PAPILLOMAVIRUS INFECTIONS OF THE HUMAN GENITAL TRACT

Papillomaviruses (PVs) form the family Papillomaviridae, a diverse taxonomic group of DNA tumor viruses that coevolved with a variety of animal hosts over millions of years.1 PVs have similar or colinear genomic organizations but their nucleotide sequences can differ by greater than 50%. PV infections can be asymptomatic, cause benign hyperplasias (eg, warts) or malignancies.

Human papillomaviruses (HPVs) are part of the family Papillomaviridae, and those viruses infecting the human genital tract are in the genus Alphapapillomavirus.2 A phylogenetic tree representing the relationships between a subset of Alphapapillomavirus is shown in Fig. 1. Over 100 HPV types have been identified to date, of which over 40 infect the genital tract. A new PV isolate can be established if the complete genome has been cloned and the DNA sequence of the L1 open reading frame (ORF) differs by more than 10% from the closest known PV type. Differences between 2% and 10% nucleotide sequence homology define an HPV subtype and less than 2% a variant. HPVs primarily target infections of the basal cells in the stratified squamous epithelium and metaplastic cells within squamocolumnar junctions. In the squamous
epithelium, their life cycles are linked closely to differentiation factors expressed within various layers of infected cells, although the biology of infections in other cell types, including glandular cells that do not have multiple stratified layers, has not been described.
HPV genomes generally encode eight ORFs. The E6 and E7 ORFs encode what have been described as the primary HPV transforming or oncoproteins. The retinoblastoma tumor suppressor protein (pRB) and p53 are the two host proteins whose role in the transformation process has been the focus of a number of studies. During the infectious process, HPV E6 and E7 inactivate or interfere with a number of requisite host regulatory functions, including those served by pRB and p53. In women who have persistent HPV infections, over expression of HPV E6 and E7 and associated host cell genomic instability can occur. It is unknown what triggers this outcome and the necessary cofactors in the process to this day are not well understood. Early dogma proposed that in some women, HPV infected cells were lethally deregulated as a result of disruption or deletion of the HPV E2 protein during integration of HPV genomes. Integrated HPV forms commonly detected in HPV-related malignancies often demonstrated E2 ORF disruption at the viral integration insertion site. One function of E2 is to act as a transcriptional regulator of HPV E6 and E7 expression. Over time, our understanding of HPV-related host cell transformation has revealed a complexity beyond the simplistic view of requirements for HPV integration associated with E2 loss, subsequent E6 and E7 over-expression, and a resultant host genomic instability from which a clonal malignancy could arise. For example, not all HPV-related malignancies have integrated viral forms detected. Even if HPV integrants are detectable, most HPV-related severe abnormalities, including cancers, harbor many HPV episomes (ie, extrachromosomal HPV genomes) with intact E2 ORFs. Model in vitro systems have now demonstrated that even low copy numbers of HPV episomes have the ability to express E2, which can regulate E6 and E7 expression in trans on integrated HPV genomes. Furthermore, HPV proteins have been found to interact with a wide spectrum of host regulatory proteins beyond p53 and pRB. Ultimately, many complex HPV-induced changes within infected host cells, including genetic and epigenetic alterations (eg, methylation) can, when infection persists, result in overall genetic instability and clonal malignancy. It is likely that viral integration of oncogenic HPV genomes in cervical lesions is a consequence rather than the cause of chromosomal instability induced by deregulated HPV E6-E7 oncogene expression. Data support differences in the induction of chromosomal instability by various high-risk carcinogenic HPV types, which is reflected by their integration frequencies in advanced lesions and the transit time for lesions to progress to invasive cancer.

