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# Prospects for controlling cervical cancer at the turn of the century

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## Abstract

Cervical cancer morbidity and mortality have decreased substantially during the last 50 years mostly due to successful organized or opportunistic screening with Pap cytology in high and middle income countries. In many low income countries Pap cytology screening is yet to be effectively implemented or has failed to reduce cervical cancer rates to an appreciable extent. The fact that infection with certain human papillomavirus (HPV) types is now recognized as a necessary cause of this disease has led to new research fronts on prevention of cervical cancer. Testing for HPV DNA has shown great promise as a screening tool with better sensitivity but somewhat lower specificity than Pap cytology. In combination with the latter, HPV testing has the potential to improve the negative predictive value of cytology, thus allowing for increased testing intervals, which would lower program costs with acceptable safety. Advances in cytology processing and automation have also led to new screening approaches that are increasingly gaining acceptance in high and middle income countries. For low income countries, visual inspection with acetic acid has proven to be an effective alternative to conventional Pap cytology, especially in settings where no screening programs have been implemented. Concerning primary prevention of cervical cancer, recent research on the safety and efficacy of candidate prophylactic vaccines against HPV have shown very promising results with nearly 100% efficacy in preventing persistent infections and development of cervical cancer precursors. However, policy makers are strongly cautioned

## Resumen

La morbilidad y mortalidad de cáncer cervical ha decrecido sustancialmente durante los últimos 50 años, debido principalmente a programas organizados de detección oportuna de cáncer basados en citología, particularmente en países con altos y medianos ingresos. Sin embargo, en muchos países de bajos ingresos el programa de detección oportuna de cáncer basado en citología apenas está siendo implantado correctamente o tiene fallas, por lo que no se puede apreciar el alcance para reducir las tasas de este cáncer. El hecho es que la infección con ciertos tipos de virus de papiloma humano es ahora reconocida como una causa necesaria de la enfermedad, lo que ha conducido a nuevas investigaciones frente a la prevención del cáncer cervical. Las pruebas de ADN del virus del papiloma humano se han mostrado como una herramienta prometedora con gran sensibilidad, pero con especificidad más baja que la citología. En combinación con citología ginecológica, la prueba del virus del papiloma humano tiene potencial para mejorar el valor predictivo negativo de la prueba convencional, permitiendo incrementar los intervalos de periodicidad de la misma y poder disminuir los costos del programa con seguridad aceptable. Los avances en el procesamiento de la prueba de citología y automatización de pruebas que determinan ADN del virus, han permitido nuevas propuestas de tamizaje lo que incrementa cada vez más su aceptación en países de altos y medianos ingresos. Para países de bajos ingresos, se ha probado que la inspección visual con ácido acético es una alternativa efectiva para la citología convencional, especialmente observada en sitios en

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to avoid deferring decisions concerning the implementation of cervical cancer screening under the expectation that a successful vaccine could obviate the need for secondary prevention strategies. This paper is available too at: <http://www.insp.mx/salud/index.html>

**Key words:** cervical neoplasms/prevention and control; papillomavirus, human; screening; Pap cytology; liquid-based cytology

los que los programas de tamizaje no han sido organizados. Referente a la prevención primaria del cáncer cervical, investigaciones recientes sobre seguridad y eficacia de la vacuna profiláctica contra el virus del papiloma humano han mostrado resultados muy prometedores con una eficacia cercana a 100% en prevención de infecciones persistentes y desarrollo de lesiones precursoras de este cáncer. Sin embargo, las políticas generadas son fuertemente cautelosas para evitar decisiones aplazadas, concernientes a la implantación del tamizaje del cáncer cervical bajo la expectativa de que la vacuna podría obviar la necesidad de estrategias de prevención secundaria. Este artículo también está disponible en: <http://www.insp.mx/salud/index.html>

**Palabras clave:** virus de papiloma humano; prevención secundaria; detección oportuna de cáncer cervical; citología base líquida

**I**t is probably fair to assume that of all malignant neoplastic diseases, cervical cancer is the one in which public health prevention initiatives have been the most successful in the western industrialized world. Widespread programmatic or opportunistic screening with the Papanicolaou cytology technique, or Pap test for short, has likely contributed to reducing about three-fourths of the cervical cancer burden in high income countries during the last 50 years. Additional factors contributing to further historical declines in cervical cancer incidence are the gradual decrease in population fertility (lower parity) and improvements in the western diet (more intake of fresh vegetables and fruits). Lung cancer prevention via tobacco cessation programs is still far from its target of about 80% reduction in disease incidence and screening efforts for other male or female neoplasms have more modest goals for curbing cancer incidence.

