Human Papillomavirus Testing in the Prevention of Cervical Cancer

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Strong evidence now supports the adoption of cervical cancer prevention strategies that explicitly focus on persistent infection with the causal agent, human papillomavirus (HPV). To inform an evidence-based transition to a new public health approach for cervical cancer screening, we summarize the natural history and cervical carcinogenicity of HPV and discuss the promise and uncertainties of currently available screening methods. New HPV infections acquired at any age are virtually always benign, but persistent infections with one of approximately 12 carcinogenic HPV types explain virtually all cases of cervical cancer. In the absence of an overtly persistent HPV infection, the risk of cervical cancer is extremely low. Thus, HPV test results predict the risk of cervical cancer and its precursors (cervical intraepithelial neoplasia grade 3) better and longer than cytological or colposcopic abnormalities, which are signs of HPV infection. The logical and inevitable move to HPV-based cervical cancer prevention strategies will require longer screening intervals that will disrupt current gynecologic and cytology laboratory practices built on frequent screening. A major challenge will be implementing programs that do not overtreat HPV-positive women who do not have obvious long-term persistence of HPV or treatable lesions at the time of initial evaluation. The greatest potential for reduction in cervical cancer rates from HPV screening is in low-resource regions that can implement infrequent rounds of low-cost HPV testing and treatment.

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Cervical cytology (Papanicolaou test) screening programs have greatly reduced the rates of cervical cancer over the past 50 years (1–3). Evidence from randomized trials now supports the incorporation of prevention methods that explicitly focus on human papillomavirus (HPV), the cause of cervical cancer, into these screening programs (4–6). Proper use of vaccines in adolescent girls to prevent HPV infections, and the addition of HPV testing to screening, can eliminate the need for tens of millions of screening visits every year in the United States alone. Low-cost HPV tests would allow excellent cervical cancer prevention to be extended to low-income women throughout the world (7,8).

To inform an evidence-based transition to a new public health approach for cervical cancer screening, we summarize HPV natural history and cervical carcinogenicity, review the efficacy of currently available cervical cancer prevention methods, discuss how optimal prevention strategies are guided by HPV biology and technology, and describe important remaining uncertainties and concerns regarding the possible misuse of new screening strategies.

HPV Natural History and Cervical Carcinogenicity

HPV Causes Virtually All Cervical Cancer
Persistent HPV infections cause virtually all of the more than 500,000 cases of invasive cervical cancer per year worldwide (9). The 250,000 deaths from cervical cancer reported in 2008 make it the third leading cause of cancer death in women (10). In 2009, the annual rate of invasive cases of cervical cancer in the United States had declined to approximately 11,000 cases per year, with 4000 deaths (11). Nonetheless, billions of dollars are spent per year on the 75 million screening visits and resultant diagnostic and treatment visits to address its precursors, and the many minor cervical cytological abnormalities that are exceedingly unlikely to become cancerous (12,13).

Cervical cancers occur primarily at the cervical transformation zone. The transformation zone is a ring of tissue located where the squamous epithelium of the vagina meets, underlines, and replaces the glandular epithelium of the endocervical canal (Figure 1).

In this review, we focus on squamous lesions, which are the most common and best understood cervical lesions caused by HPV; however, HPV also causes the less common adenocarcinomas and some even rarer histological types (14). In this context, it is worth noting that HPV testing might be especially useful for detection of adenocarcinomas, which can be difficult to find using cytology (14).

Because of its central role in the etiology of virtually all cases of cervical cancer, HPV is correctly called a (virtually) necessary but (generally) not sufficient cause of cervical cancer. With the exception of rare HPV-negative cases, cervical cancer arises via the following distinct and sequential steps: acute infection with carcinogenic HPV type(s), followed by detectable viral persistence (rather than clearance) linked to the development of cervical precancer, and invasion.
Characteristics of HPV

Papillomaviruses are 8000-base pair, double-stranded, circular DNA viruses that can cause warty changes in epithelia from many host species. Papillomaviruses have at most six early genes (involved in viral replication) and two late genes (involved in capsid formation) (15,16). Of the more than 150 HPV types identified, approximately 40 can infect the cervix (17). The varying carcinogenicity of these HPV types for the cervix is related, in part, to the expression of two early genes, the E6 and E7 oncogenes. Among other functions, the E6 and E7 oncoproteins interfere with the functions of tumor suppressor proteins p53 and pRb, respectively. During the carcinogenic process, the HPV genome may integrate into the epithelial cell genome and, during integration, parts of the HPV genome can be lost (18). But continued presence and expression of the E6 and E7 gene regions are needed to sustain cancers and cancer cell lines.

The International Agency for Research on Cancer (IARC) has classified 12 HPV types as group 1 carcinogens (ie, oncogenic or high risk): HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (19). As shown in the evolutionary dendrogram in Figure 2, these 12 HPV types belong to four species in a single evolutionary branch of the alpha genus, and all 12 HPV types can infect the cervix (17,19,21). The same evolutionary branch includes HPV68, an IARC group 2A carcinogen (ie, probably carcinogenic to humans), and several possibly (rarely) carcinogenic HPV types (IARC group 2B). Of the 12 known carcinogenic HPV types, HPV16 is by far the most carcinogenic in terms of numbers of cases of cervical cancer and its immediate precursor, cervical intraepithelial neoplasia grade 3 (CIN3) (22,23). HPV16 also causes most cancers linked to HPV in other anogenital epithelia and in the oropharynx, as discussed elsewhere (24,25). HPV18 is a distant second in terms of etiologic importance (but is disproportionately important for adenocarcinomas) (22).

Time Course of HPV Infection and Cervical Carcinogenesis

The natural history of HPV is the basis for the rational use of preventive measures. We can best build an understanding of the time course of HPV infection and cervical carcinogenesis from the “bottom up” by discussing HPV at three levels: an individual infection, a woman’s experience with HPV during her lifetime, and in a population.

The Natural History of an Individual Carcinogenic HPV Infection. Cervical cancer is typically the culmination of a decades-long process that begins with an infection with a carcinogenic HPV type (Figure 3). We refer to the moment of infection as “time zero” when discussing the subsequent course of infection because the natural history of a truly new infection is fundamentally the same regardless of an individual’s age at incident infection (27,29); for example, neither newly infected teenagers nor 45-year-old women are at immediate risk of cervical cancer.

