Human Papillomavirus and Cervical Cancer: Burden of Illness and Basis for Prevention

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Abstract

Genital infection with human papillomaviruses (HPV) is one of the most common sexually transmitted conditions. The central causal role in cervical carcinogenesis of the so-called high oncogenic–risk (HR)-HPV genotypes, such as HPV-16, has been established as a likely but not sufficient cause of virtually all cases of cervical cancer worldwide. HR-HPV infection also causes a substantial proportion of other anogenital neoplasms and oral squamous cell carcinomas. Infection with low-oncogenic–risk HPV, such as HPV-6 and -11, causes a large proportion of low-grade squamous intraepithelial lesions of the cervix and benign lesions of the anogenital areas known as condylomata acuminata (genital warts). Subclinical and clinical HPV infections are responsible for high morbidity and impose a great burden on the health-care system. Organized or opportunistic screening with Papanicolaou (Pap) cytology in high-income countries has substantially reduced cervical cancer morbidity and mortality during the last 50 years. However, Pap cytology screening has failed to reduce cervical cancer mortality in many middle-income countries, and most low-income countries cannot make the necessary public health investments to deploy organized screening. The availability of 2 prophylactic HPV vaccines represents the best hope for preventing most cases of cervical cancer and HPV-associated diseases.

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Epidemiology of HPV

Clinical and subclinical human papillomavirus (HPV) infections are the most common sexually transmitted infections in the world (**Figure 1**).[1] Among asymptomatic women, the prevalence of genital HPV infection ranges from 2% to 44%.[2-7] The age-standardized prevalence rates of HPV infection in European, Asian, South American, and sub-Saharan women without cytological abnormalities were estimated at 5.3%, 8.7%, 14.3%, and 25.6%, respectively, for a global estimate of 10.5%.[8] A recent pooled analysis that estimated HPV prevalence among women with normal cytology using data from 78 published studies largely corroborates these observations with an adjusted global prevalence of 10.4% and considerable variation by region, including an estimate for the Americas of 12.9%.[9]

The prevalence of HPV is highest among young women soon after the onset of sexual activity and falls gradually with age, possibly as a reflection of accrued immunity and a decrease in the number of sexual partners.[10,11] In some populations, however, the age-specific prevalence curve rises again at ages 45 or 50 years coinciding with the perimenopausal or immediately postmenopausal years. The reason for this second peak is unclear, but it could be related to 1 or more nonmutually exclusive mechanisms, such as reactivation of previously undetectable infections acquired earlier in life (due to a gradual loss of type-specific immunity or a sudden loss via hormonal influences during the postmenopausal years); acquisition of new infections due to sexual contact with new partners later in life; and, finally, due to a cohort effect, ie, the varying prevalence at different ages which reflect the changing experience of successive birth cohorts in being exposed to HPV in different eras.[9,12]

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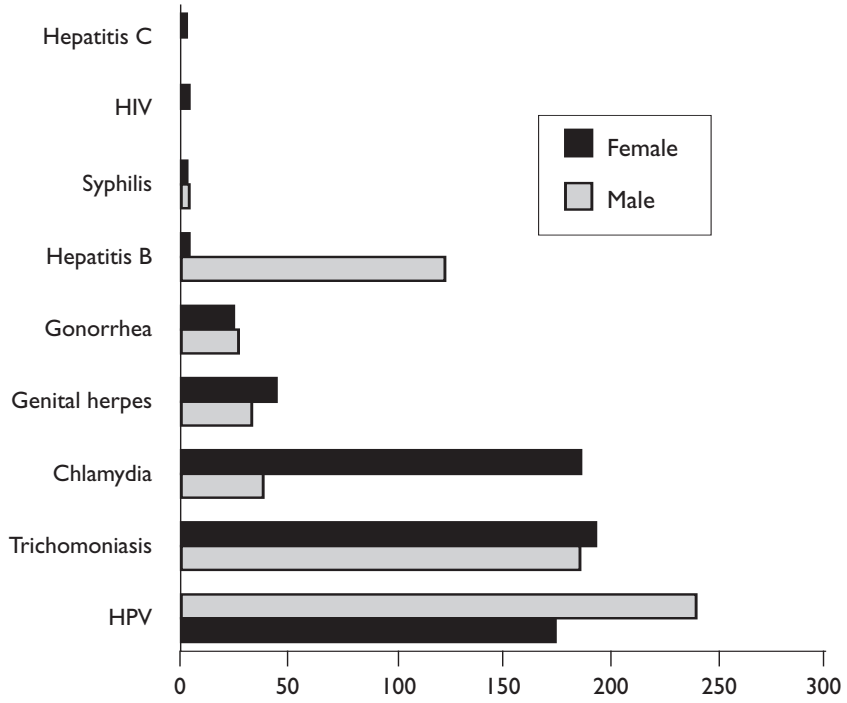
Figure 1. Sexually Transmitted Infection Incidence per 10 000 US Population, 1998