In spite of its success, Pap cytology has important limitations. A recent meta-analysis that included only studies unaffected by verification bias indicated that the average sensitivity of Pap cytology to detect cervical intraepithelial neoplasia (CIN) or invasive cervical cancer was 51% and its average specificity was 98%.<sup>1</sup> The Pap test's high false negative rate is thus its most critical limitation. About one-third of false-negative diagnoses are attributable to slide interpretation errors and two-thirds to poor sample collection and slide preparation.<sup>2</sup> 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. Pap

cytology is based on highly subjective interpretation of morphologic alterations and is also dependent on optimally collected samples. Also, the highly repetitive nature of the work of screening many Pap smears leads to fatigue, which invariably causes errors in interpretation.

Conversely, despite the test's relatively high specificity, false-positive results are particularly common in populations with low prevalence of CIN and cancer. False-positive cytology results lead to unnecessary and frequently invasive procedures in a fairly large number of women which in turn result in increased patient anxiety and costs. The solution to minimizing errors in cytology is to improve the quality of smear taking, slide processing, and overall diagnostic performance of cervical cytology, which incur high costs for a screening program. In many settings, especially developing countries, cytology-based programs have failed to reduce cervical cancer rates substantially.<sup>3,4</sup> This state of affairs elicited interest from the medical technology industry in developing new morphology or molecular tests with adequate sensitivity and specificity for detecting clinically significant cancer precursors. Ongoing research on the use of such new tests has led to new approaches to preventing cervical cancer and to reducing the costs of screening programs both in developed and in developing countries.

With the relatively recent understanding of the causal connection between infection by certain types (the so-called high risk types) of human papillomavirus (HPV) and cervical neoplasia<sup>5</sup> a new paradigm of research in the detection and prevention of CIN and cervical cancer has begun. Concerning secondary pre-

vention (screening) initiatives, this research has led to the development of tests to detect cervical HPV infection as the necessary precursor event driving cervical carcinogenesis. Use of tests to detect HPV DNA has the potential to become a useful cervical cancer screening tool either as a standalone approach or in combination with Pap cytology to augment the latter test's efficacy. Research on HPV has also led to substantial technological knowledge that is currently being used to develop candidate vaccines to prevent HPV infection and, ultimately, cervical cancer as well. Further gains in our understanding of the natural history of these infections and of the molecular biology of cervical cancer have also led to additional promising leads in prevention based on testing for genetic alterations or markers of early disease.

This overview summarizes the epidemiologic evidence for the high public health significance of cervical cancer control followed by a description of the existing prospects in all of the above areas of prevention; both primary, via control and elimination of the causes of disease, and secondary, via screening for cancer precursors (CIN) and their immediate treatment. For historical reasons, since screening by Pap cytology has been the first secondary prevention initiative in cervical cancer we review the situation with emerging screening technologies first. This is followed by a brief overview of progress in primary prevention.

### Cervical cancer burden throughout the world

Cervical cancer is one of the most common malignant diseases of women. In the US each year there are approximately 12 800 new cases of invasive cervical cancer with 4 600 deaths due to this disease.<sup>6</sup> In Mexico, a country with less than half of the US population, the estimated new cervical cancer cases in 2000 was 16 450, which was accompanied in the same year by 6 650 deaths.<sup>7</sup> During the last decade, an estimated 371 000 new cases of invasive cervical carcinoma were diagnosed annually worldwide, representing nearly 10% of all female cancers. Its incidence is the seventh overall among all cancer sites, regardless of gender, and is third among women, after breast and colorectal cancer.<sup>8</sup> In developing countries, cervical cancer was the most frequent neoplastic disease of women until the early 1990's when breast became the predominant cancer site.<sup>9</sup> The highest risk areas for cervical cancer are in Central and South America, Southern and Eastern Africa, and The Caribbean, with average incidence rates around 40 per 100 000 women per year. While risk in western Europe and North America is considered

relatively low at less than 10 new cases annually per 100 000 women rates are 10 times higher in some parts of Northeastern Brazil, where the cumulative lifetime risk can approach 10%.<sup>10</sup>