Genital HPV infection

Genital HPV infection is estimated to be the most common sexually transmitted infection; an estimated 6.2 million persons are newly infected every year in the United States. Infections with multiple HPV types (coinfections) are common (approximately 50%) principally because of their shared primary route of sexual transmission. The many different genital HPV types appear to infect, resolve, or persist, and cause cervical intraepithelial neoplasia (CIN) including low- and high-grade CIN (≥ CIN 2), and in some cases cancer, independent of each other (ie, in general infections with multiple HPV types do not seem to affect type-specific outcomes in a positive or negative manner). Sexual intercourse is not the only means for transmission of genital HPV, although other modes are believed to be very uncommon. Neonatal transmission has been reported, although detection of genital HPV infections in children beyond times closely related to actual birth and delivery remains controversial. Most studies have not detected genital HPV infections routinely in either the oral cavity or genital areas of children. In a longitudinal study, virginal women were shown to have a 2-year
cumulative HPV infection rate of 2.4%, and among those in those engaging in nonpenetrative sexual contact, approximately 10% were positive for HPV.\(^{13}\)

In Northern Europe\(^{14,15}\) and the United States,\(^{16,17}\) peak genital HPV prevalence appears generally under age 25 and decreases with increasing age. In these same regions, studies of young women who have recently become sexually active have detected a very high cumulative incidence of HPV infection (eg, about 50% in 3 years).\(^{13,18}\) It has thus been generally presumed that the vast majority of HPV infections are acquired in the first few years after sexual debut and that HPV prevalence steadily declines thereafter as a result of spontaneous clearance of prevalent infections. In a few studies, a second peak of HPV infection has been observed in older women, raising the possibility that the age distribution of HPV infection might vary within different populations.\(^{19,20}\) The distribution of HPV prevalence in representative samples of women from 15 areas in four continents has in fact revealed substantial variation in the shape of age-specific curves of HPV prevalence.\(^{21}\) In surveys conducted by investigators at the International Agency for Research on Cancer (IARC), steady declines in HPV prevalence were observed with increasing age in the highest-income countries. In contrast, a flat age curve was observed in the lowest-income areas of Asia and in Nigeria, where HPV prevalence was similar across age groups. Three areas in Latin America (Chile, Colombia, and Mexico) revealed a U-shaped curve of age-specific prevalence (ie, a second peak of HPV infection was observed in older women). Further research is needed to understand the role of screening and other reasons for the differences in age-related HPV prevalence observed in different settings.

Longitudinal studies have consistently shown that most HPV infections are no longer detectable within 1 to 2 years following initial observation.\(^{10}\) About 50% of HPV infections in women with normal cytology will have resolved in less than 1 year, and approximately 90% of women with either normal or CIN 1 diagnoses will ultimately resolve on their own.\(^{22,23}\) In fact, most HPV infections are asymptomatic and so transient that most individuals have no idea that they are infected.

For clinical purposes, HPV infections associated with normal cervical cytology and those associated with low-grade CIN (CIN 1) are considered essentially the same.\(^{24}\) Resolution or clearance of any HPV type appears to result in immunity to that type, at least based on available evidence from ongoing prospective cohort studies. It is unknown whether HPV infections can become dormant in basal cells and if so, whether future downstream reactivation of so called “latent HPV” genomes occurs. At present it is impossible to distinguish reactivation from newly acquired HPV infections and, therefore, any contribution of potential HPV reactivation to disease outcomes remains unclear.

Although cumulative HPV exposure is difficult to quantify because nearly all HPV infections are transient and HPV serology is inaccurate (ie, only about 60% of women with known HPV infections ever develop detectable HPV-specific antibodies), a substantial proportion of HPV DNA-negative, seronegative women have been exposed. A majority of women in the world are probably infected with at least one if not several types of HPV during their sexual lifetime; however, only few will progress to high-grade disease, including cancer.

In the subset of women who are diagnosed with invasive cervical cancer, the cause is virtually all attributable to persistent cervical infection with 1 of approximately 15 carcinogenic HPV types.\(^{25}\) HPVs are a necessary cause of both squamous cell carcinoma and adenocarcinoma, although HPV genotype distributions and the role of nonviral cofactors seem to differ by histologic type.\(^{26–28}\) Rapidly invasive cancers are rarely diagnosed in young women, as the transit time from initial HPV infection to
invasion is believed to be on average greater than two decades. Nevertheless, prevention strategies in a number of countries are often formulated to prevent these cases in young women. Well-organized cervical cancer screening programs in many developed countries have reduced the incidence of squamous cell carcinoma of the cervix over the past few decades, although adenocarcinoma of the cervix has been increasing in some countries\(^{29,30}\) for reasons that have not been fully defined.