Source: Ebrahim et al. *Sex Transm Infect.* 2005;81:38-40.[1]

Studies among initially virginal women strongly confirm the sexually transmitted nature of HPV infection.[13,14] A number of cohort studies around the world have clearly demonstrated the relatively high incidence of HPV infection among women who were initially free of HPV deoxyribonucleic acid (DNA). The incidence rate in these studies ranges from 14% to 36% women-years.[6,15-19] This translates into high cumulative incidence of HPV infection from the time of first sexual intercourse. Many cohort studies among young or college-aged women who were initially HPV negative have shown that the cumulative incidence of HPV infection exceeded 40% after 3 years,[15,17,18] and the cumulative incidence is higher for high-risk types than for low-risk (LR) types.[6,20] Moreover, coinfection with multiple HPV types is a common finding of many epidemiologic studies. For example, in the Brazilian Ludwig-McGill cohort, 22.3% were infected with multiple types during the first 4 years of follow-up.[21] Approximately 20 million people are currently infected with HPV in the United States, and the annual incidence of sexually transmitted HPV infection is around 5.5 million.[22] Overall, an estimated 75% of sexually active men and women have been exposed to HPV at some point in their lives.[23] In most cases, HPV infection is transient or intermittent, becoming undetectable within 1 to 2 years even by sensitive polymerase chain reaction (PCR) assays.[24]

Transmission of HPV

Sexual contact with an infected partner is important in the epidemiological chain of HPV transmission, although intromissive intercourse in which an infected penis enters the vagina is not strictly necessary.[25-27] A stochastic modeling study suggested that the probability of HPV transmission per sexual act is very high, several-fold higher than that for other viral sexually transmitted infections, such as human immunodeficiency virus or herpes simplex virus 2.[28] Moreover, condom use might be somewhat, but not completely protective.[29] In addition to the peno-vaginal

intercourse route, HPV is also easily transmitted by other sexual practices, such as oral sex, peno-anal intercourse, digital-vaginal sex, and use of insertive sex toys.[30-32] Perinatal transmission of HPV is also possible and can cause in rare instances recurrent respiratory papillomatosis in infants and young children.[33]

Risk Factors for Acquisition of HPV

Apart from sexual activity markers (ie, high number of sexual partners, young age at sexual debut, and recent new sexual partner), other risk factors of HPV infection include young age, coinfections, long-term oral contraceptive use, smoking, immunosuppression, and multiparity.[4,6,18,20,24,29,34-40] Findings about condom use are inconsistent; the majority of studies show that condoms are not protective against HPV, whereas others show that, among newly sexually active women, consistent condom use by their partners appears to reduce the risk of cervical and vulvovaginal HPV infection.[28,29,41] Certain genetic polymorphisms in the human leukocyte antigen (HLA) system and nutrition are possibly associated with reduced risk of HPV infection.[42-45] Some studies have also suggested a role for viral factors (non-European molecular variants of HPV-16 and -18 and high viral load) in persistence of HPV and progression.[46,47] Risk factors for HPV acquisition are very similar to those for cervical cancer.