Every year, an estimated 190 000 deaths from cervical cancer occur worldwide, with over three-fourths of them in developing countries, where mortality from this disease is the highest among deaths caused by neoplasms.<sup>11</sup> In general, there is a correlation between incidence and mortality across all regions but some areas seem to have a disproportionately higher mortality, such as Africa. Cervical cancer incidence and mortality in North America are relatively low. The mortality rate for Canada is the lowest among all regions.<sup>2</sup>

Less than 50% of women affected by cervical cancer in developing countries survive longer than five years whereas the five-year survival rate in developed countries is about 66%.<sup>11</sup> Moreover, cervical cancer generally affects multiparous women in the early post-menopausal years. In high-fertility developing countries these women are the primary source of moral values and education for their school-age children. The premature loss of these mothers has important social consequences for the community.

### Technologies for cervical cancer screening

The available screening technologies can be classified into morphology- or molecular-based approaches to recognize cytological or tissue-level abnormalities or molecular markers consistent with CIN or cervical cancer. Further distinctions can also be made based on the use of aided or unaided microscopy or of physical and electro-optical properties. Table I provides an overview of the various technologies considered in cervical cancer screening. The most relevant or promising among the technologies are summarized below.

*The paradigm: Pap cytology.* The Pap test is one of the first cancer screening tests and is undoubtedly the one with the best record of accomplishments in contemporary medical practice. Pap test screening targets mainly the detection of cervix cancer precursors, thereby allowing close monitoring of equivocal or low grade abnormalities on repeat tests or immediate referral for colposcopy, biopsy, and treatment of high grade or more severe lesions. Prevention of invasive cervical cancer is thus accomplished by arresting neoplastic development within the cervical epithelium before it becomes invasive. There are two types of cervical cancer screening programs: opportunistic (or sporadic) and systematic (or organized). Opportunistic screen-

Table I  
**MOST RELEVANT TECHNOLOGIES FOR CERVICAL CANCER SCREENING AND THEIR CHARACTERISTICS**

Approach	Technology	Features
Morphological, recognition of cellular level abnormalities	Pap test	Standard of cervical cancer screening, oldest medical test, proven effectiveness in reducing incidence of and mortality from cervical cancer. Suitable for most settings, particularly middle and high income countries
	Liquid-based cytology	Cleaner, more reproducible but costlier alternative to the conventional Pap test. Can be automated. Concern: dependence on proprietary technology. Suitable for high and middle income countries
	Automated cytology	Useful in settings with mandated quality control of conventional cytology. Concern: dependence on proprietary technology. Suitable for high income countries only
Morphological, recognition of cellular level abnormalities with molecular staining	P16INK4A antigen detection	Experimental, leads to more reproducible reading of Pap smears prepared with liquid cytology. Better distinction of relevant dysplastic features
Morphological, recognition of tissue level abnormalities with or without low level magnification	Simple visual inspection (downstaging)	Real-time but ineffective, leads to a high rate of referrals (high false positive rate)
	Visual inspection with acetic acid (VIA). Synonyms: direct visual inspection (DVI), aided visual inspection (AVI), VIA with low level magnification (VIAM), visual inspection with Lugol's iodine (VILI)	Real-time. Sensitivity equal or better but lower specificity than conventional Pap cytology. Suitable for low income countries. Ongoing investigations to obtain proof of effectiveness in reducing cervical cancer incidence and mortality
	Cervicography	Sensitivity lower and specificity comparable or lower (setting dependent) than conventional cytology. Still dependent on proprietary technology. Suitable for high income countries as ancillary method
Morphological, recognition of tissue level abnormalities based on physical/optical properties	Spectroscopy and speculoscopy	Experimental, real-time. Promising technology but adequate evidence of comparative efficacy still lacking. Sensitivity and specificity seems comparable to VIA (speculoscopy)
	Polar probe	Experimental, real-time. Promising technology but evidence of comparative efficacy still lacking
Molecular testing	HPV testing	More sensitive but less specific than conventional or liquid-based cytology to detect high grade lesions. In combination with cytology may allow safely increasing screening intervals, thus lowering costs. Can be automated. Concern: dependence on proprietary technology. Suitable for high and middle income countries and possibly for low income countries with no cervical cancer screening

ing is carried out by suggestion from a physician or health care provider when a woman presents for consultation for other health reasons. Systematic screening occurs within a system with mechanisms to identify the target population and invite all of its members to participate. There is widespread belief that systematic screening may be superior to opportunistic screening in terms of cost-effectiveness<sup>12</sup> but this contention has been challenged.<sup>13</sup> A discussion of available guidelines for Pap test screening is discussed elsewhere.<sup>12,14,15</sup>