As shown in Figure 3, half of new HPV infections are undetectable within approximately 6–12 months, and more than 90% clear within a few years (26). The rate of clearance is high within the first months after infection but decreases over time (30).

When a carcinogenic HPV type is detected by HPV testing, a concurrent cytological abnormality is present about one-quarter to one-third of the time (31). Most of these abnormalities are equivalent or, at most, minor. Compared with infection with other carcinogenic HPV types, a woman with an HPV16 infection is most likely to present with serious cytological abnormalities. In general, compared with the cytological and histological changes that accompany a carcinogenic HPV infection, HPV DNA is detected earlier and is detectable for a longer time (32). However, annual screening often misses these subtle temporal differences.

Details regarding the cell-mediated immune response that results in clearance of each HPV infection and its associated cytological abnormalities are largely unknown (33). HPV clearance seemingly results in long-term humoral and/or cellular protection against reinfection with the same HPV type; whether the protection is lifelong is not known. Although the term clearance is used when an HPV infection can no longer be detected using sensitive test methods, HPV might not be completely eliminated; the latent state of HPV is poorly understood.

Reappearance of HPV from “latency” (analogous to recurrent herpes or shingles from varicella), even in the absence of definite immunosuppression (34), is common, especially as women age, but probably benign: In one large prospective cohort, there were no cases of HPV reappearance followed by subsequent overt persistence and CIN3 (27).

By contrast to HPV infections that clear, the cancer risk increases dramatically for the 5% of HPV infections that persist detectably for more than a few years. Such long duration HPV infections are
associated with a high absolute risk (e.g., >40% for long duration HPV16 infection) for later diagnosis of cancer precursors (i.e., CIN3) that span the full thickness of the cervical epithelium (35–37).

The clinical emergence of CIN3 lesions among women with molecularly detectable HPV persistence is gradual; CIN3 lesions that are initially confined to just a few transformed cells are too small for cytological and colposcopic diagnosis. The CIN3 lesions gradually grow laterally within the epithelium over the course of several years (38). Current testing methods and screening intervals in longitudinal cohorts cannot pinpoint the exact moment that a persistently infected cell transforms into CIN3 or exactly when it becomes large enough to diagnosis.

Figure 2. The evolution of human papillomavirus (HPV) types predicts carcinogenicity. The evolution of papillomaviruses is very slow. Tissue specificity, natural history, and carcinogenicity of HPVs are generally consistent with evolutionary relationships. HPV species in the alpha genus (left) infect mucosa, including the anogenital region and the oral cavity. The phylogenetic tree is based on the alignment of concatenated early and late open reading frames as described in Schiffman et al. (20). HPV types in the blue clade (which comprises species α1, α8, α10, and α13) include the HPV types that cause genital warts. HPV types in the green clade (which comprises species α2, α3, α4, and α15) cause commensal infections. HPV types in the red clade (which comprises species α5, α6, α7, α9, and α11) (shown in detail on the right) are associated to different degrees with cervical cancer and cervical intraepithelial neoplasia grade 3. The eight types that most commonly cause cervical cancer everywhere in the world belong to species alpha-9 or, to a lesser extent, to alpha-7. The carcinogen group for each HPV type is according to the International Agency for Research on Cancer (19): group 1 = carcinogenic, group 2A = probably carcinogenic, and group 2B = possibly carcinogenic.

Figure 3. Risks of human papillomavirus (HPV) persistence and progression. Left graph: Proportion of prevalent carcinogenic HPV infections that clear, persist, or progress to cervical intraepithelial neoplasia grade 3 (CIN3) in the first 3 years after first detection, based on all infections found at baseline screening in the Guanacaste Natural History Study (26). The great majority represented “new” infections (27). Persistence without CIN3 is surprisingly uncommon. Uncommon reappearances of HPV types following clearance did not predict risk of CIN3. Right graph: Proportion of untreated CIN3 lesions that invade to cancer within 30 years following the initial diagnosis [based on data from New Zealand (28)].
We do know that CIN3 lesions typically grow slowly over many years before invasion (28,38). It is now clear that the development of CIN3 following a new HPV infection occurs much more quickly than does the development of invasive cancer invasion from CIN3 (38). However, it is not possible to predict if or when CIN3 lesions will break through the epithelial basement membrane into the underlying stroma. The time from infection to invasive cancer is shorter for HPV16 than for other HPV types (39), but determinants of invasion other than HPV type are unknown. Because we know so little about the transition from CIN3 to invasive cervical cancer, CIN3 is treated as soon as it is diagnosed to maximize the safety of affected women (except for delay in some pregnant women).

A Woman’s Lifetime Experience With HPV Infections. The great majority of sexually active women and men have been infected with HPV at least once in their lifetime (40,41). HPV infections are easily (co-)transmitted by sexual contact. A woman might be infected with two HPV types by one partner and become infected with a third HPV type later. One infection could persist after several others have cleared. Although the exact transmission probability per sexual contact or partnership is not known precisely, it has been estimated at approximately 0.5 (42).

HPV persistence is uncommon and represents the critical distinction between benign HPV exposure and substantial risk of cervical precancer. Infection with one HPV type does not influence the likelihood or duration of persistence of another HPV infection in a clinically meaningful way. High rates of HPV persistence estimated (30) in several studies of HPV-induced cytological abnormalities (43–45) are not reliable because sequential infections with different HPV types, each of which could cause morphological changes, were considered persistent in the absence of HPV type–specific testing persistence. Thus, the normal rapid clearance of concurrent and/or consecutive infections was conflated with more serious single-type persistence.

The risk of cervical cancer is powerfully, and almost exclusively, defined by HPV natural history. The risk factors for progression to CIN3 and possible invasive cancer (hereafter referred to as CIN3+) among HPV-infected women include a history of smoking, long-term oral contraceptive use, multiparity, and probably chronic inflammation (46–50). The mechanisms by which these exposures increase risk are not clear. None of the etiologic cofactors that are associated with a two- to threefold increased risk of CIN3 or cervical cancer among HPV-infected women causes cervical cancer in the absence of HPV. Chlamydia infections are probably associated with the risk of CIN3+ only because of coincident sexually transmitted HPV (51).

