

# From Human Papillomavirus to Cervical Cancer

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Cervical cancer is one of the most common female malignancies worldwide; 80% of cases occur in low-resource regions.<sup>1,2</sup> Screening programs have been very successful in the United States, Europe, and other regions able to achieve broad and sustained coverage. In the United States, the disease is controlled at an annual cost of billions of dollars representing a major commitment by patients and clinicians. In fact, cervical cancer screening and management of minor screening abnormalities are among the most time-consuming parts of some gynecology practices.

Cervical cancer prevention can now be made even better. Substantial modifications of practice are forthcoming, motivated by improved understanding of human papillomavirus (HPV) natural history and cervical carcinogenesis. In this update, we will summarize the new knowledge and its possible implications in the United States.

## AN UPDATE ON HUMAN PAPILLOMAVIRUS AND CERVICAL CARCINOGENESIS

### Cervical Cancer Screening Today

Most cervical cancer screening programs in 2010 still rely on cervical cytology followed by diagnosis of

screening-detected abnormalities using colposcopic biopsy. Treatment most often involves a loop electrical excision procedure.

The essentials of cervical cancer prevention have not changed much in the past 50 years. Technology has advanced, but without altering the basic strategy or performance. The major problem with U.S. cervical cancer prevention is that cytology and colposcopic biopsy are not optimally reproducible or accurate.<sup>3,4</sup> Cervical cancer screening programs have been very successful because cervical cancer usually develops slowly over decades. Repetitive rounds of screening catch precancerous lesions as they grow, while they can be easily treated.

The data summarized in the following sections suggest that future cervical cancer prevention will likely be even more effective, because it will include: prophylactic vaccination of adolescents against carcinogenic HPV infections; an increased role for HPV testing; improvements to colposcopy to increase sensitivity; and reductions in the number of lifetime screens needed for prevention.

### The Human Papillomaviruses

Papillomaviruses are 8,000 base-pair double-stranded circular DNA viruses that infect many species. The evolution of papillomaviruses is very slow, and those infecting one species do not generally infect any other. There are at most six early (viral replication) and two late (capsid-forming) genes.<sup>5,6</sup>

The tissue specificity, natural history, and carcinogenicity of HPVs also are predicted by evolutionary relationships. Many HPV species in the alpha genus infect mucosa including the anogenital region and the oral cavity (Fig. 1).<sup>7</sup>

The varying carcinogenicity of HPV species, and types within species, is mainly related to the activity of two oncogenes, E (early gene) 6 and E7. Among other functions, their gene products interact with tumor suppressors p53 and pRb, respectively.

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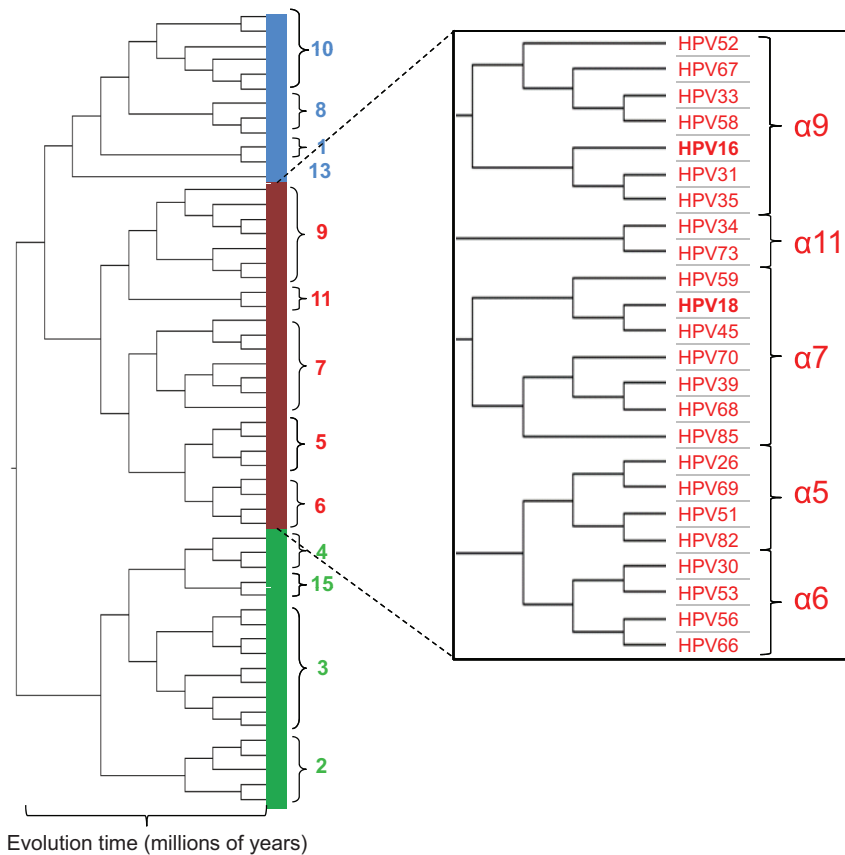
#### Financial Disclosure