There have been no prospective controlled trials of Pap screening efficacy, either randomized or not. The evidence for the efficacy of Pap smear screening in cervical cancer comes from two sources: a) epidemiologic

studies indicating that the risk of invasive cervical cancer is substantially greater in women who have not been screened and that risk increases with time since last normal smear or with lower frequency of screening, and b) population surveillance, which indicates that cervical cancer incidence and mortality rates have decreased following adoption of cytology screening in Scandinavian countries, in Canada, and in the USA, with reductions in incidence and mortality being proportional to the extent of population coverage.<sup>14</sup>

*Thin-Layer liquid-based cytology.* The ThinPrep™ system (Cytec, Inc., Boxborough, Mass., USA) and AutoCyt Prep System™ (Tripath Imaging Inc., NC, USA) are

liquid-based alternatives for the conventional method of Pap smear preparation. The sample recovered from the cervix is suspended in a cell-preserving solution instead of being placed directly on a glass slide. Virtually all cellular material is made available to the laboratory. With the conventional Pap smear, roughly 20% of the cervical cells harvested from the cervix are placed manually on the glass slide.<sup>16</sup> In the thin layer samples, excess blood and inflammatory cells are lysed and a random sample of approximately 50 000 cells are transferred by the robotic cell processor as a thin layer onto a glass slide. The slides are stained and then read by cytotechnologists. Automated thin-layer slides can improve detection of atypical cells, precursor lesions, and cancer by producing uniformly cleaner slides free of blood, inflammatory debris, and cell clumps that interfere with microscopic reading.<sup>17,18</sup>

One attractive feature of this system is the ability to save the supernatant of remaining cells in a standardized fashion for subsequent panel testing for HPV DNA and *Chlamydia trachomatis*.<sup>14</sup> Another advantage of thin smears is that they can be used in conjunction with immunocytochemical staining for specific markers of dysplastic progression. The viral oncogene E7 induces increased expression of the cyclin dependent kinase inhibitor p16(ink4a) in infected cells.<sup>19</sup> Immunostaining for p16(ink4a) using a monoclonal antibody can identify dysplastic cells with enhanced accuracy<sup>20</sup> (Table I).

The US Food and Drug Administration (FDA) approved the ThinPrep Pap test in 1996 and the Auto-Cyte Prep System in 1999, as significantly superior and equivalent to the conventional Pap smear, respectively, for the detection of CIN and cervical cancer. Since then these technologies have already gained considerable penetration in the market for opportunistic cervical cancer screening in the USA, currently approaching or exceeding 50% of all smears taken in major urban centers.

In a recent evidence-based medicine review,<sup>21</sup> the American Cancer Society concluded that liquid-based cytology was a suitable alternative to conventional cervical smears, specifying that use of this technology allows cervical screening to be performed every two years and after age 30, women who have had three consecutive, technically satisfactory normal or negative cytology results may be screened every two to three years [unless they belong to a high risk group, e.g., history of prenatal diethyls-estrol (DES) exposure, HIV positivity, or immunosuppressive conditions].

*Cytology automation.* There are several automated systems being tested and marketed, ranging from robotic

devices that process the cervical cell suspensions to prepare standardized thin-layer slides to computer-assisted slide scanners that map the smear to detect abnormal cells, thereby separating any slides that contain suspect images for subsequent reading by a cytotechnologist. A key advantage is the potential to alleviate shortage of qualified manpower in cytopathology. Comparative trials mostly funded by the private sector are ongoing in many laboratories in North America and in Europe to answer questions related to screening efficacy and cost effectiveness of automated devices.