High-oncogenic–risk HPV Types and Cancer

So far, more than 120 different HPV types have been cataloged, of which approximately 40 types infect the anogenital tract.[48] Among the latter, about 15 types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, and -82) are now considered to be high-oncogenic–risk (HR-HPV) types based on their frequency of association with cervical cancer and other anogenital cancers.[49] Today, it is well established that infection with HR-HPV is the central causal factor in cervical cancer.[8,16,24,50-55] The association is supported by strong epidemiological evidence and the detection of HPV DNA in up to 99.7% of cervical cancers from all geographic areas.[49,55-57] HPV-16 is the most prevalent HR-HPV, and is present in approximately 54% of cervical tumor specimens worldwide, whereas HPV-18 is associated with approximately 17% of cervical cancers. The remaining tumors have been shown to contain DNA from other HR types, such as HPV-45, -31, and -33.[8] It is now widely accepted that HR-HPV infections are a necessary, but not sufficient, cause of virtually all cases of cervical cancer worldwide. An estimated 85% of anal cancers; 50% of cancers of the vulva, vagina, and penis; 20% of oropharyngeal cancers; 10% of laryngeal and esophageal cancers; and an unknown but presumably substantial fraction of nonmelanoma skin cancers (the latter by different HPV genera that cause cutaneous infections) are attributable to HPV infection.[58-60]

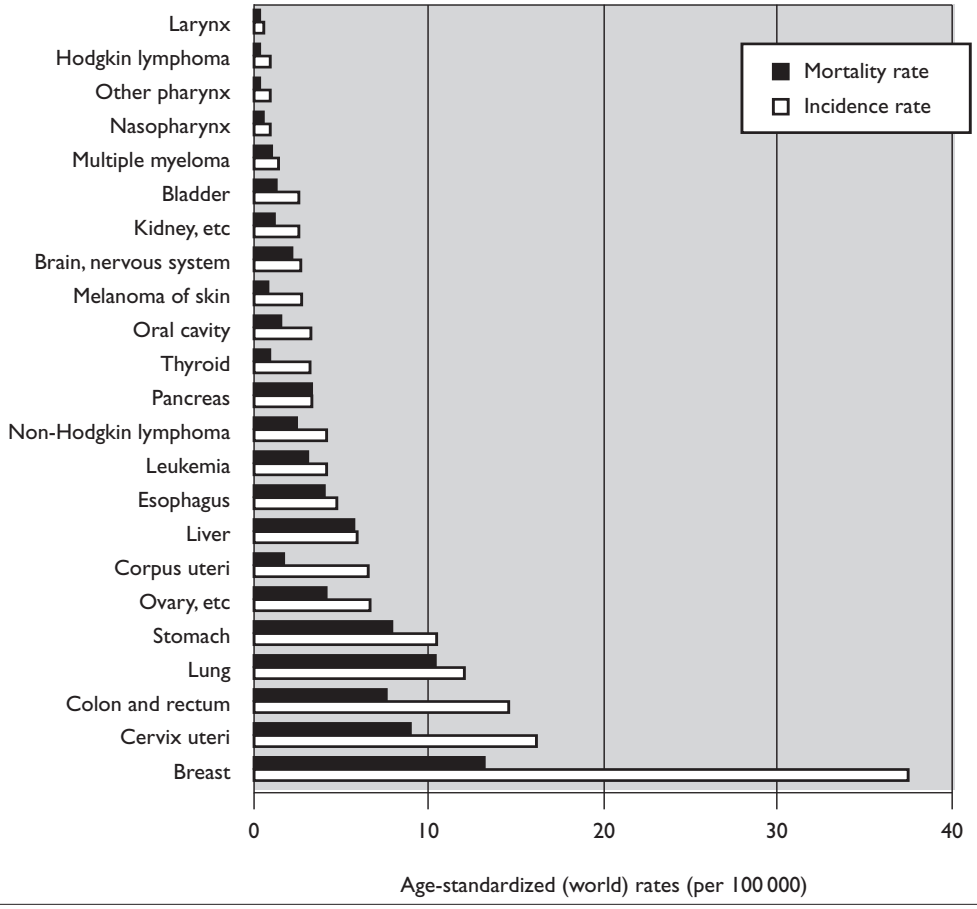
Low-oncogenic–risk HPV, Genital Warts and Low-grade Squamous Intraepithelial Lesions