*Both authors work with Qiagen to help evaluate the CareHPV test in Africa. There is cost-sharing only. This will not be sold except for public health use in low-resource countries, where it will be sold at a few dollars per test. Dr. Schiffman works with the U.S. Food and Drug Administration as well as the National Cancer Institute (NCI). He is the Medical Monitor of the independent human papillomavirus (HPV) vaccine trial of Cervarix, being conducted by THE NCI, for which he does not receive compensation. GlaxoSmithKline pays costs related to regulatory use of the data. He also works on the development of HPV tests for low-resource public health settings and is collaborating with Qiagen on this effort. Qiagen is providing free test supplies for this research effort but has no role in the evaluation of performance.*

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**Fig. 1.** Phylogenetic tree of anogenital human papillomavirus (HPV) types. The phylogenetic tree is based on the alignment of concatenated early and late open reading frames as described by Schiffman M, Herrero R, DeSalle R, Hildesheim A, Wacholder S, Rodriguez AC, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology* 2005;337: 76–84. The most important HPV types in the blue clade ( $\alpha$ 1, 8, 10, 13) are associated with genital warts. HPV types in the red clade ( $\alpha$ 5, 6, 7, 9, 11) are associated with cervical cancers and precursors (shown in detail). HPV types in the green clade ( $\alpha$ 2, 3, 4, 15) are commensal infections.

Schiffman. From *Human Papillomavirus to Cervical Cancer*. *Obstet Gynecol* 2010.

The 12 types classified as definitely carcinogenic are in species that form the branching or clade shown in red (Chen and Burk, personal communication; Fig. 1). These include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. When present, they cause cytologic abnormalities ~30% of time, including almost all of the severe lesions.<sup>8</sup> Only types from this clade should be considered for HPV testing and for vaccination to prevent cancer (of course, preventing genital warts is a separate goal). Unless otherwise specified, when we discuss HPV in the context of cervical cancer screening, we are referring to carcinogenic types in the high-risk clade. The eight types that most commonly cause cervical cancer everywhere belong to species alpha-9 (HPV16-related) or to a lesser extent to alpha-7 (HPV18-related, which are disproportionately important for adenocarcinoma).<sup>9</sup>

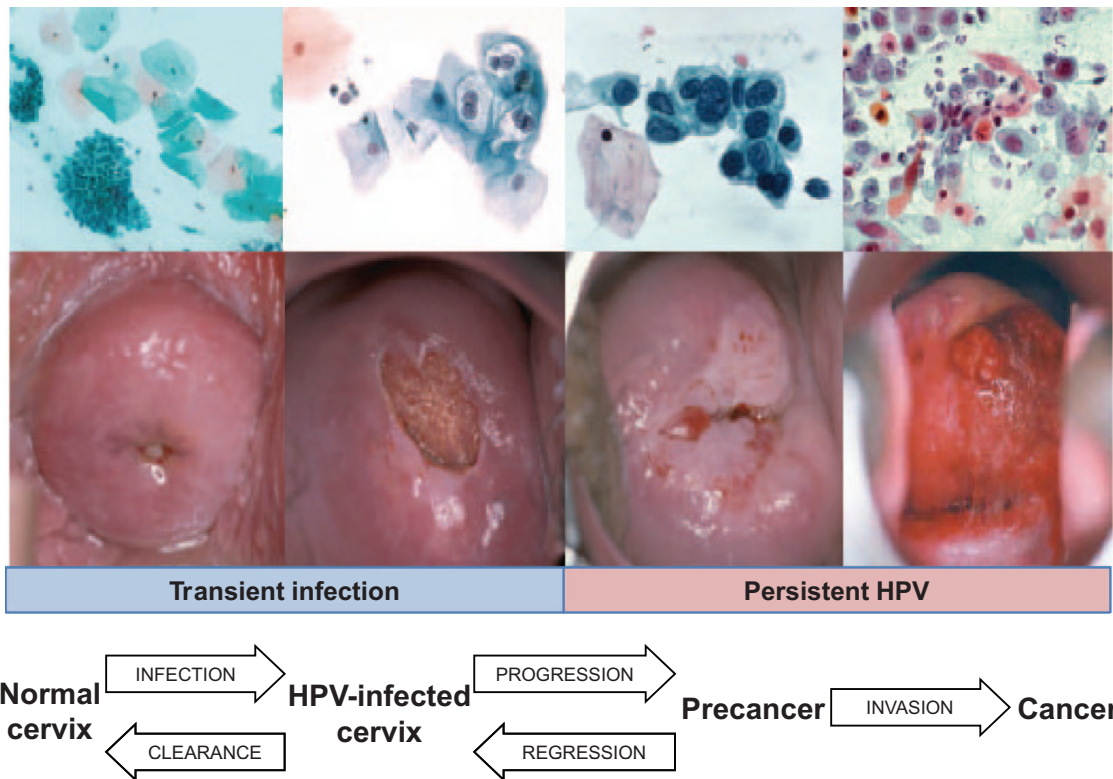
Of the individual HPV types, HPV16 is by far the most carcinogenic in terms of numbers of cases of cancer and cervical intraepithelial neoplasia grade 3 (CIN3). It also is most important for cancers caused by HPV in other anogenital epithelia and in the oropharynx. Human papillomavirus 18 is a distant second in terms of importance.