HPV type 16 is the most common carcinogenic HPV type and is detected in approximately 50% of high-grade squamous intraepithelial lesions (HSIL) and invasive cervical cancers worldwide.\(^{31–33}\) The risk of a severe CIN 3 and cancer outcome is remarkably greater for HPV type 16 infections when compared with risk estimates for all other carcinogenic HPV types.\(^{34}\) HPV types 16 and 18 are detected in about 50% and 10% to 20% of invasive cervical cancers,\(^{31–33}\) respectively. HPV 18 is found in a greater proportion of adenocarcinomas than squamous-cell cervical carcinomas.\(^{28}\) Other carcinogenic HPV types contributing to the global burden of cervical cancer include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82. Each of these HPV types contributes 5% or less to the cumulative incidence of HPV-associated cervical cancers worldwide. A number of additional HPV types infecting the genital tract are considered low-risk or noncarcinogenic. These include HPV types 6 and 11, which are responsible for over 90% of anogenital warts. Because noncarcinogenic HPV types cause cytologic and histologic abnormalities, detecting infections with carcinogenic HPV types is more important than detecting the presence or absence of equivocal or low-grade cytologic or histologic abnormalities.

For the past few decades, cervical cancer prevention has primarily been based on screening by cytology, evaluation of the cervix with colposcopy, and biopsy of potentially abnormal tissues. Biopsy-proven high-grade abnormalities are treated by excision or ablation of the cervical transformation zone. Despite enormous expenditures on cervical cancer screening and over 60 million Papanicolaou (Pap) tests performed each year, the American Cancer Society estimates that in 2008, approximately 11,070 cases of invasive cervical cancer will be diagnosed in the United States.\(^{35}\)

A brief overview of the major abnormal cytology and histology diagnostic categories and their relationship to HPV infections is provided below. Clinical management of various diagnostic categories is not detailed here but guidelines recommending clinical management strategies have been published elsewhere.\(^{24}\)

**HPV AND ABNORMAL CYTOLOGY**

Carcinogenic and noncarcinogenic HPV types result in abnormal cervical cytology. A cytologic diagnosis of atypical squamous cells (ASC) is the most common of all cytologic categories, but ASC is also the least reproducible among pathologists. Atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells cannot exclude HSIL (ASC-H) represent the two subcategories of ASC. The proportion of high-risk HPV-positive women reported among these two categories ranges from 40% to 51% for ASC-US, and from 74% to 88% for ASC-H.\(^{36–41}\) Similarly, the prevalence of CIN 2 and 3 is higher among women with ASC-H than among women with ASC-US.\(^{42}\) ASC-H is typically considered equivocal HSIL and a productive HPV infection. A 2004 meta-analysis reported that the pooled estimate of the sensitivity of HPV testing for detecting women with CIN 2 and 3 in women with atypical or equivocal cytology is considerably higher than that of a single repeat cytology.\(^{43}\) The overall prevalence of invasive cervical cancer is low among women with ASC.\(^{44}\)

Low-grade squamous intraepithelial lesions (LSIL) have previously been described using a number of terms, including HPV effects, koilocytosis, parakeratosis, mild
dysplasia, and CIN 1. Cytologic LSIL are, however, not equivalent to histologic CIN 1. LSIL is highly correlated with HPV infection. For example, in the United States National Cancer Institute’s (NCI) ASCUS/LSIL Triage Study (ALTS) trial, when testing for 38 possible HPV types, HPV DNA positivity among women with LSIL diagnoses was 85%. The risk of CIN 2 or 3 and the clinical management of women with LSIL is the same for women with ASC-US who are positive for carcinogenic HPV DNA. The prevalence of CIN 2 or 3 or cancer among women with LSIL has been reported to be between 12% and 17%. In contrast to other cytology diagnoses, which have generally remained constant, the prevalence of LSIL diagnoses in the United States has nearly doubled over the past decade. The increase has been largely attributed to an increase in liquid-based cytology.