Host genetics and other influences on host immunity might influence immune response to HPV infection; weak associations of HLA with risk of CIN3+ have been noted (52). Coinfection with HIV is important because HIV-induced immunosuppression impairs cell-mediated immune control of HPV infections (53). Even in the absence of severe immunosuppression, some women might have difficulty clearing HPV infections due to inherited or acquired deficiencies (54).

HPV at the Population Level. For public health planning of cervical cancer prevention efforts, an awareness of the average age distributions of the three increasingly severe stages in cervical carcinogenesis—acute HPV infection, CIN3, and cancer—is essential (Figure 4). The peaks of these distributions vary by

Figure 4. Cervical cancer progression model and optimized prevention strategy. A) The three steps in cervical carcinogenesis are acute human papillomavirus (HPV) infection, HPV persistence associated with the development of cervical precancer (cervical intraepithelial neoplasia grade 3 [CIN3]) in particular, and invasion. Infection and clearance are extremely common and together contribute to the sharp peak of HPV prevalence in the years following average age of first sexual intercourse in the population. The average age at CIN3 diagnosis depends on the intensity of the screening effort in the population. Typically, it takes decades for a CIN3 lesion to grow and eventually invade, although there are rare and rapid exceptions. Panel B schematically displays current and future screening options integrating cytology (C), HPV testing (H), and prophylactic vaccination (V). The current emphasis on repeated cytology screening is inefficient. Even cotesting at 3-year intervals would not be optimal. At some point, an ideal program could emphasize HPV vaccination before average age at first sexual intercourse and reliance on increasingly spaced HPV tests for primary screening (or another equally sensitive method). Note: the prevalence curves are not drawn to scale. The graph shows age-related prevalence of HPV infections (green), CIN2 and CIN3 (blue), and cervical cancer (red) in the United States. Data on HPV infections are based on a summary of US-based HPV prevalence studies (55). The age distribution of CIN2 and/or CIN3 is based on data from Kaiser Permanente Northern California Health Maintenance Organization (P. E. Castle, personal communication) and the data on cancers are from the Surveillance, Epidemiology, and End Results 17 database (56).
geographic region (57,58) and reflect the local average age at first sexual intercourse, given that HPV infection “starts the clock” for the events that follow. A few years after the average age at which women become sexually active, there is a high peak of incident HPV infections usually followed by a gradual decline (57,59); a lower peak of CIN3 occurs 5–15 years later (the peak of diagnosis of CIN3 shifts to younger ages with increasing intensity of a screening program); and the long-drawn-out peak or plateau in invasive cancers occurs over the subsequent decades.

The prolonged time typically required to transition from infection to invasive cancer has two important implications: extremely few rapid-onset cases of cervical cancer occur before the age of 25 years and most cancer diagnoses are made after age 40 years (56). The rapid-onset cases of cervical cancer are intrinsically difficult to prevent by screening and are too rare to determine the starting age and frequency of screening as a public health activity that will affect tens of millions of women. In addition, because of the steep decline in HPV infection incidence and the prolonged time required to develop cancer and with increasing age, new HPV infections that are acquired at older ages contribute little to cervical cancer in populations.

Use of HPV Testing in Cervical Cancer Prevention

In this section, we present the evidence about the performance of existing cervical cancer prevention technologies and discuss how HPV testing can be integrated. We consider all screening and diagnostic tests, including HPV molecular tests, cervical cytology, and colposcopy, as well as histology, to be “biomarkers” of risk of cervical cancer. Ideally, an essential function at each stage of a screening program, including screening, triage, diagnosis, treatment decisions, and follow-up, should be risk stratification. The choice of tests used is likely to change in the coming years as even newer technologies and test combinations are shown to stratify risk more accurately.

Screening

Screening is a public health activity to detect disease among people thought a priori to be well. In the United States, the major cervical screening target is treatable CIN3 (or, to be especially cautious, CIN2), not invasive cervical cancer, for which treatment causes far more morbidity and is less certain to succeed. Therefore, cervical screening distinguishes between the few women who might become patients because they are at highest risk of cancer and the overwhelming majority of women who are at far lower risk. Screening that targets the common, minor, and typically benign cytological and histological evidence of acute HPV infection cannot be cost-effective because the risk of invasive cancer is so low. However, finding a woman with CIN3 is considered a screening success because she has a high risk of invasive cancer and can be treated before cancer develops.

Screening Using Cervical Cytology. We will mention key aspects of cervical cancer screening programs based on cytology, in which exfoliated cervical cells are examined to predict the underlying risk of cervical cancer, as the referent against which other biomarkers are compared. The consistently observed substantial reduction of cervical cancer incidence after introduction of cytology screening and the marked difference in cervical cancer incidence between countries with and without screening programs indicates that Pap testing does prevent cervical cancer (1).

Papanicolaou originally introduced cervical cytology with morphological classifications that were based on probability of underlying cancer (Supplementary Figure 1, available online). However, the current US cytology classification—the Bethesda system—incorporates a view of cervical carcinogenesis that is explicitly based on the natural history of HPV (60). For example, the classification of low-grade squamous intraepithelial lesion (LSIL) is based on microscopic signs of an acute HPV infection, whereas high-grade squamous intraepithelial lesion (HSIL) suggests the possibility of an underlying CIN3 (or the more uncertain precancer diagnosis, CIN2). The great majority of HSIL and approximately two-thirds of LSIL are associated with carcinogenic HPV types (61,62). Very common and equivocal cytological changes, which are classified as atypical squamous cells of undetermined significance (ASC-US), form the boundary between normal and abnormal cytological interpretations; roughly half of changes classified as ASC-US are positive for carcinogenic HPV (63). In the United States, ASC-US is more common than all other abnormalities combined. Because this finding is common and some represent true abnormalities, a sizeable fraction of CIN3+ cases are detected by ASC-US cytology, despite poor interobserver reproducibility (64).

With some noteworthy exceptions (65,66), typically a single cervical cytological screen is insensitive for detecting CIN3; sensitivity estimates as low as 50%–60% have been reported in various settings (67). Although a single negative high-quality Papanicolaou test does indicate a substantially lowered risk of cervical cancer lasting multiple years, stronger reassurance of safety (ie, a high negative predictive value) requires repeated rounds of screening to detect growing CIN3 lesions (68,69).