At present, there is only one device approved by the FDA for quality control of cytology and for primary screening for cervix cancer and its precursors in the USA, the AutoPap Screening System (Tripath Imaging Inc., NC, USA), which scans with a high speed video camera close to 200 conventional Pap smears a day. Morphometric algorithms indicate to the cytotechnologists to manually screen slides that contain the most likely abnormal cells. Conversely, those without likely abnormalities are filed (approximately 25% to 50%) without the need for human review. The device outperforms human review of manually screened negative smears (for quality control) by a factor of 5 to 7, and in screening mode of low-risk women, performs as well as humans with a sort rate (no review of smears needed) of up to 50%. On the other hand, the device is cumbersome and its large throughput and high per-slide cost make it cost-effective only for large-volume laboratories.<sup>22</sup>

*Visual inspection with acetic acid application (VIA):* Visual methods have emerged as a non-technology intensive, alternative to cytology screening in low-income countries. The visual methods of screening include unaided, non-magnified visual inspection of the cervix (the so-called 'downstaging'), visual inspection with acetic acid (VIA) (also known as direct visual inspection [DVI], cervicospoty, or aided visual inspection), VIA with low level magnification (VIAM), visual inspection with Lugol's iodine (VILI), and cervicography.

Downstaging has been shown to be inaccurate and ineffective.<sup>12</sup> Of all visual methods VIA has been the most extensively investigated in different countries with respect to its screening accuracy in detecting cervical neoplasia. VIA involves naked eye examination of the uterine cervix, usually by a nurse or other non-medical health worker, after swabbing it with 3-5% acetic acid and using artificial bright illumination. Findings of characteristic acetowhite lesions are considered positive. VIA provides results immediately (also referred to as real time screening test) which allows for



treatment and management decisions to be taken during the same patient visit. VIA seems to be at least as sensitive as, if not more sensitive than, conventional cytology to detect high-grade CIN, but it has lower specificity than the latter test.<sup>12</sup> As it stands, VIA is the most promising low technology alternative to cytology, which led international agencies such as WHO to study its efficacy in reducing incidence of and mortality from cervical cancer. These investigations are currently ongoing.<sup>23</sup>

**HPV testing in screening.** There have been several studies assessing the value of HPV testing compared to the Pap test as a cervical cancer screening tool. Most investigations have used first or second generation Hybrid Capture™ (HC) systems (Digene, Inc., Gaithersburg, MD), the only HPV test that is currently FDA approved. A few studies have used different polymerase chain reaction (PCR) protocols to detect HPV. PCR has a lower threshold of detectability for HPV DNA than the HC assay but HC2 (the second generation assay which became available commercially in 1997) has substantially improved molecular sensitivity (as compared with its first generation counterpart, the Hybrid Capture tube assay) for detecting HPV DNA that approaches that of PCR techniques. The HC2 test is a nucleic acid hybridization assay with signal amplification using microplate chemiluminescence for the qualitative detection in cervical specimens of HPV DNA of 13 high-risk types, defined as those that are frequently associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. PCR protocols are based on target amplification with type-specific or consensus or general primers followed by hybridization with specific oligoprobes. No PCR technique to detect HPV is yet available commercially.

Studies using HC or PCR in cervical cancer screening for detection of high grade squamous intraepithelial lesions (HSIL) (CIN of grades 2 or 3) have targeted European,<sup>24-27</sup> African,<sup>28-30</sup> Asian,<sup>31</sup> Latin American,<sup>32</sup> and North American<sup>33,34</sup> populations. As shown in Table II, HPV testing has 25%-30% higher sensitivity than cytology in absolute terms but somewhat lower specificity, 8%-10% lower for detecting high grade lesions. Screening of women ages 30 or older or 35 or older 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.

An important finding of some studies was the realization that the combination of cytology and HPV testing attained very high sensitivity and negative predictive values (approaching 100%).<sup>31-33</sup> A testing com-

Table II  
ESTIMATES OF SCREENING PERFORMANCE INDICES FROM STUDIES COMPARING HPV TESTING WITH PAP CYTOLOGY\* IN SCREENING FOR CERVICAL CANCER AND ITS PRECURSOR LESIONS. ESTIMATES SHOWN ARE FOR HIGH GRADE CIN OR CANCERS AS DISEASE OUTCOME. UNLESS NOTED OTHERWISE RESULTS APPLY TO ALL AGE GROUPS