## The Importance of the Cervical Transformation Zone

Carcinogenic HPV infections are particularly prone to cause cancer at transformation zones where two kinds of epithelium meet, eg, the cervix, anus and oropharynx.<sup>2</sup> In the transformation zone of the cervix, squamous epithelium gradually undermines and replaces glandular epithelium (squamous metaplasia). Although HPV infections are very common at genital sites such as the vagina, penis, and vulva, rates of HPV-induced cancer are much lower owing to the lack of transformation zones. This review will not deal further with noncervical sites.

Squamous metaplasia continues throughout a woman's life and, eventually, the transformation zone is located inside the cervical os. Hence, it is critical to sample the transformation zone in screening, but a sampling centered at the os will not always collect the optimal cells. Atrophy can reduce cell yields as well. There is hope that HPV testing including endocervical cells might reduce false-negative screening compared with cytology. However, whichever screening method is used, a diagnostic problem remains; even when properly performed, colposcopists can not eas-





**Fig. 2.** Cervical cancer progression model. The functional progression model is displayed at the bottom. Classical cytological and colposcopic correlates of normal cervix, human papillomavirus (HPV)-infected cervix, precancer, and cancer are displayed above.

Schiffman. *From Human Papillomavirus to Cervical Cancer*. *Obstet Gynecol* 2010.

ily diagnose lesions at the poorly visible transformation zone among postmenopausal women.

### The Stages in Cervical Carcinogenesis

With the exception of rare HPV-negative cases, cervical cancer arises via clear necessary steps: acute infection with carcinogenic HPV type(s), viral persistence (rather than clearance) linked to development of cervical precancer, and invasion (Fig. 2).<sup>2</sup> For brevity we will discuss the more common and better-understood squamous lesions (although HPV also causes adenocarcinomas).

Each stage in cervical carcinogenesis occurs at well-known average ages (Fig. 3). There are three important peaks in the natural history of HPV and cervical cancer:

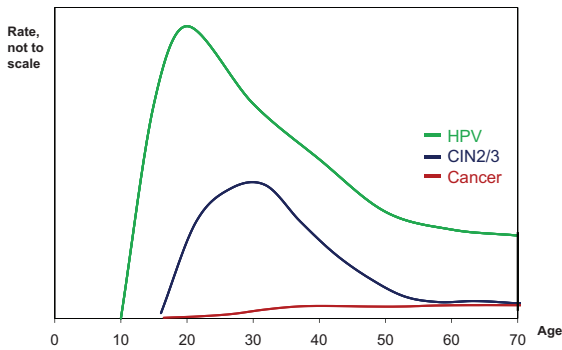
The ages at which the peaks occur vary by region, and can be timed from the average age at first sexual intercourse for that region, because HPV infection “starts the clock” for the events that follow.<sup>10</sup> There is a large peak of HPV incidence in the first years after women becoming sexually active; a secondary peak of precancer (here including CIN2 and CIN3) 5–15 years

later (the timing is dependent on the intensity of screening and precancer diagnosis); and the long drawn-out peak or plateau in invasive cancers decades later.<sup>2,11</sup> The average time between HPV incidence and CIN3 development is much shorter than the time between CIN3 and invasion.<sup>12,13</sup> Notably, new infections at older ages are just as likely to clear as in young women.<sup>14</sup> Because of the overall time required to move from HPV to invasive cervical cancer, new infections acquired at older ages contribute little to cervical cancer in populations. We will briefly describe each of the steps of cervical carcinogenesis.