Infection with low-oncogenic–risk (LR-HPV) types, such as HPV-6 and -11, can cause benign lesions of the anogenital areas, known as condylomata acuminata (genital warts), as well as a large proportion of low-grade squamous intraepithelial lesions of the cervix. Genital warts are very common. Approximately 1.4 million (1%) individuals currently have genital warts in the United States,[34] and the incidence is on the risk, with 500 000 to 1 million new cases occurring annually.[61,62] LR-HPV clinical infections are responsible for substantial morbidity and lead to high costs associated with the treatment of clinically relevant lesions.[63]

Cervical Cancer

Epidemiology. Cervical cancer is the second most common malignant neoplasm affecting women worldwide (**Figure 2**). In 2002, 493 000 new cases were diagnosed in the world (83% of them in developing countries). Less than 50% of women affected by cervical cancer in developing countries survive longer than 5 years, whereas in developed countries the 5-year survival rate is about 66%,[64,65] which translates into high mortality rates. Every year, an estimated 190 000 deaths from cervical cancer occur worldwide, with more than 75% of them in

Figure 2. World Age-standardized Incidence and Mortality Rate by Cancer Type for Women in 2002



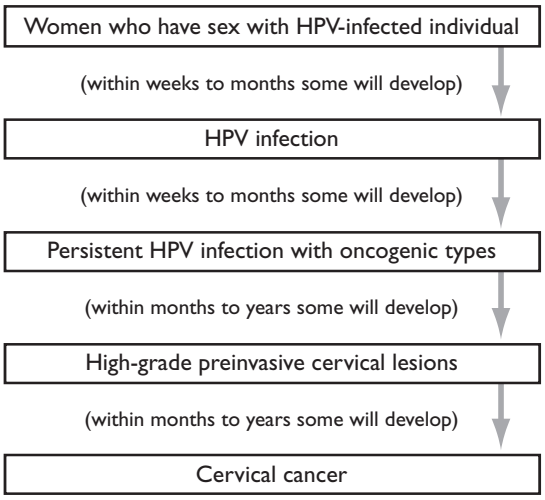
Source: Reference 64.

developing countries, where mortality from this disease is the highest among deaths caused by neoplasms.[65] In the United States each year, there are approximately 9800 new cases of invasive cervical cancer with 3700 deaths due to this disease.[66] The highest risk areas for cervical cancer are in Central and South America, Southern and Eastern Africa, and the Caribbean, with average incidence rates of approximately 40 per 100 000 women per year.

It is important to note that epidemiologic information on incidence rates of cervical cancer in the developing world is derived by interpolation and averaging using data from population-based registries, which are established in capitals and urban areas in many countries. One should bear in mind that cervical cancer risk is usually lower in such areas relative to urban or remote areas of the same country. Consequently, it is likely that average rates for a given country tend to be biased toward the relatively low level of cervical cancer burden that is typically experienced in urban centers in which women have the benefits of screening. Therefore, it is quite possible that the overall burden of cervical cancer worldwide may be much greater than what can be reliably estimated.

Cervical cancer and its precursors are basically of 2 main histological lineages depending on whether they originate in squamous or in glandular cervical epithelium. Compared with squamous cell carcinoma, adenocarcinoma is a much rarer occurrence in most statistical compilations of cervical cancer incidence or histopathology series. Adenocarcinomas accounted for 13.4% of all

Figure 3. Natural History of Cervical Cancer Showing the Steps Amenable to Intervention Via HPV Vaccination and Screening



Source: Reference 68.

invasive cervical cancers registered in the Surveillance, Epidemiology, and End Results program from 1973 to 1987, including adenosquamous morphology and other glandular types.[67] There are differences between these 2 types in terms of etiology, natural history, detection, and prevention.