HSIL have previously been described as moderate dysplasia, severe dysplasia, carcinoma in situ, CIN 2, and CIN 3. Cytologic HSIL are not equivalent to histologic CIN 2 or 3. An HSIL cytology result is highly correlated (>85%) with HPV infection and indicates a high risk for significant cervical disease, with 53% to 66% of women having a CIN 2 or 3 or cancer diagnosis following biopsy. An estimated 2% of women with HSIL have invasive cancer.

Cytologic abnormalities of glandular cells that are less severe than adenocarcinoma are divided into three categories: atypical glandular cells (AGC; endocervical, endometrial, or “glandular cells” not otherwise specified); AGC, either endocervical or “glandular cells” favor neoplasia (AGC favor neoplasia); and endocervical adenocarcinoma in situ (AIS). AGC results are overall uncommon. By comparison to ASC, LSIL, and HSIL, which are common in younger women, AGC is more common in women over age 40. AGC is frequently caused by benign conditions, such as reactive changes, but a fair number of women with AGC have significant intraepithelial neoplasia (CIN 2 or 3, AIS, or cancer), and 3% to 17% have invasive cancer.

It is worth commenting on the psychosocial morbidity of the previously described abnormal cytology diagnoses. Research has shown that distress and anxiety are reported by a majority of women (59%) after having even a low-grade abnormal Pap test. Women also report negative impacts on their sexuality, fear about developing cancer, and wondering if the abnormalities could interfere with their ability to bear children. The significant psychosocial morbidity and health care expenditures associated with abnormal Pap tests requires improved identification of those HPV infections that are destined to persist and progress, as very few women with abnormal cytology will ever develop invasive cervical cancer.

**HPV-RELATED HISTOLOGY OUTCOMES**

Among women of reproductive age, abnormal histology or CIN is a relatively common diagnosis. It has been estimated that in the United States, greater than 1 million women are diagnosed each year with CIN 1 and that approximately 500,000 are diagnosed with high-grade cervical cancer precursor lesions that include both CIN 2 and 3. The histologic diagnosis of CIN represents the standard for determining clinical management. Fig. 2 provides a schematic diagram to show the disease continuum of CIN development following HPV infection.

High rates of spontaneous regression, ranging from 70% to 90%, have been reported for CIN 1 lesions that remain untreated, and thus progression of CIN 1 to CIN 2 or worse is rarely observed. In the NCI ALTS trial, the risk for having a CIN 2 or 3 lesion during 2 years of follow-up after initial colposcopy was nearly identical in women with a histologic diagnosis of CIN 1 (13%) and in women whose initial colposcopy and biopsy were negative (12%). CIN 1 lesions are associated with high-risk...
carcinogenic types of HPV, but the distribution of HPV types in women with normal cytology and CIN 1 is markedly different than what is detected in CIN 2 and 3 and invasive cervical cancer, as shown in Table 1.

In designing cervical cancer prevention strategies, precancer or CIN 3 or worse is a reasonable surrogate for invasive cervical cancer, as numerous studies demonstrate essential equivalence on a molecular basis. By comparison, CIN 2 is a highly heterogeneous entity where the biologic importance varies greatly. Therefore, for a number of reasons, CIN 2 has severe limitations when included with CIN 3 as a surrogate endpoint for cancer. For example, there are a number of noncarcinogenic HPV types that can cause CIN 2 but which rarely if ever cause invasive cancer. There is even direct evidence that CIN 2 lesions have an intermediate cancer risk when compared with CIN3. A review of the literature found 43% of untreated CIN 2 lesions regressed in the absence of treatment, 35% persisted, and 22% would progress to carcinoma in situ or become invasive. The rates of regression, persistence, and progression for CIN 3 were 32%, 56%, and 14%, respectively. Furthermore, CIN 2 is not a reproducible diagnosis among pathologists because of an overall lack of agreement on specific cytomorphologic criteria. In the NCI ALTS trial, only 43% of CIN 2 diagnosed among community center pathologists was accepted as CIN 2 by the expert consensus panel. Many continue to debate whether a CIN 2 diagnosis should be considered a low-grade or high-grade lesion, as there is good evidence demonstrating CIN 2 often represents acute HPV infection with worrisome microscopic features that will...
inevitably regress. None-the-less, a significant proportion of CIN 2 lesions associated with high-risk carcinogenic HPV types harbor incipient precancers, with a high risk of invasive outcome. As such, in the United States, CIN 2 is combined with CIN 3 and represents the clinical threshold requiring ablative or excisional therapy. Although treatment of CIN 2 may currently be appropriate to insure a high degree of safety, given the high prevalence of CIN 2 in reproductive-aged women, the potential for negative-reproductive outcomes associated with loop electrosurgical excision