### Human Papillomavirus Transmission and Early Natural History

Human papillomavirus infections are transmitted easily, and there is no evidence of HPV type interactions; each infection seems to be separate.<sup>15,16</sup> A woman can acquire several HPV infections at the same or different times. Because transmission is by direct contact (ie, sexual), the peak incidence in populations is at young ages. Condom use is only partly protective, even when

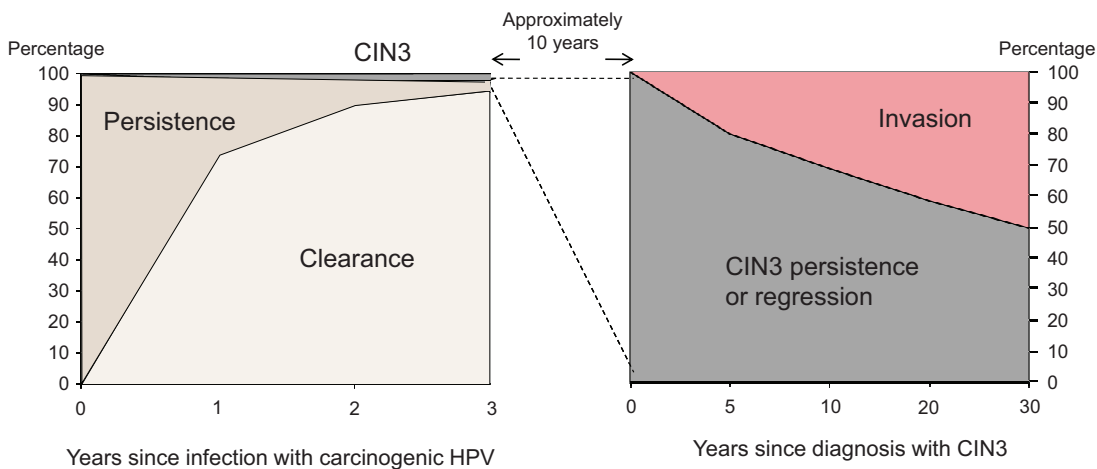




**Fig. 3.** Prevalence of human papillomavirus (HPV) infections, precancer, and cancer in the United States. The graph shows age-related prevalence of HPV infections, cervical intraepithelial neoplasia (CIN) grades 2/3, and cervical cancer. The rates are approximate and drawn not to scale. Schiffman. From *Human Papillomavirus to Cervical Cancer*. *Obstet Gynecol* 2010.

used conscientiously, because the entire anogenital skin can be infected including the scrotum, perineum, and other surfaces not covered by condoms.<sup>17</sup>

Rapid clearance is the rule, with half of infections no longer apparent within about 6 months and more than 90% inapparent by a few years (Fig. 4). The longer an infection lasts the higher the likelihood it will continue to persist.<sup>14,15</sup>



**Fig. 4.** Risk of human papillomavirus (HPV) persistence and progression. Left graph: Proportion of carcinogenic HPV infections that clear, persist, or progress to cervical intraepithelial neoplasia (CIN) grades 2/3 in the first 3 years after incident infection (Data from Rodriguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, et al Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst* 2008;100:513–7). Right graph: Proportion of CIN3s that invade to cancer when left untreated within 30 years after the initial diagnosis (Data from McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;9:425–34). Although regression of CIN3 has been reported anecdotally, we have no data to estimate the magnitude and therefore assume for this graph that all noninvasive CIN3s persist. Schiffman. From *Human Papillomavirus to Cervical Cancer*. *Obstet Gynecol* 2010.

### Persistence Associated With Progression to Cervical Intraepithelial Neoplasia Grade 3

Human papillomavirus can be detected after initial exposure either because of overt viral persistence or because of clearance, a period of latency, and re-appearance. Overt viral persistence is the key risk factor for CIN3.<sup>15,18</sup> The issue of HPV latency and reappearance is complicated and poorly understood. It is relevant, however, to married or sexually inactive women who unexpectedly screen HPV-positive. In some populations, many older women have detectable HPV DNA usually without cytologic abnormalities. Infection with HPV at older ages can be due to recent transmission from new partners of the woman or her partner or may represent reactivation from latency, perhaps due to a partial failure of immune control. Most importantly, cases of CIN3 and cervical cancer found at older ages typically relate to HPV infections acquired decades earlier.

We do not know the biological mechanisms of overt persistence, eg, whether continuous presence of the virus is related to foci of abnormal cells that can at least initially escape detection by cytology or colposcopy. It is even more complex when multiple HPV types infect the cervix, potentially causing benign productive infection and CIN3 at the same time. So

far, there is only little understanding of the topographic relation of different lesions on the cervix.