Study	Sensitivity		Specificity		Characteristics
	HPV	Pap	HPV	Pap	
Cuzick, 1995	75	46	96	96	
Clavel, 1999	100	79	86	96	
Cuzick, 1999	95	79	94	99	
Kuhn, 2000	88	78	82	97	
Ratnam, 2000	68	27	91	96	All ages, bias-adjusted <sup>†</sup>
	82	40	94	97	Age ≥ 30, bias-adjusted <sup>†</sup>
Schiffman, 2000	88	78	89	94	
Wright, 2000	84	61	83	96	
Schneider, 2000	89	20	94	99	Bias-adjusted <sup>†</sup>
Belinson, 2001	95	87	85	94	Liquid-based cytology
Blumenthal, 2001	80	44	61	91	Bias-free <sup>†</sup>
Clavel, 2001	100	68	87	95	All ages
	100	58	90	96	Age > 30
Kulasingam, 2002	63	36	83	96	Age ≥ 30, bias-adjusted <sup>†</sup>

\* LSIL threshold (majority of studies) or LSIL or persistent ASCUS (Kulasingam, 2002)

<sup>†</sup> Verification bias either adjusted for or avoided by having colposcopies performed in all subjects

bination with such a high negative predictive value could potentially allow increasing screening intervals safely, e.g., from 1-3 years to 3-5 years, depending on the population and risk profile. The drawback of this approach is the loss in specificity with respect to either test in isolation due to the excessive number of patients who would need to be referred for colposcopy, many of which will turn out to be false positive results. 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 this strategy may be cost saving upon long term assessment, via the reduced patient flow for primary screening clinics. Economic models based on valid estimates of screening efficacy across different settings are urgently needed to assess the potential benefit of combined screening in relation to its costs.

One of the advantages of HPV DNA testing is that it is suitable for self-sampling. In one study of 1 365 South-African women aged 35 to 65 years old the rate of detecting cervical cancer precursors was compara-

ble between self-sampling for HPV testing (66.1%) and conventional cytology performed by healthcare providers (67.9%).<sup>29</sup> Self-sampling is likely to improve compliance, which is particularly appealing in countries in which cultures have social and religious limitations on the acceptability of vaginal examinations.

A few large randomized controlled trials of HPV testing in primary cervical cancer screening are currently ongoing. Of note are the UK HPV in Addition to Routine Testing (HART) investigation,<sup>35</sup> the UK "A Randomized Trial In Screening To Improve Cytology" (ARTISTIC) [Henry Kitchener, personal communication], and the Canadian Cervical Cancer Screening Trial (CCaST), led by the authors.

*HPV testing for secondary triage of cervical abnormalities.* One of the first applications of HPV DNA testing in clinical practice was for the triage of women referred for colposcopy because of an abnormal Pap smear. The adoption nearly 15 years ago of the Bethesda system for cervical cytology reports<sup>36</sup> has dramatically increased the proportion of Pap smears with cytological abnormalities that merit clinical attention. The new terminology increased the overall proportion of low grade lesions by combining the original mild dysplasia category with cytological abnormalities consistent with koilocytotic atypias, thus creating the low grade intraepithelial lesion (LSIL) designation, and created a new category for borderline lesions, the "atypical squamous cells of undetermined significance", or ASCUS. While there is consensus that women with high grade SIL (HSIL) on cytology need immediate referral for colposcopy, uncertainty has existed about management options for ASCUS and LSIL. Such cases have been managed by immediate colposcopy, repeat Pap testing, and HPV DNA testing, the latter two tests either alone or in combination.

Preliminary evidence that HPV DNA testing has clinical value in triaging ASCUS or LSIL has been provided by several studies conducted in the early and mid-90's, which indicated for the most part that HPV DNA testing could increase the sensitivity of a repeat Pap when used as an adjunct test.<sup>37</sup> Two recent large-scale studies (the Kaiser-Permanente and the ALTS investigations) have provided more conclusive evidence of benefit for women of all ages, specifically for the triage of ASCUS smears.<sup>38,39</sup> HPV DNA testing is significantly more sensitive (about 10% higher in absolute terms) than repeat Pap cytology in detecting histologically confirmed HSIL among such cases, even when the latter is used at a lower threshold of positivity. These two studies have shown also that the HPV and Pap tests have comparable specificities in ASCUS triage.

While the value of HPV DNA testing in the triage of ASCUS smears is well established, it cannot be recommended as a tool to orient clinical management of women with a referral LSIL smear. A component of the aforementioned ALTS trial found that more than four-fifths of such cases are HPV positive. Given the very high rate of HPV positivity (with high risk types) among women with LSIL there would be limited or no value in using HPV DNA testing in triaging such cases for colposcopy.<sup>40</sup> Recent analyses from the latter study using restriction on age or viral load corroborate this interpretation.<sup>41</sup>

### Primary prevention of cervical cancer

Recognition that HPV infection is the central cause of cervical cancer and its precursor CIN<sup>42</sup> has created new research fronts in primary prevention of this disease.

