Why Am I Scared of HPV?

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As a physician community, we must develop proven educational methods to explain human papillomavirus (HPV) so that we do not invoke patients’ confusion, guilt, anxiety and psychological distress.1–3 Patient participation in any type of medical care is dependent on their understanding of the problem, confidence in their knowledge and choice of medical options, and the cost of care relative to other important aspects of their life. HPV education should address the sexually transmitted nature of HPV, the natural history and outcomes of HPV infection, the medical nomenclature encompassing HPV, and where HPV testing fits within current cervical cancer screening guidelines.

HPV AS A SEXUALLY TRANSMITTED INFECTION

Starting with Rigoni-Stern who, in 1842, reported to the IV Congress of Italian Scientists that cervical cancer never occurred in celibate nuns, investigators have suspected that cervical cancer was caused by a sexually transmitted infection.4 During the past three decades, new technologies for detection of HPV DNA started an avalanche of research into the molecular, cellular, and epidemiologic components of the association of this sexually transmitted infection with cervical cancer.5

Since that time, over 100 distinct types of HPV have been identified, causing tissue and site-specific human diseases.6 For instance, HPV types 2 and 4 cause common warts on the fingers and HPV type 1 causes plantar warts. The importance of cellular immunity in controlling HPV infections is well demonstrated by an autosomal recessive hereditary deficiency, epidermoidiisplasia verruciformis, which predisposes affected individuals to lifelong infections with HPV types not usually pathogenic. In these genetically predisposed individuals, HPV (predominantly types 5 and 8) causes multiple warty infections of the skin that can progress to squamous cell carcinoma. Likewise, on the mucosal epithelial surfaces (oral and anogenital), there are approximately 30 HPV types that cause sexually transmitted HPV infections of the oral and anogenital mucosal surfaces. Two of the 12 low-risk HPV types (types 6 and 11) are responsible for human external genital warts (EGWs), but do not cause cervical cancer. Approximately 18 types of HPV are strongly or moderately linked to cervical cancer, with HPV type 16 responsible for half of all the infections.7 All HPV infections are transmitted from one epithelial surface to another through social or sexual transmission.

NATURAL HISTORY AND NOMENCLATURE OF HPV INFECTION

There are three forms of the HPV infection. The first is an episomal infection where the virions from superficial cells of one epithelial surface attach to and are internalized by receptors on the basal cells of another epithelial surface, replicating only when the host basal cell replicates. This infection, on the anogenital epithelium, is usually associated with low viral copy numbers and no cytologic abnormalities, and is only detected if basal cells are sampled in the cervical scraping.8

The second form of HPV infection of the anogenital epithelium is also episomal and can be from low- or high-risk HPV types. The HPV DNA is replicated more frequently than the host cell DNA and is therefore present at higher copy number. Viral proteins are expressed, which increases the frequency of the host basal cell replication and disrupts the normal maturation of the squamous epithelium. Instead of the normal basal to parabasal to intermediate to superficial squamous cell maturation, the epithelium shows morphologic features of CIN1, and there is complete virus assembly in its upper layers.

The third form of HPV infection occurs when high risk types of HPV DNA integrate into the host basal cell DNA, causing genetic instability and p53 inactivation, leading to CIN 2/3 lesions.9 This unchecked cellular growth may eventually develop into cancer.
Combining the nomenclature of mucosotropic HPV types (low and high risk) with the nomenclature of cervical cytology (low- and high-grade squamous intraepithelial lesions) can muddle the understanding of HPV results for some patients. Although high-grade squamous intraepithelial lesions (SILs) are invariably the result of infection with high-risk HPV types, some patients and providers incorrectly assume that low-grade SILs are always caused by low-risk HPV types. In fact, more than 75% of low-grade SILs occur when a high-risk HPV type is present in the episomal/nonintegrated state.6

CURRENT FOLLOW UP AND SCREENING GUIDELINES

The three medically equivalent options after a cytology result of atypical squamous cells of undetermined significance (ASC-US) are: referral to colposcopy, HPV testing, or follow up by repeat cytology.10 These are based on a large prospective randomized controlled trial, and smaller historically prospective trials.11,12