<table>
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<th>LSIL&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>(% of total sample)</td>
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<td>(9.2)</td>
<td>(71.1)</td>
<td>(84.9)</td>
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Abbreviation: ND, not reported.


<sup>c</sup> LSIL cases (n = 8,308) from 55 published studies were included in a meta-analysis. Regional distribution of included cases: Europe 46.5%, North America 32.9%, South/Central America 14.8%, Africa 3.0%, and Asia 2.9%. Data from Clifford GM, Rana RK, Franceschi S, et al. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. Cancer Epidemiol Biomarkers Prev 2005;14(5):1157–64.

<sup>d</sup> Includes HPV IS39, now designated as a variant of HPV82.
procedures must be considered. Loop electrosurgical excision has been reported to
double the risk for subsequent preterm delivery, premature rupture of membranes,
and of having a low birth-weight infant. Identification of biomarkers to predict which
CIN cases represent true precancers requiring treatment remains an important area
for further discovery work.

The immediate precursors of invasive cervical cancer are squamous cell carcinoma
in situ (CIS) and adenocarcinoma in situ. AIS is much less commonly observed than are
CIN 2 and 3 and CIS. The earliest form of invasive cancer is histologically recognized
as microinvasive carcinoma: cancers that have invaded no more than 5-mm deep and
7-mm wide into the underlying cervical stroma. Early invasive cancers appear as a tiny
bud of invasive cells that have penetrated through the basement membrane and
pushed into the underlying stroma. Histologically, approximately 90% to 95% of inva-
sive cervical cancers arising from the uterine cervix in developing countries are squa-
mous cell cancers, and about 5% are adenocarcinomas. Adenocarcinoma arises in
the endocervical canal from the glandular epithelium. Virtually all of squamous- and
adenocarcinomas of the uterine cervix are caused by high-risk carcinogenic HPV ge-
notypes. The most widely used staging system for invasive cervical cancer is based on
tumor size and the extent of disease spread into the vagina, parametrium, urinary blad-
der, rectum, and distant organs. Clinical stage of disease at presentation is the single
most important predictor of survival from invasive cervical cancer.

UNDERSTANDING COFACTORS OF HPV PERSISTENCE AND PROGRESSION TO HIGH-GRADE
CERVICAL ABNORMALITIES

Several factors are implicated in enhancing HPV persistence and HPV-related disease
progression to high-grade cervical abnormalities and cancer; however, it is difficult to
disentangle persistence from HPV-related disease progression. Persistence can be
declared as the detection of the same HPV genotype two or more times with a specific
time interval between samples. There is currently no agreed upon definition of an ap-
propriate interval (eg, 6, 12, 18 months) to define “meaningful” persistence. Data dem-
onstrate that the longer an HPV infection has persisted, the more likely it is to remain
persistent. Additionally, some data indicate that HPV 16 persists longer than other
genotypes.

Studies have demonstrated that older women with HPV infections are more likely to
persist longer than infections in younger women. Because these studies were
cross-sectional, it is probable that the older women already had these persistent
HPV infections for some time, and thus it should not be presumed that new infections
in older women by nature have an increased risk of longer persistence. Long-term per-
sistence (>5 years) is not a strict correlate of carcinogenicity. Noncarcinogenic HPV
types can also persist for long periods.