About 5% of acute HPV infections persist past a few years. Among those, CIN3 may develop and is typically diagnosable within 10 years. The probability of clearance decreases as the probability of CIN3 increases.<sup>14</sup> Therefore, the utility of waiting for clearance wanes after 1–2 years of follow-up especially for infections among older women tested for the first time; their infections might already have been present for a while. Note that risk of CIN3 among persistent infections rises and falls again such that CIN3 diagnosis is most common between 25 and 35 years of age. A small pool of HPV infections persist overtly for many years without producing CIN3 but this is the least common outcome of infections.<sup>10</sup>

Etiologic cofactors that increase the risk of CIN3 and cancer do exist but are not critical determinants. They are cofactors of moderate strength (increasing risk twofold to threefold) among HPV-infected women. The factors include smoking, long-term oral contraceptive use, and multiparity. The mechanisms are not certain. In the absence of HPV, none would cause cervical cancer.<sup>2</sup>

Sexual factors such as infections with *Chlamydia* are related to risk of cervical cancer and CIN3 because of the sexual transmission of HPV. An important coinfection is human immunodeficiency virus (HIV) and its related immunosuppression which weakens control of HPV infections and elevates the risk of CIN3.

### Difficulty With the Diagnosis of Cervical Precancer

Although it is critical for clinicians to distinguish between acute infection and precancer, it can be challenging to define cervical precancer clinically. In most settings, the threshold for excisional treatment of the cervix is histological CIN2 or greater. However, a diagnosis of CIN2 is poorly reproducible between pathologists. Also, CIN2 is biologically heterogeneous including both transient HPV infections and early precancers. Many CIN2 cases regress spontaneously; current guidelines permit more expectant management of CIN2 especially among young women. However, in most settings, CIN2 is treated immediately resulting in frequent overtreatment that can lead to obstetric complications.<sup>19</sup> Although biomarkers of viral transformation might help to clarify the prognosis of CIN2 cases, prospective studies are lacking currently.

Although CIN3 is more reproducible and serious, we know from historical data that not even CIN3 consistently progresses to cancer. Cervical intraepithelial neoplasia grade 3 lesions grow from extremely small to large over a period that can last a decade or more. It is the large lesions that are most likely to invade.

Retrospective follow-up of women in an unethical study in New Zealand in the 1960s, which left women with CIN3 untreated, showed that ~30% eventually progressed to cancer (Fig. 4).<sup>13,20</sup> The women had a median age of 38 and their lesions were very large. In contrast, CIN3 in countries with good screening are diagnosed much earlier and smaller. One can thereby estimate that progression from small to large CIN3 might take more than 10 years, and an unknown fraction of small CIN3 cases might regress.

Recent data have questioned the accuracy of colposcopic grading for identification of prevalent CIN3.<sup>3,21</sup> A colposcopic examination can miss the earliest and most treatable lesions. Even with the introduction of grading systems to target colposcopic biopsies, such as the Reid Index, sensitivity of colposcopy for the identification of underlying early CIN3 has been estimated from less than 60% to 70–85%. The only visual category with sufficient sensitivity for prevalent precancer is acetowhitening, however, the specificity of this finding is low.

### Invasion

CIN3 lesions typically grow slowly before invasion although early invasion is, unfortunately, occasionally seen in younger women.<sup>22</sup> Currently, we have no way to predict which CIN3 will invade. There are no important known risk factors. Therefore, CIN3 is treated in all settings and expectant management is only exceptionally performed in pregnant women. Once a cancer is invasive we do not know whether particular aspects of HPV status influence prognosis.

## IMPLICATIONS FOR CLINICAL PRACTICE

### Human Papillomavirus Vaccines

As proven by large randomized trials, the two licensed HPV vaccines are highly effective at preventing new infections with HPV16 and HPV18.<sup>23,24</sup> There might be some possible cross protection against HPV31 and HPV45. The minority of cancers due to other HPV types are not covered.