Natural History of Cervical Cancer and Clinical Symptoms. The natural history of cervical cancer begins as a slow process of disruption of the normal maturation of the transformation zone epithelium of the uterine cervix near its squamo-columnar junction.[66] This process of abnormal changes is initially limited to the cervical epithelium. These preinvasive lesions, known as dysplasia (or as cervical intraepithelial neoplasia [CIN] or as squamous intraepithelial lesion [SIL]), are invariably asymptomatic and can be discovered only through cytological examination using the Papanicolaou (Pap) smear and confirmed by colposcopic examination and biopsy. If left untreated, the low-grade lesions may eventually extend to the full thickness of the cervical epithelium (cervical carcinoma in situ [CIS]) and traverse the lining formed by the basement membrane to become invasive. This process may take a decade or longer, but will eventually occur in a substantial proportion of patients with CIS. As an invasive cancer, the lesion will grow unconstrained and reach small blood and lymphatic vessels to finally become metastatic in body sites. Women with clinically invasive cancer usually present with symptoms and signs such as post-coital bleeding, recurrent cystitis, and exophytic and ulcerated cervical lesions. As soon as invasion of pelvic lymph nodes occur, the disease becomes considerably worse clinically, and when the original lesion infiltrates the parametrium and obstructs the ureters, it can cause renal failure and uremia. Pressure against nerve trunks and the sacral plexus produces persistent pain.

The major steps known to be necessary in cervical carcinogenesis include HR-HPV infection, persistence of that infection over a certain period of time, progression to precancerous lesions, and, eventually, invasion (**Figure 3**). HPV infects the stratified squamous epithelium and stimulates cellular proliferation. Infected cells display a wide range of alterations, from benign hyperplasia to dysplasia to invasive neoplasia. Provided that the latter step has not yet occurred, this process is reversible, including clearance of HPV infection and regression of precancer, which happens in many women who experience HPV infection.[68]

The vast majority of HPV infections are transient, with only a small proportion becoming persistent.[8,11,15,16,69-71] Several natural history studies have analyzed risks of progression in the continuum of preinvasive lesion stages. The **Table** shows the average probabilities of regression and progression of CIN that were derived from a pooled analysis of studies published from 1950 to 1993.[72]

Differences between precursor and invasive lesions with respect to the age when incidence rates peak provide important clues to the duration of the preclinical phase of the natural history of cervical cancer. The incidence rate for CIS increases more steeply with age than for invasive cancer, reaching a peak at ages 25 to 29 years, and then declines gradually at older ages, whereas the incidence of invasive cancers levels off after ages 40 to 44. This leaves a gap between peak incidence rates for CIS and invasive cancer of approximately 15 years.[68]

Cytopathology and Diagnosis

Various classification systems for cervical cytopathology have been used historically to define preinvasive lesions (Pap class system exclusively for cervico-vaginal cytology [not histology], dysplasia terminology, original CIN terminology, modified CIN terminology, and Bethesda system [SIL terminology]). Koilocytotic atypia is specific to mild dysplasia (CIN 1 or low-grade SIL [LSIL]) which is manifest in otherwise mature superficial or intermediate cells by enlarged, irregular nuclei with hyperchromasia, and perinuclear halo.[68] Other features include a slightly convoluted nuclear membrane, occasional binucleation, a moderately increased nuclear:cytoplasmic ratio, and sometimes, the cytoplasm around the halo stains densely eosinophilic. Moderate and severe dysplasia and CIS (CIN 2 and 3, respectively, or high-grade [HSIL]) contain malignant basal/parabasal cells of different numbers (on Pap test) or level of epithelial involvement in histology. Overall, LSIL is best viewed as a well-differentiated, clinically unstable lesion that is characterized morphologically by the cytopathic effects of a productive HPV infection. HSIL, on the other hand, shows a variable degree of transepithelial disorganization with malignant basal/parabasal cells.