In many countries, conventional Papanicolaou smears are still the standard of care. In the United States and a few other countries, liquid-based cytology techniques that create more uniform slides and computer-assisted cytology evaluation systems have been adopted to achieve greater laboratory productivity, but there is no evidence that they detect CIN3 more accurately than conventional cytology (70,71); therefore, we do not distinguish among cytological techniques when considering the new role of HPV testing.

Screening Using HPV Tests. There is now overwhelming evidence from randomized clinical trials that carcinogenic HPV DNA screening is more sensitive than cytological screening for detecting histological CIN3 (72–77). Even more important, a negative HPV test provides long-term risk stratification: 5–10 years of reassurance (ie, a high negative predictive value) of not developing CIN3 and even stronger reassurance of not developing invasive cancer among HPV DNA–negative women. High negative predictive value permits safe and cost-effective lengthening of the cervical screening interval when HPV testing is used (78,79) (Figure 5).

Because the vast majority of HPV infections represent acute HPV infections that are destined to clear without causing cancer, HPV testing has mediocre specificity and positive predictive value for cervical cancer screening. Women who test positive for carcinogenic HPV DNA or RNA, especially the first time they are
tested (when the infections might already be persistent), are at sufficiently high risk of CIN3+ to merit intensified scrutiny and follow-up. Current practice in the United States to restrict carcinogenic HPV testing to women aged 30 years or older, who are past the peak of acute HPV infections (Figure 4), results in a higher positive predictive value of HPV testing because a higher proportion have HPV infections that are persistent (3).

Successful risk stratification based on HPV screening depends on whether the infections found are already persistent (and thus possibly high risk) or new (low risk), especially among older women. In this context, proponents of HPV screening have paid insufficient attention to the downstream course of such screening programs. For example, women who test HPV positive 3 years after a negative HPV test [the current recommendation for cotesting (80)] are at much lower risk of CIN2 or CIN3+ than women who are HPV positive at their first screen and, therefore, may already have a persistent infection (Figure 6). This important fact mandates much longer HPV screening intervals than current

Figure 5. Cumulative incidence rate of cervical intraepithelial neoplasia grade 3 or invasive cervical cancer (CIN3+) over 15 years following a single human papillomavirus (HPV) test. A cohort of 20,000 women from Kaiser Permanente (Portland, OR) was followed up by conventional cytology screening for approximately 15 years (78). Archived cervical specimens obtained from the women at enrollment

(baseline) were tested for carcinogenic HPV types. The risk estimates, adjusted for loss to follow-up, show primarily that in this older cohort (average age approximately 35 years), a negative HPV test predicts very low risk of subsequent CIN3+. Baseline test positivity for HPV16, HPV18, or HPV31 was most strongly linked to subsequent CIN3+.

Figure 6. Negative impact of testing for HPV too frequently. We plot the results of HPV testing performed at two time points (at enrollment \([t = 0]\) and at year 3) in women enrolled in the Guanacaste Natural History Study; disease ascertainment occurred annually. The cumulative incidence rate of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) is shown for women testing positive and negative at enrollment and again for women testing positive and negative at year 3 among those who tested negative at enrollment (27). The risk stratification of the first HPV test is excellent, but the second test is less effective in detecting prevalent disease if performed too soon. Testing HPV positive for prevalent HPV infections predicts an elevated risk of CIN2+ (the treatment threshold) found before the screening at year 3, whereas testing HPV negative predicts a very low risk. Among women with an HPV-negative test at enrollment \([t = 0]\), those who test HPV positive 3 years later (i.e., at the currently recommended interval) are at much lower risk of CIN2+ than women who were HPV positive at the first screen and who may already have a persistent infection.
cytology screening intervals of every 2 years and suggests that the current 3-year interval for cotesting (see below) will still be too frequent. The corollary of high sensitivity of HPV testing for incipient as well as prevalent CIN3+ is a high negative predictive value that lasts for years. Although the ability to lengthen screening intervals is a great advance, it poses a major challenge for transition from cervical screening programs that are based on repeated cytology. In particular, in the United States, the considerable general reluctance to move to long-interval screening is due at least in part to reasons unrelated to theoretical best public health practice. By contrast, in some European settings, where cervical cancer screening practices are dictated more directly by public health considerations, detailed planning is underway for a transition to long-interval HPV testing (81).

The variety of HPV tests that are currently available is shown in Table 1. HPV tests rely on detection of overt, current infection through DNA or, more recently, RNA testing, because there is no clinically useful serological assay of HPV exposure or susceptibility. The two major methods for detection of carcinogenic HPV DNA are hybridization with signal amplification and genomic amplification using polymerase chain reaction or other techniques. Currently, the workhorse of HPV testing in the United States is a Food and Drug Administration (FDA)–approved hybridization method, Hybrid Capture 2 (HC2; Qiagen Corporation, Gaithersburg, MD) (82). To date, HPV DNA detection by polymerase chain reaction–based methods have been used mainly for research. They typically have used a pool of primers for broad-spectrum amplification of HPV DNA followed by specific detection of target HPV types using type–specific hybridization probes (83). The best-validated HPV tests (Table 1) have reasonably comparable performance (i.e., they are more reproducible than interpathologist comparisons of the distinction between normal and abnormal cytology), but there are exceptions.

HPV testing has an apparently unavoidable trade-off between sensitivity and specificity. Acute HPV infections are common and usually benign; therefore, the sensitivity–specificity trade-off is far different for HPV testing than it is for screening of pathogens like HIV, for which the sensitivity of the first test (indicating the need for confirmation assays) is paramount.

Optimizing the clinical specificity of HPV testing while maintaining its sensitivity for detecting CIN3+ requires careful choices about which HPV types are targeted and the threshold for a positive result. First, inclusion of common HPV types that cause CIN3 and more minor lesions but rarely if ever cause cancer (e.g., HPV53 and HPV66) in an HPV test increases the number of false positives but has little population benefit (84). As an analogous point, HC2 cross-reacts with some noncarcinogenic HPV types, which decreases its specificity (85). Second, the threshold for a positive test should be chosen in clinical validation studies to maximize the sensitivity–specificity trade-off for CIN3+ rather than for a less severe diagnostic reference. Because CIN3 lesions are initially tiny and difficult to detect visually, positive HPV tests that appear to be false positive when judged against cytology or same-day colposcopic biopsy tend to predict elevated risk (true positive results) of subsequent CIN3+ over the following decade or more (86). Therefore, the diagnostic reference should be CIN3+ diagnosable during the subsequent interval (at least until the next screening visit) and not just cases detectable by colposcopy at the time of testing.