Studies assessing the risk of CIN 3 or cervical cancer among HPV-positive women
have been consistent in finding smoking as a cofactor, but this association is less clear
for persistence of HPV. In women infected with high-risk carcinogenic HPV geno-
types, long-term oral contraceptive use can significantly increase the risk of develop-
ing high-grade cervical lesions including cancer. Some sexually transmitted
infections have been suggested as cofactors for HPV outcomes. The majority of stud-
ies examining Chlamydia trachomatis in HPV-positive women have demonstrated an
association with high-grade cervical lesions and invasive cancer. Chlamydia tracho-
matis has also been associated with increased HPV persistence. Studies of other
sexually transmitted infections as cofactors for HPV-related outcomes, including her-
pes simplex virus and Trichomonas vaginalis, have reported inconsistent results.
Nutrients, intake of fruits and vegetables, and alcohol intake have also been implicated inconsistently. Genetic and immunologic host factors, such as HLA class I and II genes and viral factors, such as HPV variants, viral load, and viral integration, appear important in determining risks for HPV-related cervical disease outcomes, although a great deal of work is needed to further clarify specific roles of these factors.

Natural immunity has been implicated as an important modifier of HPV infection and HPV-related disease; however, because HPVs have evolved to evade host immune recognition, specific immune responses have been difficult to characterize. Extremely low-level responses are often not measurable by existing immunologic methods. Cell-mediated immune responses are often barely above background measures, and detectable HPV-specific antibodies are only detectable in about 60% of infected women, although this varies somewhat among different HPV types studied. Women with transient HPV infections are less likely to develop detectable HPV-specific antibodies or cell-mediated responses than women with persistent HPV infections. Thus, innate immunity may have an important role in the elimination of many HPV infections. Women with transient HPV infections are less likely to develop detectable HPV-specific antibodies or cell-mediated responses than women with persistent HPV infections. Thus, innate immunity may have an important role in the elimination of many HPV infections. HPV-specific antibody is associated with prior HPV exposure but does not appear to provide protection against HPV persistence or disease. In longitudinal cohort studies, once clearance of any HPV type is observed, it is very uncommon to detect that specific HPV type again, giving support to the notion that some aspect of natural immune protection is generated.

INTEGRATING PRIMARY AND SECONDARY CERVICAL CANCER PREVENTION STRATEGIES

Given the discovery of carcinogenic HPVs as a single primary cause of invasive cervical cancer, numerous opportunities for developing targeted primary and secondary interventions have been realized. In those countries where high coverage has already been achieved for cervical screening, improving the sensitivity of the screening test has become a primary goal. In a number of studies, HPV DNA testing alone has emerged over the past decade as a more sensitive primary screening test in women who are at least 30 years of age. The IARC has stated there is sufficient evidence indicating that the efficacy of HPV testing using a validated system as the primary screening modality can be expected to be at least as good as that of conventional cytology. In comparison to cytology, HPV testing is objective and amenable to automation and it can be performed in a more reproducible and accurate manner. As HPV testing costs are reduced, and if lower cost HPV tests are made available to developing countries, a variety of HPV-based cervical screening programs can be envisioned throughout the world. It is further possible that HPV tests capable of distinguishing specific, individual HPV genotypes will find utility in classifying women at greatest risk of disease outcome: those with persistent HPV infections. Some of the most common HPV types found in cancer, including HPV 16, 18, 31, 33 and 45, are currently being considered in longitudinal studies that will assess the clinical utility of algorithms employing multiple HPV genotype-specific measurements.