The Hybrid Capture 2 HPV test, a test for 13 of the high-risk HPV types, is the only FDA-approved commercially available HPV test. The combination of this HPV test with cytology is promoted as an option for primary screening of cervical cancer by some guidelines, for women aged 30 and older.13 Current guidelines do not recommend use of the HPV test for cervical cancer screening in women younger than 30 years. Although the prevalence of detectable HPV infections in this group is high, most of these infections are transient and require no further evaluation or treatment. Thus, HPV testing in these women frequently leads to the dilemma of a positive HPV result with a Pap test result negative for intraepithelial lesion or malignancy (NILM), and the accompanying risk of unnecessary diagnostic and therapeutic interventions.

FEAR, GUILT, ANXIETY AND PSYCHOLOGICAL DISTRESS

Women and men alike are not pleased to hear that they have a sexually transmitted infection, regardless of its warty or cancerous outcome. Warty outcomes appear to be most anxiety provoking for those men and women of all ages not in monogamous relationships, as they feel it may diminish their social worth as a future partner.14 The possibility of cervical cancer appears to be most frightening to older women with children or to those in a stable relationship, as the fear of death disrupting normal family function is foremost in their minds.15 Those concerned with the cancer outcome often focus on the steps needed for their precancer treatment and cure, ignoring the viral etiology of the disease. Whether this coping strategy may delay psychological healing for many years is a question answered only by long-term follow up of these women.

Health care providers may be acting contrary to the wishes of some of their patients if they choose to order reflex HPV testing (ordered prior to and contingent upon laboratory identification of the cytologic diagnosis of ASC-US) without having discussed in advance the potential implications of a positive HPV result. Although reflex HPV testing is efficient from the laboratory perspective and minimizes patient time and physical discomfort, other factors influence patient preferences, and providers should not assume that this option that will be preferred by all, or even the majority of, patients.

As with any other aspect of patient education, clinicians should ask questions that clarify a patient’s interest in learning more about their condition, offer information relevant to patient needs and desires, and respect the choice of some patients to receive limited information. This issue presents a challenge to clinicians, as it requires skill and sensitivity. Many women with CIN or cervical cancer are surprised and upset upon learning about HPV; among these, some are nonetheless grateful to have this information, whereas others would have preferred not to know. Information about HPV should neither be withheld from patients who might have preferred to know, nor forced upon those who prefer not to know.

A few health plans do not pay for HPV testing, and some women may prefer options for cervical cancer screening that do not explicitly reveal this sexually transmitted infection. Billing women for
a test they do not want or providing information they do not want may promote cancer screening avoidance, especially in those ethnic and socio-economic groups of women most affected by competing life events.

It is therefore essential that information regarding HPV be provided to patients prior to ordering the test. This may be done prior to choosing reflex testing. Alternatively, discussion of follow-up options can take place after an ASC-US result, within the three–week window allowed for performing the HPV test.

The same principles apply to choice of primary screening options. HPV testing combined with cytology is being tested in randomized controlled trials throughout the world for women aged 30 and older. As the evidence for the effectiveness of cervical cancer prevention using this combination of screening tests accumulates, research into effective methods for presenting the options for different screening modalities to women must be done.

**SHARE DECISION MAKING**

Methods for the screening of cervical cancer, and the results of the screening, present many options for patient and provider interaction. The science of Shared Decision Making has shown that patients are more comfortable and less anxious about their diagnosis and management if they understand the disease and their choices for management; if they understand their own values and preferences for the choices of care; and if they are able to participate in the decisions made about their management. Anxiety, decisional conflict, and regret about the outcome are effectively diminished by this communication technique.

Decision aids based on Shared Decision Making for men and women should be developed and tested (ideally, in randomized controlled trials) to determine effective and clear messages to explain HPV and the patients’ choices surrounding the medical conditions it causes. The decision aids must be continually tested and updated to continue to be valuable as new therapeutic options are developed for those with any type of HPV infection, and as type-specific vaccines are offered to those not yet exposed to HPV, providing another option for preventive medical care.

As Anhang and colleagues describe in their article in this issue of CA, replacing the fear of HPV with knowledge and options for care is truly our goal. Let’s not lose sight of it.

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