Commonly used HPV tests have not completely optimized the threshold for positivity in cervical screening of general populations. A slightly higher threshold for HC2 positivity would reduce the influence of cross-reactivity with noncarcinogenic HPV types (87) and eliminate the effect of low–viral load HPV infections that bear little risk of clinical disease, thereby stratifying risk even more efficiently than does the current threshold for positivity (88). In this same regard, the limited available data on the second FDA-approved HPV test—Cervista (Hologic, Bedford, MA)—are concerning. In the earliest comparisons of Cervista with HC2, two- to threefold more women were called HPV positive with Cervista, but without concomitant gain in sensitivity for CIN2+; the use of Cervista in cervical cancer screening is questionable until this discrepancy can be understood and resolved (89).

HPV test results are interpreted as either positive or negative. When the result is positive, there is a temptation to view the viral load measurement as a kind of “dose effect”; however, the use of higher HPV viral load measurements for clinical decision making is not FDA approved and should be avoided. A higher HPV viral load is only a weak predictor of CIN3 (90,91). Acute (“productive”) HPV infections tend to have a very high viral load, whereas many women with small CIN3 lesions (in which the acute infection has cleared) have low viral loads (90,91).

Screening Using Cotesting With Cytology and HPV Tests: the Kaiser Permanente of Northern California (KPNC) Experience. To our knowledge, there is only one large US experience with HPV testing in primary cervical screening: the KPNC experience (81,92). The basis of the KPNC approach is the recognition that, when both cytology and HPV tests are negative, the high negative predictive value for subsequent risk of CIN3+ permits extension of screening intervals. In 2003–2005, KPNC adopted the FDA-approved cotesting strategy of cytology with HC2 as an alternative screening method to routine (annual or biennial) cervical cytology alone for women aged 30 years or older (who are past the peak of acute infections), with a policy that women who tested negative for both assays would not be rescreened before 3 years. Subsequent experience with more than 1 million cotests has shed light on the practicality, advantages, and potential pitfalls of cotesting (92).

The transition from annual cytology to cotesting at 3-year intervals has proven to be acceptable to patients and providers. Currently, 95% of women opt for cotesting. Determining how to manage women with HPV-positive and cytology-negative screening results, the most common discordant finding, is a major remaining challenge to the widespread use of cotesting. The risk of CIN3+ in women who are HPV positive and cytology negative is much greater than it is among HPV-negative women but remains low in absolute terms. The risk does not justify immediate colposcopy; and, referring all HPV-positive women (4% of all screened women aged 30 years or older in KPNC) would roughly double the colposcopy rates compared with referral of only women with ASC-US or worse. In an effort to avoid unnecessary procedures and overdiagnosis, KPNC defers colposcopic referral among HPV-positive cytology-negative women in favor of repeated
Table 1. Human papillomavirus (HPV)-based tests*

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* CE = Conformité Européenne (European conformity); FDA = Food and Drug Administration; FISH = fluorescence in situ hybridization; IVD = in vitro device; n/a = not available; NASBA = nucleic acid sequence–based amplification; PCR = polymerase chain reaction; sFDA = State Food and Drug Administration (China); TMA = transcription-mediated amplification.

† Cross-hybridization with noncarcinogenic HPV types described.
cotesting at 1 year. Many acute infections resolve without treatment, but some cases of CIN3+ are likely missed, especially if women do not return for testing. Therefore, other biomarkers besides cytology would be desirable as a triage test to identify which women need immediate colposcopic (diagnostic) evaluation.

**Triage**
Triage is similar to cotesting except that a second test is performed in the laboratory only if the first (screening) test gives an equivocal result. Cost and logistics (eg, the feasibility of women returning for a triage visit) are the determinants of whether cotesting is superior to triage.

**Cytology With Triage by HPV Testing.** In its first FDA-approved clinical use, HPV testing was demonstrated to be an effective triage option for ASC-US cytology results (93,94), which account for approximately 3 million cytological interpretations per year in the United States. Risks of CIN3+ in women with HPV-negative ASC-US (approximately 50% of all women with ASC-US are HPV negative, depending on the pathologist) and women with negative cytology are similar (95). Appropriately, in the United States, the majority of ASC-US cytology interpretations are now triaged using HPV testing. Nonetheless, standard practice following HPV negativity at triage is annual rescreening rather than a complete return to 2-year routine screening intervals (68). The heightened clinical attention given to HPV-negative ASC-US, despite the low risk of CIN3+, is an example of the difficulty of “doing less” once a more intensive management strategy is established and has become routine for patients and providers.

Less certain is the utility of using HPV testing for triage of cytological interpretations other than ASC-US, such as LSIL, “atypical squamous cells, cannot exclude HSIL (ASC-H)”, atypical glandular cells, and HSIL. Although most women with LSIL are positive for carcinogenic HPV types, triage of women older than 45 or 50 years who have LSIL cytology with HPV testing may be effective because a high percentage of older women will be reassured after a negative HPV test indicates very low risk (63,96). The risk of CIN3+ in women with ASC-H cytology who are HPV negative is elevated enough that triage by HPV testing is rarely done (92,97). HPV test results for women with atypical glandular cells cytology may not be useful for triage but may guide clinicians to the anatomical site—cervix or endometrium—where a problem may exist: for postmenopausal women with atypical glandular cells cytology, those who test HPV positive have exceptionally high risks of prevalent cervical precancerous lesions and cancer, whereas those who test HPV negative have a high risk of prevalent endometrial neoplasia (98).

**HPV Screening With Triage by Cytology.** Primary HPV testing without cytology will be nearly as sensitive as cotesting; however, too many women would be sent for colposcopy because of the mediocre specificity of HPV testing. Triage of women who have a positive HPV test with cytology is more economical than cotesting all women with both tests. However, cytology is also an imperfect second test for triaging HPV-positive women; an abnormal cytology finding (especially HSIL) further increases risk (positive predictive value) of CIN3+ among HPV-positive women, but their risk remains substantial after a negative cytology triage result. Therefore, at least in the United States; HPV-positive cytology-negative women require some kind of intensified follow-up before resumption of routine screening.