Current vaccines do not treat existing infections or lesions.<sup>25</sup> They must be given before exposure; in public health programs this implies that vaccinating young adolescent girls is optimal (Fig. 3). The cost-effectiveness of vaccination decreases substantially at older ages because many women are already exposed and immune, or past the age at which subsequent exposure is likely. Because HPV exposure decreases with age and new infections are no more dangerous at older ages than among young women, it does not make sense from a public health perspective to vaccinate older women (the exact age cutoff is debatable); it is more



logical to screen them carefully. Lacking accurate serology, there is no accurate way to know which women have been exposed or who remains susceptible.<sup>26</sup>

### Human Papillomavirus Testing

Human papillomavirus is not a typical pathogen for which testing should be exquisitely sensitive. An HPV test must cover the right carcinogenic types and must have a correct analytic positivity threshold, to provide excellent detection of precancer and cancer while avoiding detection of too many transient infections with negligible cancer risk.<sup>27</sup> Age of use is another important factor. Human papillomavirus infections peak in women at age 20–25 with up to 40% of the female population HPV positive, but cervical cancer is very rare at this age. To screen all young women by HPV, hoping to detect the handful of tragic rapid-onset cases, would cost on the order of a billion dollars annually in the United States, and would lead to detection and great over-treatment of many tens of thousands of minor lesions that would regress. Because of its benign early natural history, testing for HPV is best used after the peak of acute infection, to detect treatable CIN2 and CIN3 before invasion (Fig. 3). In short, HPV screening at young ages should be avoided because it would detect too many new, transient infections posing low cancer risk.

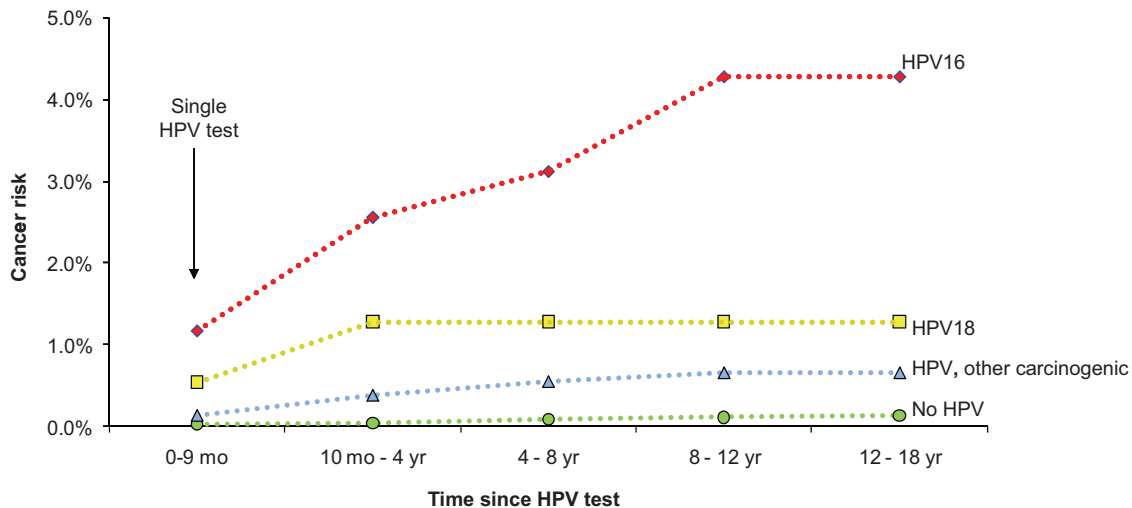
Large randomized trials have shown that HPV testing is more sensitive than cytology for detection and prevention of CIN3, cervical cancer incidence, and cervical cancer death<sup>28,29</sup>; as a corollary, screening inter-

vals can and should be extended among HPV-negative women. One or two negative HPV tests (currently recommended at 3 years apart) can almost exclude the development of cancer in the next 5–10 years (Fig. 5).<sup>30</sup> Importantly, if HPV testing is performed in too short screening intervals, the infections found will be new and consequently will generally clear; the predictive value of a positive test will go down substantially. In other words, the HPV infections found will mean less, leading to overly aggressive management. The optimal interval for HPV screening is not established, but 3 years might still be too short for cost-effective use.

The combined sensitivity of cytology and HPV testing is very similar to HPV testing alone.<sup>31</sup> This indicates that HPV testing might eventually be used as a single primary screening assay followed by cytology or a new biomarker test as a triage to be used only for HPV-positive women. It will be very important to validate the assays and protocols for HPV testing, before any large-scale shift away from cytology occurs in the United States.

### Integrating Vaccination and Screening

In a world of limited health resources, HPV vaccination and screening are competing for attention and resources. It is not supportable to combine them without integration. The proven duration of effectiveness of prophylactic HPV vaccines against HPV16 and HPV18 is now approaching a decade and vaccination coverage is increasing. Thus, vaccination of adolescents will largely prevent the first step in cervical carcinogenesis (acute



**Fig. 5.** Cumulative cancer risk by human papillomavirus (HPV) status over 18 years. Cumulative cancer risk over 18 years after a single HPV test is displayed stratified by the HPV type result. The risk is highest for HPV16 followed by HPV18 and other carcinogenic types. The risk of cervical cancer after a single negative HPV test is minimal. The graph shows data from more than 20,000 women from the Kaiser Portland HPV Study.<sup>30</sup>

Schiffman. From *Human Papillomavirus to Cervical Cancer*. *Obstet Gynecol* 2010.