In addition to improvements expected in secondary cervical cancer prevention through HPV testing, two manufacturers have developed prophylactic HPV vaccines that have demonstrated high efficacy in populations that are naïve to the HPV vaccine types. The vaccines are composed of noninfectious, recombinant HPV viral-like particles (VLPs) that target reductions in the two HPV types, HPV 16 and 18. HPV 16 and 18 are responsible for approximately 70% of invasive cervical cancer worldwide. One of the vaccines also includes VLP immunogens for HPV types 6 and 11, which cause the majority of anogenital warts. However, for cervical cancer incidence to be reduced, women will require both screening and vaccination, as
first-generation HPV vaccines do not provide protection against a number of carcinogenic HPVs. Thus, cervical cancer screening programs must continue, and the relative roles of HPV vaccination in young women and HPV testing in older women (alone or in conjunction with cytology) will be determined over the next decades. Presently, no change in current screening is planned in vaccinated or unvaccinated women. As HPV vaccines are implemented, there are certain reductions in screening diagnoses that can be anticipated, primarily because of reductions in circulating HPV16. A small impact on ASC-US and LSIL diagnoses is expected, and the number of HSIL and cancer diagnoses will diminish to a greater extent. However, HSIL and cancer diagnoses represent a very small proportion of the overall abnormalities encountered. The positive-predictive value of an abnormal cytology for predicting CIN 3 and cancer will therefore decrease. The same decrease in the positive-predictive value will apply to current high-risk carcinogenic HPV assays, as the primary value of this testing lies in the detection of HPV 16 and 18. Vaccination will, in effect, eliminate some of the intrinsic value of cervical cytology programs. The addition of HPV vaccination will therefore require adjustments in the associated cervical cancer screening programs, particularly because HPV vaccines are costly and will add billions of dollars to the estimated $5 to $6 billion already spent each year in the United States on current cervical screening programs. For example, if HPV vaccines achieve high coverage, then removal of HPV 16 and 18 from the circulating HPV pool will most likely justify increasing the age of first cervical screening. Other carcinogenic HPV types are less common in precancer and cancers detected in younger women, and cost-effectiveness analyses support increasing the age of first cervical screening to approximately 25 years. Over time, as more data become available, extension of screening intervals in vaccinated populations may also be warranted. This would be particularly important if HPV testing is routinely used in screening. The cost-effectiveness of HPV vaccination will depend on the duration of vaccine immunity and will be optimized by achieving high coverage in presexually active adolescent girls, targeting initial catch-up efforts to women up to 18 or 21 years of age and revising screening policies. To enable the appropriate and timely integration of HPV vaccination and screening, it will be important to conduct surveillance in populations for which any coordinated modifications are under consideration. This may be particularly relevant in settings such as the United States, where there are no national cervical screening programs with call and recall support and where HPV vaccination may take several years to achieve high population coverage. In the short term, population-based registries and information systems collecting longitudinal data on cervical screening (Pap tests and ≥ CIN 1), treatment, and vaccination will be needed to inform appropriate decision-making and to determine the population-based effectiveness or lack thereof for these interventions.

SUMMARY

There are over 40 common genital HPV types that are primarily sexually transmitted. The vast number of women will be infected with one or more HPV types in their sexual lifetime. Persistent infection with HPV types can cause abnormal cytology (Pap tests) including diagnoses of ASC, AGC, LSIL, and HSIL, as well as abnormal histology identified following biopsy diagnosis as CIN 1 to 3, AIS, and cancer. Only a small subset of women infected with high-risk carcinogenic HPV will develop invasive cervical cancer. Although carcinogenic HPV is a necessary cause of invasive cervical cancer, a number of cofactors have been associated with HPV persistence and HPV-related disease
progression, including: (1) viral factors such as genotype (eg, HPV 16) and variant; (2) tobacco and long-term oral contraceptive use; and (3) genetic and immunologic host factors including innate immunity. About 15 carcinogenic HPV types are responsible for the global burden of invasive cervical cancer with HPV type 16 demonstrating the greatest risk. Given the identification of carcinogenic HPV as a necessary cause of cervical cancer, primary and secondary interventions have been highly successful. HPV testing has been used in cervical screening and may one day be used as a primary cervical screening test at least in women greater than or equal to 30 years. Prophylactic HPV vaccines based on VLPs have demonstrated high efficacy in sexually naïve populations. For cervical cancer incidence to be reduced, however, women will require both screening and vaccination, as first-generation HPV vaccines do not provide protection against a number of carcinogenic HPVs. Thus, cervical cancer screening programs must continue and the relative roles of HPV vaccination in young women and HPV testing in older women (alone or in conjunction with cytology) will be determined over the next decades. Population-based registries and information systems collecting longitudinal data on cervical screening (Pap tests and ≥CIN 1), treatment, and HPV vaccination will be needed to inform appropriate decision-making and to determine the population-based effectiveness or lack thereof for these interventions.

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REFERENCES