**HPV Screening With Triage by Novel Biomarkers.** Although novel biomarkers measuring the interaction of HPV with cervical cells may one day become the basis of primary screening tests, they will first be used to triage women with positive cytology and/or HPV tests. Most of the biomarkers identified thus far are markers of HPV-associated transformation, which occurs after HPV infection, and they are more prevalent in CIN3 than in acute infection. Because they indicate infections that have already led to CIN3, they cannot provide quite as long a period of risk stratification (particularly negative predictive value) as does HPV DNA. Currently developed biomarkers can be grouped as follows: 1) markers of increased HPV oncogene expression, such as HPV oncogene mRNA and protein; 2) markers of increased cell proliferation, such as Ki-67, MCM2, TOP2a, and p16; and 3) markers of chromosomal instability, such as a gain of chromosome arm 3q and HPV DNA integration (99–101).

At present, the most promising candidate as a biomarker for triage after a positive HPV test is immunocytochemical staining of Ki-67 that was recently introduced into the diagnostics market can highlight rare transformed cells (105). Because its sensitivity for CIN3 is far higher than cytology’s and almost equal to that of HPV testing and its specificity is comparable to cytology’s, this stain could be used as a triage following primary HPV testing if it proves reliable and the cost for routine use is low (105).

**Diagnosis of Screen-Positive Women**

**Colposcopy and Biopsy.** Diagnosis and treatment are intrinsic to any screening program. Therefore, any review of HPV testing should consider what happens to women who screen positive, whether by a single test, cotesting, or triage. Currently, the magnified colposcopy examination and biopsy result determine how screen-positive women are managed and treated (eg, excision of the entire transformation zone thought to contain a CIN3).

The current poor performance of colposcopic impression, colposcopically-guided biopsy, and histological diagnosis (56) limits the potential benefit of very sensitive screening tests (eg, primary HPV or other molecular tests) (86,106). The typical current practice of targeting the most worrisome lesion on magnified visual inspection misses more than one-third of prevalent small HPV-positive CIN3 lesions (107).

Like cytology, colposcopy was developed in an era when detection and diagnosis of larger CIN3 lesions and even cancer were paramount. In the United States and similar settings today, due to high screening coverage and treatment, sensitivity for very small CIN3 lesions, which constitute most disease that is now found, is considered important. The shift to less severe disease challenges the performance of colposcopy. For example, some data have demonstrated the poor reproducibility and inaccuracy of colposcopic...
grading using grading systems, such as the Reid Index (106,108,109), for distinguishing between acute HPV infection and CIN3.

Intercolposcopist agreement as to where a cervical biopsy sample should be taken is also mediocre (86,106). Gains in sensitivity of colposcopically directed biopsy can be obtained by increasing the number of biopsy samples that are taken (107,110,111), regardless of the experience of the colposcopist. Biopsies should target acetowhite areas; the only visual diagnostic criterion with sufficient sensitivity for prevalent precancer is acetowhiteing, but the specificity of this visual finding is very low (106). Thus, colposcopy protocols based on biopsy samples from many if not all distinct acetowhite lesions on the cervix may improve the sensitivity of colposcopy and the accuracy of diagnosis of CIN3+. For example, the difference between finding CIN1 and normal histology, or between finding CIN2 and CIN3, in an HPV-positive woman might be due to misclassifications reflecting the technical limitations of colposcopy.

Histology. Histology provides the reference standard for cervical disease. At present, histology is based on morphology and does not consider HPV biomarkers. Advancing grades of CIN (grades 1–3) are distinguished mainly according to the amount of vertical extension of abnormal cells in the cervical epithelium. Abnormal cells restricted to the lower third are designated CIN1, abnormal cells restricted to the lower two-thirds are designated CIN2, and full-thickness extension of abnormal cells are designated CIN3. This division is arbitrary. Currently, a histologically confirmed CIN3 lesion is a clear indication for surgical treatment. Because diagnosed CIN2 is known to be a mixture of acute infections and evolving CIN3, its management is more heterogeneous. For example, a woman in her early 20s with a CIN2 lesion might be managed with close follow-up (69).

The lack of reproducibility of cervical histological classifications is an important source of error and poor performance because the distinctions guide treatment. Even when excision and processing of the entire cervical transformation zone removes possible error due to location of the colposcopic biopsy sample, CIN1 and CIN2 diagnoses are difficult to distinguish, leading to high inter- and intraobserver variability (112–114). CIN1 is a poorly reproducible, morphological correlate of acute HPV infection. CIN2 is biologically heterogeneous and includes both acute HPV infections and incipient CIN3. Because vertical extension of abnormal cells in the cervical epithelium, and not lesion size, is the primary criterion for morphological grading, small CIN3 lesions are combined with the larger CIN3 lesions at higher risk of invasion for patient management.

As another aspect of the heterogeneity of histopathologic diagnoses, it is worth noting that the diagnoses are summarized to give the worst finding found on the examination of all cervical tissue from a woman. However, the cervix may harbor multiple lesions of various grades and sizes at the same time (see Figure 1).

The accumulated evidence regarding cervical histopathology suggests that CIN3 is the most reliable surrogate of cancer risk, especially when accompanied by a description of lesion size because large lesions are most likely to invade (38). Eventually, we should aim to triage CIN2 lesions and to phase out the use of the term CIN1 in favor of molecular rather than histopathologic evidence of acute HPV infection.

Use of HPV Testing During the Diagnostic Phase. At any stage in a cervical screening program, a negative HPV test, in contrast to negative cytology, provides substantial and sustained negative predictive value. Under current clinical guidelines (69), women who are referred to colposcopy for minor HPV-related abnormalities should have repeat HPV testing at 1 year or cytology every 6 months if the colposcopy visit yields no CIN2 or worse (CIN2+) histological lesion. As we emphasize elsewhere in this review, however, frequent HPV testing provides little value: HPV testing at 6 months is too soon to judge viral persistence or to evaluate risk of subsequent CIN3+. Adding cytology to HPV testing at 1 year adds cost but not sensitivity (115).