HPV infection in the years after initiation of sexual intercourse), especially as newer vaccines under final evaluation cover more HPV types. The efficiency of all cervical screening tests will decrease due to reduced prevalence of precancers.<sup>32</sup> Vaccination especially will reduce efficiency of cytology-based screening because the lesions that remain increasingly will be nuisance look-alikes (particularly atypical squamous cells of undetermined significance [ASC-US]) not caused by carcinogenic HPV types and not at risk of progression to cancer. Thus, various proposals are under consideration, including a delay of initial screening in vaccinated young women and a switch in emphasis from cytology to primary HPV testing.

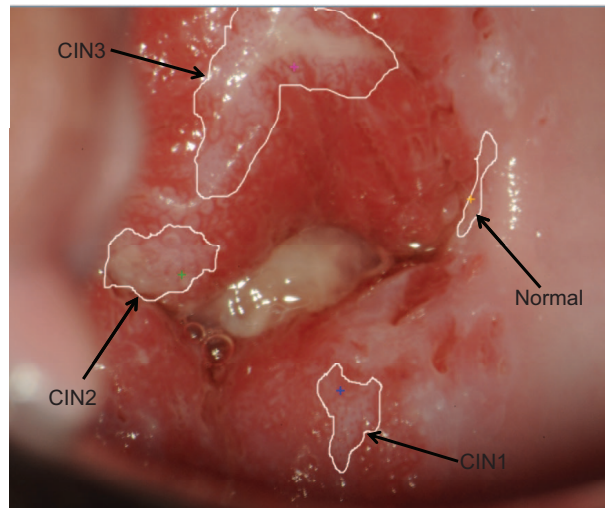
### Novel Biomarkers

Beyond cytology, several new biomarkers are currently evaluated that might be used to triage HPV positive women.<sup>33</sup> The most widely studied marker is p16, a cellular tumor suppressor that is strongly expressed in high-grade CIN. p16 staining has been used in histology to improve diagnosis of CIN3.<sup>34</sup> Cytology incorporating p16 has shown better performance as a triage test of HPV positive women compared with Pap cytology. Viral oncogene RNA tests also aim at detecting high-grade CIN.<sup>34</sup> Two assays based on HPV RNA detection with different type coverage are currently under evaluation. Large clinical studies using these tests in a triage scenario are still awaited; it is not clear whether they perform much differently from DNA tests, the current HPV tests. Other markers for high-grade CIN include MCM2/Topo2a, 3q and methylation marker panels, but there is only limited information about their performance.

### Improvement of Colposcopic Biopsy

The introduction of very sensitive screening tests has increased the demand on colposcopists for sensitive and specific diagnoses. The sensitivity of colposcopy for the identification of prevalent CIN3 has been estimated between 60% and 80%.<sup>21,35</sup> It was demonstrated that a better performance in detecting prevalent precancer is related to the number of biopsies taken rather than the experience of the colposcopist. The only visual category with sufficient sensitivity for prevalent precancer is acetowhitening, but its specificity is very low.

Thus, to improve disease ascertainment, many colposcopy protocols now recommend taking multiple biopsies. Obtaining biopsies from all distinct acetowhite lesions on the cervix is a promising approach for improving colposcopic sensitivity (Fig. 6). The optimal number of biopsies, choice of equipment, and revised histology protocols are under study.



**Fig. 6.** Colposcopy with multiple biopsy sampling. The image shows the colposcopic impression of a 19-year-old patient referred for a high-grade squamous intraepithelial lesion Pap test. Human papillomavirus (HPV) testing with genotyping at the colposcopy visit showed infections with HPV16, 35, 40, 52, and 53. Distinct acetowhite lesions are marked in white. Biopsy sites are marked by colored plus symbols. Four biopsies of acetowhite lesions were performed; the histologic results are indicated on the image. CIN, cervical intraepithelial neoplasia.

