this clinical entity. In general, we know that the association of HPV infection in a nonsmoking head and neck cancer patient is a favorable prognostic factor; however, the literature addressing HPV-related head and neck cancers is growing exponentially. This paper does not attempt to provide a comprehensive review of the topic, but will discuss the ethical issues surrounding the disclosure and discussion of HPV status among head and neck cancer patients.

Ethical Tenets of Honesty and Transparency

Contemporary medical ethics is based on a foundation in which patients and their healthcare providers are partners. Patients and their designated decision-makers are charged with using the expertise and recommendations of their physicians to make informed and reasoned decisions. Rather than make paternalistic judgments concerning what patients should know or must do, physicians are obligated to present all relevant and pertinent information in a way that is accurate and honest, and allow their patients to act autonomously. One model of this process involves the implementation of both informal conversational ethics and formal deliberative ethics.⁶ The former process centers on the creation of a partnership between physician and patient that fosters open lines of communication, honesty, and discussion. The latter involves careful deliberation of choices, alternatives, and outcomes, taking both the clinician's and the patient's input and assimilating

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them into a workable solution that is both practical and in accordance with the patient's preferences. In reality, these 2 processes are cohesive and frequently occur simultaneously, but the model highlights the importance of the physician-patient relationship itself, which must exist before specific decisions are approached.

Uncertainty of HPV Status

Many patients and physicians will not know conclusively whether a specific cancer is related to prior HPV infection. Although a sexual history, demographic factors such as age, and the presence or absence of comorbid behaviors (alcohol and tobacco abuse) may help predict HPV status, they are by no means foolproof.⁷ Identification of molecular biomarkers for HPV and/or immunohistological staining of tumor specimens for p16 are effective methods of determining HPV status.⁸ However, this information currently does not affect the patient's care or impact treatment decisions other than to suggest a trend with regard to prognosis, and is not routinely performed at most institutions.

Given the uncertainty of HPV status in each individual patient's neoplasm, and the finding that HPV seems most closely related only to oropharyngeal cancers, do all patients diagnosed with squamous cell carcinoma of the head and neck deserve to be educated about the virus and its implications? Physicians can and should be honest with patients, using patient history and clinical judgment to shape the conversation. Patients for whom HPV infection is an exceedingly unlikely prospect (the elderly pipe-smoking celibate bachelor, for example) may be assured that they are unlikely to have an HPV-related neoplasm, but the virus and its role in related neoplasms should still be discussed. In contrast, a young professional nonsmoker might appreciate more information, identifying a potential causative factor for what is likely a devastating and unexpected diagnosis. As the patient community continues to receive medical information from sources other than their healthcare workers, such as other patients, friends, family members, and the Internet, we are obligated to ensure that patients receive accurate information and that we dispel inaccuracies. A patient's right to know exceeds the need to shield them from the potential psychological stress of an emotionally charged conversation with their physician.

HPV as a Sexually Transmitted Infection

HPV is a sexually transmitted infection with a high prevalence in the general population. In general, orogenital

sexual encounters are considered the etiology of HPV infections that may contribute to the development of head and neck cancer.⁹ As with all other sexually transmitted infections, safer sexual practices may be considered the mainstay of prevention. The association between HPV infection and head and neck cancer does not suggest direct transmissibility of oncogenic infections, and patients with head and neck cancer are not considered contagious with regard to their partner's risk of developing cancer. That said, a recent study has demonstrated that the odds of contracting oral HPV infection are significantly raised with progressive increases in the number of oral sexual and open-mouthed kissing partners.¹⁰ Specific HPV genetic markers have also been identified among couples in which both members contracted tonsil cancer, associating direct viral transmission with cancer in both exposed parties.¹¹

Despite this information, there is little medical justification to support counseling newly diagnosed head and neck cancer patients that they must inform prior sexual contacts that they have an increased risk for head and neck cancer, or to suggest that changes in behavior will affect their or their partner's future risk of malignancy. Despite an increased relative risk with certain sexual behaviors, HPV infections are very common and HPV-related malignancies are relatively rare, so that the absolute risk, even for close contacts of infected patients, is much smaller. Moreover, it is likely that there is considerable latency between the time of HPV infection and the development of cancer, indicative that previous viral infection, rather than current or future exposures, is the source of the disease.¹² In addition, it behooves physicians counseling patients to disclose that there is a great deal of uncertainty with regard to HPV's transmissibility and its relationship with head and neck cancer, obviating the ability to make ironclad recommendations.