Treatment

Usual Threshold for and Mode of Treatment. A willingness to avoid even small risks of invasive cancer has led to low diagnostic thresholds for treatment (ie, CIN2+ or even persistent CIN1) (69,116). More sensitive screening tests and more aggressive colposcopy protocols will increase the detection of the smallest, earliest (CIN2 and) CIN3 lesions, which have the highest likelihood of spontaneous regression. Screening programs that exploit the extra sensitivity for CIN3+ conferred by HPV testing must still minimize treatment of women that is unnecessary on both public health and individual grounds.

In the United States, the predominant mode of treatment for CIN2 or CIN3 is the excision of the transformation zone using a wire loop cautery, commonly known as loop electrosurgical excision procedure (LEEP) or large loop excision of the transformation zone. This office-based procedure has two advantages: it can be performed under local anesthesia and it produces a tissue specimen. The concern over the risk of premature delivery following this treatment (117) motivates recent efforts to reduce overscreening and overtreatment, especially among young women. However, the societal trade-offs that come from trying to prevent every case of cervical cancer, vs the desire to prevent overtreatment of many women, should and will be debated.

Use of HPV Testing to Monitor Success of Treatment. HPV testing following treatment with LEEP can identify women who remain at high risk of recurrence (118). Successful treatment of the transformation zone often leads to HPV negativity in cervicovaginal specimens for the causative HPV type (119), although HPV infects the vagina (and vulva and anogenital skin) and not just the cervix. The reason for viral clearance even when the excision heals, thus creating a new transformation zone, is not certain. Nonetheless, negative HPV tests after LEEP predict a high probability of cure (118). Thus, an HPV test can be used to replace cytology for this clinical role with greater sensitivity and negative predictive value (reassurance).

Key Elements of Optimal Cervical Cancer Prevention

Panel B of Figure 4 summarizes optimal cervical cancer prevention from a public health perspective based on our current understanding of HPV natural history, multistage cervical carcinogenesis, and the performance of preventive technologies. Vaccinating girls against the carcinogenic HPV types a few years before the median age of first sexual intercourse in the population should
eliminate the peak of HPV transmission that leads, eventually, in some women to CIN3 and, in even fewer women, to cancer. The cost-effectiveness of HPV vaccination at older ages decreases substantially because these women are more often exposed and immune to carcinogenic HPV types, more often have a prevalent infection that will not be affected by a vaccine, and are less likely to be exposed to HPV subsequently (120). Because HPV exposure decreases with increasing age and new HPV infections are no more dangerous among older women than among young women, vaccination of older women with such an expensive vaccine is not the best public health practice; the maximum age for which vaccination should be indicated is debatable and specific to different settings. In the absence of accurate HPV serology, there is no way to know which women have been exposed to HPV or who remains susceptible to HPV infection (121).

The successful introduction of HPV testing into screening would require that such screening begin at ages 25–30 years rather than at 21 years, as is the current practice for cytology in the United States, and that screening intervals among women who are found to be HPV negative increase substantially. The HPV screening interval for women after repeated negative screens could, and eventually should, extend beyond 3 years. Screening could be stopped altogether among women with a proven repeated history of HPV negativity who reach an age still to be determined mainly by societal expectations when their risk of cancer is sufficiently low.

Longer-Term Uncertainties in the Transition to HPV-Based Screening Technologies

In the first section of this review, we presented the evidence of HPV and cervical carcinogenicity. In the second section, we outlined the technical performance of each of the cervical cancer prevention technologies. On the basis of these facts, we outlined the currently optimal design of cervical cancer prevention programs from a public health perspective. However, cervical cancer prevention is also a social and political process. In this final section, we describe the remaining uncertainties and barriers to the adoption of HPV-based screening technologies.

Integration of HPV Screening With HPV Vaccination

The thoughtful introductions of HPV screening and HPV vaccination require consideration of how they complement each other. The two licensed HPV prophylactic vaccines—Gardasil (Merck) and Cervarix (GlaxoSmithKline)—have very high and proven efficacy against new infection with HPV16 and HPV18 and the resultant CIN2 and CIN3 lesions (122,123). They also confer partial protection against HPV31 (which is closely related to HPV16) and HPV45 (which is closely related to HPV18). Within the next few years, augmented prophylactic vaccines that prevent virtually all carcinogenic types of HPV infection may be licensed. The proven duration of protection of a three-dose regimen of HPV vaccination is now approaching a decade based on follow-up of vaccine trial participants. Thus, vaccination of girls before the median age of first sexual intercourse in the population would eliminate much of the peak transmission of HPV. High population coverage with an effective multivalent HPV vaccine will be the best primary preventive strategy against CIN2+, including cervical cancer.

However, HPV vaccination will not help older women who are beyond the age of vaccination or women who have an HPV infection present at vaccination (124).

Meanwhile, in a world of increasingly restricted health resources, cervical screening must be reduced in HPV-vaccinated populations to maximize net public health benefits. As HPV vaccination increases, carcinogenic HPV infections and their associated CIN3+ lesions will become rarer, and almost all abnormal cytological results will be ASC-US or LSIL predicting only a low risk of cancer (125,126). As a matter of public health policy, we do not screen for rare diseases even in the United States. HPV vaccination will further strengthen the argument for less frequent screening than occurs in routine practice today and for accelerating the switch from increasingly ambiguous cytology to HPV testing.

Moving From Clinical Algorithms to Risk-Based Management

In the United States, clinical guidelines from professional medical organizations provide recommendations for cervical cancer screening, the management of women with an abnormal screening test, and treatment (68,69). These recommendations are usually developed through consensus meetings that review the evidence and, when possible, develop evidence-based guidelines. Of note, in the United States, cervical cancer screening is often viewed as a clinician–patient decision, not as a public program as it is in some other countries. Clinicians and patients may view a particular level of risk and cost differently from public health planners who are faced with limited resources.

In any case, the introduction of new HPV tests with varying test performances, new biomarkers, and the HPV vaccine will eventually make clinical algorithms regarding cervical screening and management of screening abnormalities untenably complex (95,127) and quickly out of date. Each round of revised algorithms will need to account for past virological, cytological, and histological test histories (27,128), as well as the results of any novel tests that emerge.