Prevention of invasive cervical cancer is accomplished by arresting neoplastic development within the cervical epithelium before it becomes invasive. Because cytology is a screening tool, not a diagnostic test, cytologically detected atypical squamous cells of undetermined significance (ASC-US) and LSIL cases may, in fact, be HSIL by histology. This occurs in about 30% to 40% of LSIL and 5% to 10% of ASC-US.[73,74] Accordingly, international consensus guidelines[75,76] recommend that women with these cytological abnormalities be closely followed by Pap cytology every 6 months to discover those with HSIL. Persistence of ASC-US or LSIL results constitutes grounds for referral for colposcopy and biopsy, and all HSIL cases must be immediately referred for colposcopy, either on primary screen or follow-up. Consensus Guidelines of the American Society for Colposcopy and Cervical Pathology recommend 2 repeat cytology tests, immediate colposcopy, or DNA testing for high-risk HPV types as equivalent management options for women with ASC-US abnormalities.[76]

Table. Probabilities of Regression and Progression for CIN

	CIN 1	CIN 2	CIN 3
Regression	57%	43%	32%
Progression to CIS	11%	22%	—
Progression to invasive	1%	5%	12%

CIN indicates cervical intraepithelial neoplasia; CIS, carcinoma in situ.
Source: Reference 72.

Prevention of HPV and Cervical Cancer

Cervical cancer is a malignant neoplastic disease for which public health prevention initiatives have had the greatest success. Organized or opportunistic screening with the Pap smear has reduced the cervical cancer burden by about 75% in high-income countries during the past 50 years.[77] It is estimated that each year, 40 million to 50 million Pap smears are performed in the United States for detecting cervical cancer and its precursors.[78,79] Surveillance of Pap smear abnormalities found at screenings in the United States indicate the following distribution of results: 81.4% normal, 7.9% benign cellular changes consistent with either infection or reactive atypia, 5.2% ASC-US, 2.9% LSIL, 0.8% HSIL, and <0.1% invasive cancer. Unsatisfactory and other diagnoses comprises 1.7% of all smears.[80] In fact, in the United States, for each new case of invasive cancer found by Pap cytology screening, there are approximately 50 other cases of abnormal smears consistent with precursor lesions. Women harboring these lesions need close monitoring by cytology and, if abnormal results persist, by colposcopy and biopsy as well. Moreover, twice as many cases of equivocal or borderline atypias (ASC-US abnormalities) have to be added to this triage burden[81] and either followed by repeat cytology, triage by HPV testing, or sent for colposcopic examination. Altogether, ASC-US and SIL findings account for more than 10% of all Pap smears that are processed in screening programs, which imposes a great burden on the

healthcare system. It is estimated that 55% to 60% of cervical cancer cases occur in women who have not received a Pap test within the previous 3 years.[82,83]

Overall, cervical disease induced by HPV infection incurs a very high direct medical cost. Annual cervical cancer prevention and treatment costs in the United States have been estimated at $26 415 per 1000 women.[82] Insinga et al concluded that cervical HPV-related disease accounted for total healthcare costs of $3.4 billion, with expenditures for routine screening of $2.1 billion, false-positive Pap test results of $300 million, CIN 1 of $150 million, CIN 2/3 of $450 million, and invasive cancer of $350 million.[84]

HPV Vaccination

Pap smear screening offered an immediate solution to the critical problem of a high cervical cancer burden throughout the world 40 to 50 years ago. Recent research on the safety and efficacy of 2 candidate prophylactic vaccines against HPV has shown nearly 100% efficacy in preventing persistent infections and development of cervical precancerous lesions.[46,85,86] These 2 candidate prophylactic vaccines (quadrivalent Gardasil®, already available commercially, and bivalent Cervarix™, in final stages of clinical development) protect against the 2 main HPV types (HPV-16 and -18) that together cause about 75% of all cervical cancers. Moreover, a small degree of cross protection against other HR-HPVs, such as HPVs 31 and 45 may be expected.[86] HPV vaccination has the potential to significantly decrease the incidence of HPV type-specific cervical cancers and the burden associated with such infections. High vaccine coverage, sustained over many decades, with a long duration of vaccine-conferred protection would have a great impact on cervical cancer incidence. Even with high uptake of the vaccine, however, a statistically noticeable reduction of the burden of cervical cancer via HPV vaccination is unlikely to be observed for at least a decade or longer because of the latency required for averted high-grade lesions to progress to invasive disease.