Sharing information concerning sexually transmitted infections can be difficult for clinicians and patients alike, even when the facts are more concrete. Current practices regarding HIV testing and communication of HIV status may be instructional and bear some similarities with the HPV issue. With regard to disclosure of HIV test results, patient autonomy drives decision making. Although individuals are encouraged to participate in routine screening, and to share their test status with sexual contacts, neither is mandatory.¹³ Some have questioned whether the rights of sexual partners should trump the autonomy and confidentiality enjoyed by patients who either test positive or who refuse testing despite significant

risk factors.¹⁴ Most importantly, HIV testing should be preceded by in-depth counseling, and all test results should be delivered concordant with information about their implications, just as should be the case when discussing HPV.

Patients with suspected HPV-related head and neck cancer should be educated regarding the sexually transmitted nature of the virus, as well as the uncertainty concerning epidemiology, health behaviors, and transmissibility. Given the associated risk factors and the Centers for Disease Control and Prevention (CDC)'s routine recommendations for human immunodeficiency virus (HIV) testing, patients with HPV-related tumors should also be counseled to be tested for HIV.¹³ As with HIV testing, knowledge of HPV status requires preparation and education for patients to understand the context of the information.

Oncologic Prognosis

Currently, there are no data suggesting that treatment modalities should differ among patients with head and neck cancer dependent on their HPV status. Thus, clinical decision making does not depend on this knowledge, and is unlikely to fundamentally change the medical or surgical approach to these patients. However, there are ample data to suggest that HPV-related cancers are distinct clinical entities, and have different biological behaviors. Multiple studies have confirmed that patients with HPV-related oropharyngeal cancer have a better prognosis than patients with tumors not associated with HPV.^{15,16} To date, this has not led to any change in the treatment or staging of these malignancies, and has not been applied to a systematic method of adjusting prognosis.¹⁷ However, future clinical trials may attempt to decrease the intensity of treatment in this subset of patients to limit morbidity, thereby taking advantage of the less aggressive biology of HPV-related tumors.

The ethics of sharing prognostic information has been discussed comprehensively in the genetics literature. With regard to mutations in genes predisposing women to breast cancer, the ethical issues regard the involvement and testing of relatives with uncertain risk, as well as the potential for closer screening exams and even prophylactic ablative surgery for those carrying the genetic mutation.¹⁸ Established guidelines dictate how this process occurs, ensuring that only appropriate candidates are included, pretest education and counseling are stressed, results are shared in a tactful manner, and decisions thereafter are made autonomously with careful thought.¹⁹ In the case of

HPV-related cancers, interventions are not based on the outcome of testing; thus, the situations are distinct. However, the approach to the process itself applies directly.

An example of prognostic information that does not affect management exists with regard to Huntington disease, an autosomal dominant, progressive neurologic disease without any definitive treatment for which genetic testing is possible for asymptomatic relatives of affected patients. There is a wealth of information specific to this field. Most ethicists agree that patients, equipped with the appropriate medical knowledge, have the right to obtain the results of genetic tests for the disease.²⁰ Our current discussion has similarities to the ethical issues in Huntington disease; both involve disclosure of prognostic information without the availability of interventions dependent on the outcome of testing. Of course, there are significant differences in magnitude and outcome; Huntington disease has a devastating clinical course, whereas knowledge of HPV status modestly, and favorably, alters the prognosis of a patient with a known diagnosis.

The prognostic value of HPV status with regard to head and neck cancer is very different from other entities such as breast cancer and Huntington disease, but certain themes are shared. Patients require medical expertise to understand the implications of their choices, but individuals are ultimately allowed to make their own decisions. Contemporary medical ethics shirks paternalism and the concept of protecting patients from themselves. In general, with regard to dilemmas in disseminating prognostic information, the best solutions honor patient autonomy and limit harm to others, while also ensuring that patients are counseled appropriately both before and after testing is performed.²¹ Thus, patients are privy to the knowledge that HPV-related tumors may have a better than expected outcome (and vice versa), despite the absence of any further clinical measures resulting from this information.

The Case of HPV and Cervical Cancer

HPV is considered the causative agent in the majority of cases of uterine cervical cancer, and this association is well established. Taking into consideration the significant differences between gynecologic and head and neck cancers, we can use this model to guide our discussion. In most cases, in contrast to HPV in head and neck cancer, HPV's role as a causative agent in cervical cancer is proven; thus, a diagnostic dilemma is not much of a factor. In addition, data suggest that persistent and recurrent infection is associated with subsequent unprotected sexual encounters.²² For this reason, patient education encouraging safer sexual

practices is not only valid from a public health standpoint, but is actually designed to decrease the chances of recurrent neoplasm. In contrast, there are no data yet to suggest that this is true for patients with HPV-related head and neck cancer.

Although there is a stigma associated with sexually transmitted infections, clinicians should not hesitate to disclose clinical information (such as the existence of or suspicion for HPV infection) to protect patients from their own emotions. Tactful education and providing resources for safer sexual practices are valuable interventions, whether or not this decreases the likelihood of recurrent cancer. In addition, taking a sexual history not only assists with risk stratification, but will assist the clinician in providing sound advice to patients regarding how best to modify their risk for future exposure. These principles apply to patients with suspected HPV-related oropharyngeal cancers as well as patients with cervical neoplasms.