Compared with branching algorithms, a properly constructed and validated risk assessment tool would be more powerful and easier to update and use for clinical decision making, even for clinician–patient discussions (95,127). The estimated risk of CIN3+ (eg, if colposcopy were performed that day, or in 1 year, or at a 3-year follow-up) is the relatively objective, quantifiable outcome that scientists can provide as the basis for cost-effective clinical and public health decisions.

Initially, such risk estimates will be most helpful to clinicians in practice settings with good continuity of care and long-term medical records. Risk-based screening and management (at the clinical or population level) would be dictated by the risk range or risk band into which the risk estimate falls (Figure 7). These risk bands, which would be defined by the lower and upper thresholds of each band, would be established by professional medical societies that have considered the evidence related to the benefits and potential harms for each level of intervention. Risk estimates, updated with most recent test results, would be the basis for choosing the appropriate step to take after the most recent set of tests: 1) when the woman should next be screened; 2) whether a woman should be referred immediately for a colposcopically directed biopsy; and...
Review around specific risk-based questions, such as “What would be the useful and focused comparative effectiveness research structured serving as the main surrogate of invasive cancer) permits very health interventions in terms of well-defined risks (with CIN3 HPV natural history and cervical carcinogenesis. Framing public algorithm-based perspective, relying on a current understanding of components of vaccination and screening, is a public health activity, not an clinical activity. We have emphasized a risk-based rather than an prevention, with its core components (vaccination and screening, is a public health activity, not a clinical activity. We have emphasized a risk-based rather than an algorithm-based perspective, relying on a current understanding of HPV natural history and cervical carcinogenesis. Framing public health interventions in terms of well-defined risks (with CIN3 serving as the main surrogate of invasive cancer) permits very useful and focused comparative effectiveness research structured around specific risk-based questions, such as “What would be the change in programmatic effectiveness of shifting from cytology every 2 years to cotesting every 5 years?”

The public health perspective necessarily must consider costs and cost-effectiveness of cervical cancer prevention strategies, not just comparative effectiveness (ie, benefits and harms). For comparably effective benign interventions, the question is simple: “Does one approach cost less for the health care system?” However, there is usually a trade-off between cost and effectiveness, given the multiple outcomes—lives saved, morbidity, age at cancer incidence or death, economic or family impact, iatrogenic adverse events—one might consider. This trade-off forces a consideration of the societal value of preventing a cancer or cancer death. Because the proportion of women in the general population who are truly at high lifetime risk of cervical cancer is so low, a screening test must incorporate triage or follow-up before treatment to achieve the high specificity necessary for a high positive predictive value. In other words, any cervical cancer screening program must weigh the impact of false-negative screens (ie, cancer risks associated with a missed CIN2 or CIN3 lesion) vs the impact of many more false positives (ie, the harm of telling someone her result is abnormal, with adverse effects possibly including treatments that may increase the risk of subsequent premature delivery).

Determining the specific value of a single life is a social issue beyond the scope of this scientific review. Clearly, however, assigning an infinite value to a single life regardless of the financial cost, if extended broadly as a policy, will undermine any public health–oriented consideration of the opportunity for other public health benefits from the same financial investment.

**Prevention of Cervical Cancer in the United States**

From a scientific and public health perspective, we conclude that cervical screening intervals can be safely extended by incorporation of HPV testing. However, such a change is not likely to happen soon in the United States, where cancer prevention policies are only partly dictated by evidence regarding optimal practice. It is notable that current evidence-based guidelines for cervical cancer screening and management are being widely ignored in the United States (13). Each interest group with input into policy, including various government agencies, has its own mandates and constraints. Much of screening practice is dictated by clinical groups; in considering clinical recommendations, we should not ignore that the economic threat to practicing gynecologists and cytologists inherent in reducing the amount of screening is real. Also, it is essential for all to acknowledge, when advocating an extension of screening intervals or other incremental improvements, that no prevention strategy is perfect. Demanding perfect safety would doom the rational introduction of HPV technology.

**Prevention of Cervical Cancer in Low-Resource Settings**

In this review, we have focused on the incorporation of HPV testing in wealthy countries like the United States. However, cervical cancer is associated with poverty even in rich countries (119), and 90% of deaths from cervical cancer worldwide occur in developing countries (10,129). Despite its high-technology roots, HPV testing will likely save far more lives in low-resource high-risk populations where no preventive health-care structure is in place (76) than in rich nations. The high sensitivity of HPV DNA
testing indicates that one or two screens in a lifetime, between approximately age 30 years and menopause, would be sufficient to make a major impact on mortality (130). Most women (80%–90%) will test HPV negative and gain reassurance for at least 10 years that they are at low risk of cervical cancer; women who test HPV positive will be immediately treated. An expanded discussion of HPV testing for low-resource settings, including information on the first low-cost HPV test, is presented as Supplementary Material (available online).

Conclusions

This review of the introduction of HPV testing technology into cervical cancer prevention in the United States is a microcosm of the health-care reform debate. In terms of cost-effectiveness (pending definitive analyses), we could likely improve cervical cancer prevention by replacing frequent cytology examinations with HPV vaccination and HPV screening. However, the societal issues involved in such a change, which would affect tens of millions of women per year, will likely take decades to sort out; meanwhile, lives may be lost (even in the United States), innumerable women will be overtreated, and billions of dollars will be spent unnecessarily. Now that the sensitivity of HPV tests is beyond question, waiting for results of randomized clinical trials of the various possible HPV screening and management protocols relative to cytology would risk postponing health benefits for many women. Where practical, and following proper regulatory approvals, we advocate implementation of HPV tests as the primary cervical screening test in a well-controlled and evaluable fashion that will allow the best strategies to be sorted out as HPV-based screening (and vaccination) methods continue to improve [eg (81,131)]. As we start to use HPV testing for the key function of screening—risk stratification—what we need most is to determine how best to 1) make use of negative HPV tests to lengthen screening intervals substantially and 2) manage women with positive HPV tests while avoiding overtreatment.

To save the most lives, HPV testing should be adopted worldwide, especially in low-resource settings where the burden of cervical cancer is the greatest. Now that practical tests are available, the most pressing need is for simple and inexpensive treatments for HPV infections to permit optimal screen-and-treat programs in the poorest places, where women are most threatened by invasive cervical cancer.

References


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