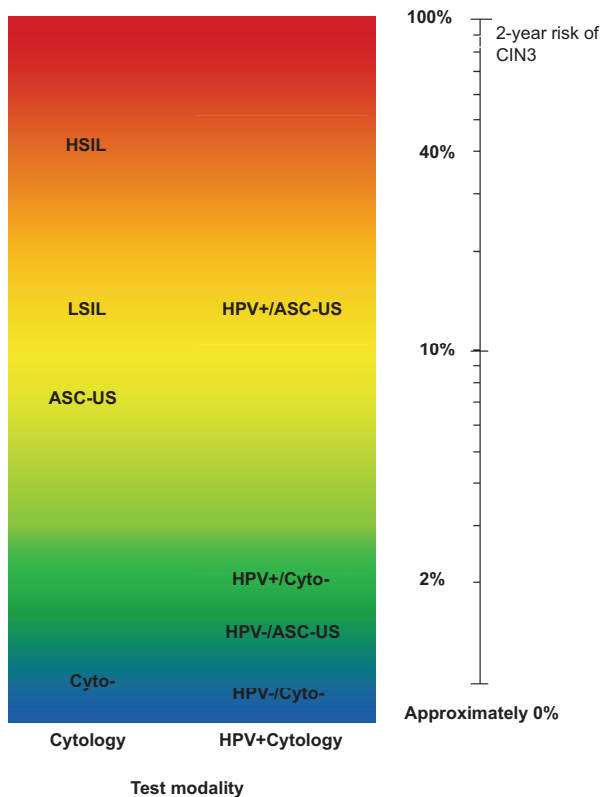
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### Moving From Algorithms to Risk-Based Management

At each stage of cervical cancer prevention, there are many tests which, alone or combined, predict similar levels of risk (Fig. 7).<sup>36</sup> For example, the risk of CIN3 after HPV-positive ASC-US equals that of low-grade squamous intraepithelial lesions, whereas the risk of HPV-negative ASC-US equals a normal Pap result. The presence of HPV16, particularly when persistent, elevates risk of CIN3. A negative colposcopy reduces risk.

The various combinations of test results, and whether the woman was vaccinated or not, argues for similar treatment of women who, in fact, are at the same risk of CIN3 and cancer. Instead of algorithms, a clinician could be provided with a risk score that captures all the known clinical information. Risk-score calculators are being developed to be used for clinicians; societies such as the American College of Obstetricians and Gynecologists can promote explicit agreement on treatment of women at different risk levels.<sup>37</sup> Comparative effectiveness studies can be structured around specific risk-based questions, such as “What is the best treatment strategy for women whose prior tests (whatever they are) in combination place her at 5–10% risk of





**Fig. 7.** Risk of cervical intraepithelial neoplasia grade 3 (CIN3) related to screening test results. The risk of CIN3 is drawn on a log scale on the Y axis. For each test result based on cytology alone or combined HPV and cytology testing, approximate risks for CIN3 within the next 2 years are indicated. HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HPV, human papillomavirus; ASC-US, atypical squamous cells of undetermined significance. Modified from Am J Obstet Gynecol, Volume 197, Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer, Page 356, Copyright Elsevier (2007).

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CIN3 in the subsequent 2 years?" Health economists are beginning to research such questions.

### Adapting to Different Settings

Cervical cancer prevention efforts must be adapted to the resources available in each region, and the local tolerance for residual risk, knowing that no program will prevent every case. In rich countries striving for the very lowest rates of cervical cancer, such as the United States, the challenge is to use new technology but to avoid excessive interventions and overtreatment. The answer must include reliance on the reassurance provided by negative HPV screening to permit a reduced number of screening visits and less referral to colposcopy. At present, HPV is

approved as an adjunct to cytology, performed in women 30 years and above.<sup>38</sup> But HPV-based screening might eventually supplant cytology. Moving away from annual Pap tests starting at young ages will challenge the practice models of some clinicians, but the move is inevitable particularly as HPV vaccine coverage reduces the cost-effectiveness of screening, particularly by cytology.

The great burden of cervical cancer is in low-resource regions, which are not the focus of this review. However, the advent of very low cost, accurate HPV tests has finally produced a practical possibility of extending sustainable screening once or twice per lifetime to poor countries.<sup>39</sup> Women past the peak age of acute HPV infections can be screened and those HPV-positives without obvious contraindications on visual inspection (eg, signs of invasive cancer) can be treated with cryotherapy.<sup>40</sup> This combination, although imperfect, is far superior to the current situation in almost all low-resource countries, where no organized cervical screening is performed.<sup>41</sup>

### CONCLUSIONS

Based on improved understanding of HPV natural history and the stages of cervical carcinogenesis; the development of sensitive and reliable HPV assays with high reassurance value; and the introduction of still-improving HPV vaccines, we can further improve cervical cancer prevention. Specifically, we can decrease interventions while improving patient safety by adherence to rational guidelines, and spread screening to low-resource settings. The critical challenge is to rethink our current prevention model based on frequent cytology and colposcopic referral. Inevitably, future programs will depend on vaccination, much less frequent screening, and fewer treatments to permit the clearance of resolving HPV infections.

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