*Primary prevention by education.* Primary prevention of cervical cancer can be achieved through prevention and control of genital HPV infection. Health promotion strategies geared at a change in sexual behavior targeting all sexually-transmitted infections of public health significance can be effective in preventing genital HPV infection.<sup>14</sup> Although there is consensus that symptomatic HPV infection (genital warts) should be managed via treatment, counseling, and partner notification, active case-finding of asymptomatic HPV infection is currently not recommended as a control measure. Further research is needed to determine the effectiveness of such a strategy.

*Primary prevention by HPV vaccination.* Two main types of HPV vaccines are currently being developed: prophylactic vaccines to prevent HPV infection and associated diseases, and therapeutic vaccines to induce regression of precancerous lesions or remission of advanced cervical cancer. Strictly speaking, however, the latter type cannot be considered as part of a primary prevention effort because of its curative intent.

DNA-free virus-like particles (VLP) synthesized by self-assembly of fusion proteins of the major capsid antigen L1 induce a strong humoral response with neutralizing antibodies. VLPs are thus the best candidate immunogen for HPV vaccine trials. Such vaccines are already under evaluation in efficacy and safety trials in different populations sponsored by pharmaceutical companies (e.g., Glaxo Smithkline and Merck) and by the US National Institutes of Health and can produce strong type-specific antibody responses.<sup>43</sup> The preliminary results of one such a trial were extremely promising.<sup>44</sup> It indicated that an HPV 16 VLP vaccine



was 100% effective in preventing acquisition of persistent infection with HPV 16 and 90% effective in preventing any incident HPV 16 infection, transient or persistent. As a noteworthy secondary finding was the fact that all HPV 16 associated CIN cases occurred in the non-vaccinated group.

Immunization against HPV may have greatest value in developing countries, where 80% of the global burden of cervical cancer occurs each year and where Pap screening programs have been largely ineffective. In this regard, many issues are being considered by those involved in HPV vaccine research. Long-lasting protection against HPV 16 may translate into prevention of nearly half of all cervical cancers. Although evidence from controlled trials has been obtained mostly for monovalent or bivalent vaccines there is a general consensus that a future vaccine will have to include at least the most common high risk HPV types associated with the disease to be largely effective against cervical cancer. Other concerns include the development and standardization of surrogate assays for protective antibodies, the definition of the target population to be vaccinated, agreement on trial endpoints, e.g., early (HPV) vs. late (lesions) for prophylactic vaccines and criteria for regression of established lesions for therapeutic vaccines, the establishment of roles for the public sector and regulatory agencies; identification of funding sources for studies in which the pharmaceutical sector will not be involved, and last, but not least, coordination with secondary prevention strategies.

## Conclusions

In summary, although much has been gained in the last 50 years in reducing the burden of cervical cancer by organized or opportunistic cytology screening, the benefits have been seen particularly in high and middle income countries. Cervical cancer remains an important public health problem in low income countries, especially in Africa and in Latin America. Despite its history of success when performed in well controlled conditions, the Pap test has several limitations. Efficacious alternatives are available but their cost effectiveness needs to be assessed in different settings. Some of the most promising alternatives to conventional Pap cytology, such as HPV testing or liquid-based cytology, may be effective in high and middle countries that have not yet made substantial investments in establishing Pap-based screening programs or overhauling existing ones that seem inadequate. In this regard, an important concern is the possible dependence on a proprietary method that is controlled by one or a few commercial monopolies. On the other hand, VIA seems to be a viable

and cost effective option for low income countries with little infrastructure resources.

Public health authorities in middle and low income countries have monitored closely the ongoing debate on the role of new screening technologies. Between the fear of increased health care costs consequent to the adoption of a new screening test and the promising results coming from the research front on HPV vaccines it is tempting to take a wait-and-see attitude concerning cervical cancer prevention. It is not unreasonable to consider that this posture could lead to decreased funding for cervical cancer screening in the false hope that HPV vaccines will be available soon to eradicate the disease. This scenario could prove disastrous by abolishing the hard-earned gains made in the last half century in reducing cervical cancer morbidity and mortality by Pap screening.

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