HPV Testing in Screening

Despite its success, Pap cytology has important limitations. It is based on highly subjective interpretation of morphologic alterations present in cervical samples that must be collected with proper attention to sampling cells of the transformation zone. Also, the highly repetitive nature of the work of screening many smears leads to fatigue, which invariably causes errors in interpretation. A recent meta-analysis that included only studies unaffected by verification bias indicated that the average sensitivity of Pap cytology to detect CIN or invasive cervical cancer was 51%, and its average specificity was 98%.[87] Therefore, the Pap test's high false-negative rate has been its most critical limitation. False-negative diagnoses have important medical, financial, and legal implications; the latter being a particularly acute problem in North America where false-negative smears are among the most frequent reasons for medical malpractice litigation.

The advent of liquid-based cytology has helped to mitigate the problem of efficiency in processing smears in screening programs, but the limitations of cytology remain the same. This low sensitivity for an individual testing opportunity has to be compensated by the requirement to have women entering screening age with an initially negative smear to repeat their tests at least twice over the next 2 to 3 years before they can be safely followed as part of a routine screening schedule. This effectively brings the screening program sensitivity to acceptable levels, but safeguards must be in place to ensure adherence, coverage, and quality, costly undertakings that have worked well only in Western industrialized countries. Many developing countries that have invested in screening programs have yet to witness a reduction in cervical cancer burden. Furthermore, the reductions in many Western countries have begun to stabilize, which brings a sense of diminishing returns.

Of the molecular-based technologies for cervical cancer screening, HPV testing is eliciting the greatest interest in Western countries. There are primarily 2 technologies for this purpose. The Hybrid Capture aassay (Digene, Inc., Gaithersburg, MD) is currently the most widely used in clinical and screening settings. The Hybrid Capture is a nucleic acid hybridization assay with

signal amplification using microplate chemiluminescence for the qualitative detection in cervical specimens of HPV DNA of 13 HR genotypes, defined as those HPV genotypes that are associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Different PCR protocols have also been used to detect HPV. PCR protocols are based on target amplification with type-specific or consensus or general primers followed by hybridization with specific oligoprobes. PCR techniques to detect HPV will soon be commercially available.

HPV testing found its first application niche in triaging ASC-US smears. A recent meta-analysis found that it is a suitable and cost-effective option in deciding whether such cases need to be referred for colposcopy.[88] There have been several studies assessing the value of HPV testing compared with the Pap test as a cervical cancer screening tool in European, African, Asian, Latin American, and North American populations. As reviewed recently,[89-91] HPV testing has 25% to 35% higher sensitivity than cytology in absolute terms, but somewhat lower specificity of 5% to 10% for detecting high-grade lesions. Screening of women older than 30 years of age tends to improve the performance of HPV testing, because viral infections in this age group are less likely to be of a transient nature than those in younger women.

Of note is the fact that the combination of cytology and HPV testing attains very high sensitivity and negative predictive values (approaching 100%). This feature could potentially allow increasing screening intervals safely (eg, from 1-3 years to 3-5 years, depending on the population). The drawback of this approach is the excessive number of patients who would need to be referred for colposcopy initially, many of whom will turn out to be lesion-free. Resource-rich countries can absorb the extra costs related to the secondary triage of cases that will be referred via a dual-testing screening approach, because of the reduced patient flow in primary screening clinics afforded by the extension in the screening interval for women who are cytology and HPV negative. In addition, such a strategy may be cost-saving over time.

A few large randomized controlled trials of HPV testing in primary cervical cancer screening are currently ongoing in countries with centralized healthcare systems.[92-97] The results so far continue to point to the superior sensitivity of HPV testing compared with Pap cytology, with only a small difference in specificity, favoring the latter. These randomized controlled trials, embedded in ongoing opportunistic or organized screening programs, will provide the level of evidence necessary for public health policy makers to make informed decisions about the future of their cervical cancer screening programs. It is imperative, however, that decisions concerning changes in screening programs be made in concert with policies regarding implementing HPV vaccination in the same settings. Effective use of healthcare resources requires synergy among the various public health fronts involved in cervical cancer control.

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