HPV Vaccination

The emergence of a multivalent HPV vaccine adds yet another layer of complexity to this discussion. The ethics of HPV vaccination has been previously reviewed concerning adolescent girls and cervical cancer specifically, and will not be discussed in detail here. The interested reader is directed to excellent commentaries on the topic.^{23,24} Generally speaking, the proponents of vaccination highlight the efficacy and safety of the vaccine and the public health responsibility to protect citizens from avoidable dangers, often citing the finding that other vaccines such as polio have been mandated with great success.²⁵ Opponents question the safety of the vaccine and length of follow-up data in clinical trials, the need for a vaccine given the availability of screening programs for premalignant lesions, as well as the potential violation of privacy, family values, and civil liberties.²⁶ Some warn that mandating vaccination is akin to “opening the flood gates to governmental regulation of behavior in the name of public health.”²⁷ Nevertheless, the majority of medical societies support widespread vaccination.²⁸

In theory, assuming an HPV vaccine is efficacious, prevention of infection with high-risk HPV serotypes will decrease the incidence of HPV-related head and neck cancers.²⁹ Unfortunately, given the latency between infection and neoplasm, and the generally low incidence of this clinical entity (even when compared with cervical neoplasms), data confirming this hypothesis are many years away.³⁰ Thus, it is not justified to mandate vaccination of

all adolescents in an effort to prevent head and neck cancer, as this outcome has not been clinically studied to date. However, despite the dearth of data, the scientific principle is sound. Although public health policy should not be based solely on theory, physicians can certainly advise their patients regarding the proven as well as the potential benefits of a proposed intervention, so long as the information is not misrepresented.

The other issue surrounding vaccination regards whether men should be targeted. Men can develop HPV-related genital and anal lesions, albeit with a considerably lower incidence than cervical neoplasms in women. That said, many women contract HPV from male sexual partners, and the concept of herd immunity suggests that decreasing the incidence of infection in the general population will decrease the risk in those with a higher prevalence of symptomatic disease, including sexually communicable diseases.³¹ Moreover, men contract HPV-related head and neck cancers with a similar incidence to women. Currently, men are not targeted as candidates for vaccination, nor have they been included in many of the clinical vaccine trials to establish vaccine safety and efficacy.³² The US Food and Drug Administration recently approved the vaccine for males in order to prevent genital warts, with no mention of the potential prevention of cancer-causing infections.³³ Nonetheless, to decrease the risk of HPV-related tumors, as well as to decrease the prevalence of HPV infection in the general population, vaccination of both sexes is medically and epidemiologically sound.

On the basis of the potential advantages of male vaccination, from the standpoint of both herd immunity and the theoretical prevention of head and neck cancer, further studies and discussion of HPV vaccination in men are warranted. Attitudes and education with regard to vaccination deserve mention. Men are generally uninformed regarding the existence and consequences of HPV infection.³⁴ Male attitudes toward HPV vaccination will need to be clarified to tailor education and eventual vaccination campaigns, as the direct benefits may be less apparent to men than they are to women.³⁵ The risk of HPV-related head and neck cancer might assist in the education of both sexes regarding risks, safer sexual practices, and the applicability of vaccination.

Specific Recommendations

- To ensure that patients receive factual and accurate information, HPV should be discussed as a possible etiologic agent with all patients with oropharyngeal squamous cell carcinoma.

- Patient factors and physician judgment should dictate the utility of discussing HPV in the setting of head and neck cancers presenting at other head and neck sites in which HPV is unlikely to be a causative factor.
- The transmissibility of HPV may be discussed at the discretion of physicians, acknowledging that other than standard barrier methods, there exists no convincing evidence that specific behavior modifications or sexual contact precautions are necessary.
- The favorable prognosis of HPV-related neoplasms may be discussed with patients as is clinically appropriate, understanding that treatment is not currently adjusted based on this information, and other factors can significantly affect prognosis.
- Physicians may discuss the belief that HPV vaccination theoretically might help prevent certain head and neck cancers despite the absence of conclusive evidence.

Conclusions

Medicine is an imperfect science. The dynamic expansion of scientific knowledge leaves rifts in our ability to effectively counsel our patients. HPV-related head and neck cancer is an emerging biologically distinct subset of head and neck cancers for which best practice guidelines are far from established. Patients deserve honesty, transparency, and integrity with regard to information disseminated and counseling provided, in the knowledge that the implications of this information may well change with the advent of further scientific knowledge. Although a definitive decision-making algorithm does not yet exist, physicians and patients should embark on a partnership in which the role of HPV in head and neck cancer is shared and discussed.

CONFLICT OF INTEREST DISCLOSURES

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