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Emerging trends and recommendations

CERVICAL CANCER PREVENTION

Promises and perils in a changing landscape

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Top-line summary

Universal deployment of organized or opportunistic screening with Pap cytology in high-income countries has substantially reduced cervical cancer morbidity and mortality during the last 50 years. Cervical cancer remains a critical public health problem, however, because in many low-income countries, Pap screening has not yet been effectively implemented or it has failed to reduce cervical cancer rates. Infection with certain human papillomavirus (HPV) types is now recognized as a necessary cause of this disease. Testing for the presence of the DNA of these HPVs in genital samples shows great promise as a screening tool, with much greater sensitivity but slightly lower specificity than Pap cytology. Combining both methods has the potential to improve the negative predictive value of cytology, thus allowing testing intervals to increase and lowering program costs with acceptable safety. As well, recent research on the safety and efficacy of candidate prophylactic vaccines against HPV has shown nearly 100% efficacy in preventing persistent infections and development of cervical precancerous lesions. Licensed HPV vaccines will be available in 2006–7. To achieve cost-effectiveness, policymakers are urged to consider screening and immunization as integrated preventive approaches.

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Cervical cancer is the malignant neoplastic disease for which public health prevention initiatives have had the greatest success. Organized or opportunistic screening with the Papanicolaou cytology technique (Pap test) has reduced the cervical cancer burden by about 75% in high-income countries during the last 50 years.

In comparison, lung cancer control via tobacco cessation is still far from its target of 80% reduction in disease incidence, and screening efforts for other neoplasms have much less ambitious targets.

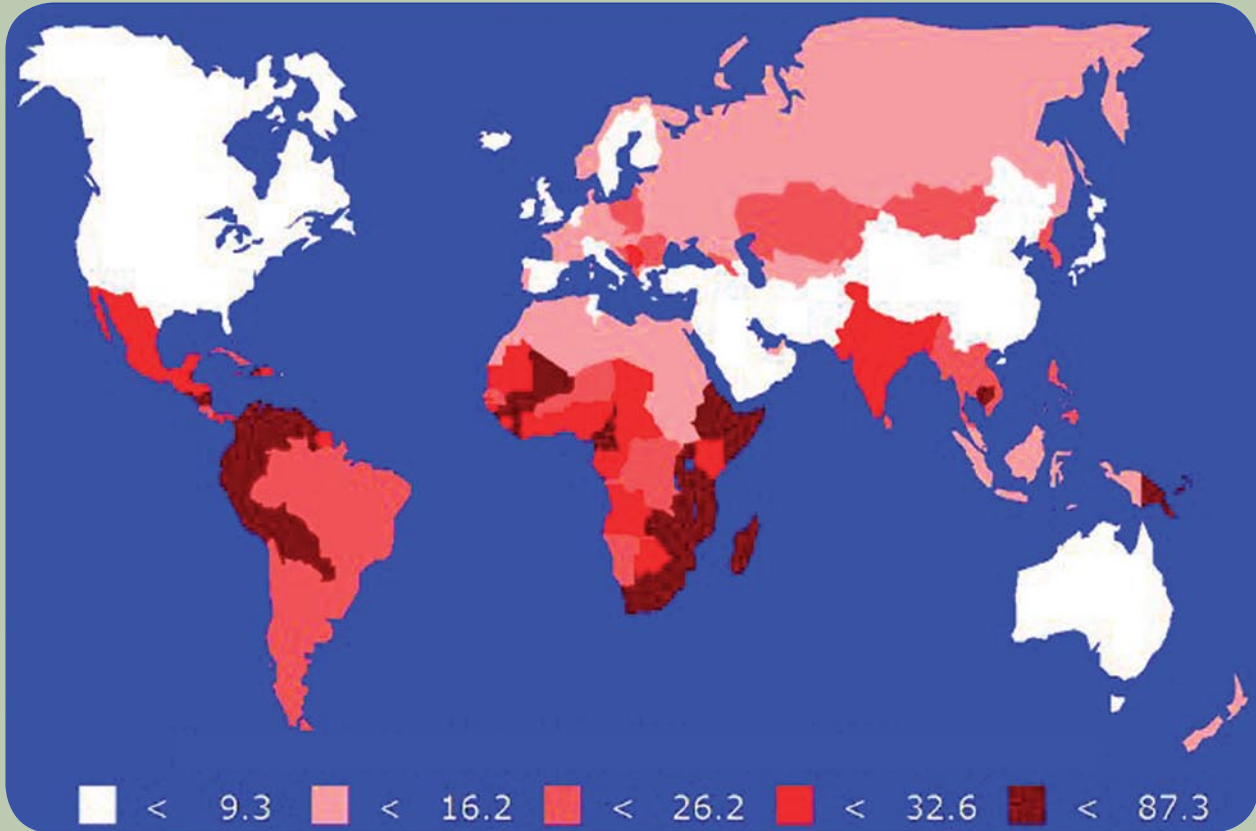
In Canada, the early experiences of British Columbia and other provinces are considered a model for implementation of organized programs. Unfortunately, however, few developing countries have fully reaped the benefits of screening. Cervical cancer remains an important public health problem: with 493,000 new cases diagnosed in 2002 — 83% of them in developing countries — it is the second most common malignant neoplasm affecting women worldwide.¹ The highest-risk areas for cervical cancer are in Southern and Eastern Africa, Melanesia, the Caribbean, and Central and South America, with average incidence rates well above 30 per 100,000 women per year (**Figure 1**, page 10). 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%.²

Recent understanding of the necessary causal connection between infection by certain types of human papillomavirus (HPV) — the so-called high-risk, or oncogenic types — and cervical cancer^{3,4} has paved the way for new approaches to cervical cancer prevention. For secondary prevention (i.e. screening), both the Pap test and a DNA test for the oncogenic HPVs are available. HPV vaccination has also emerged as a promising new front in primary prevention of cervical cancer.

SCREENING TECHNOLOGIES

The available screening technologies can be classified into morphology- and molecular-based approaches to recognizing cytologic or tissue-level abnormalities or molecular markers

FIGURE 1. Age-standardized* rates of cervical cancer per 100,000 women per year



* based on the world population in 1960

consistent with cervical intraepithelial neoplasia (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 1** outlines the various technologies considered in cervical cancer screening, most of which are still under evaluation.

Cervical cancer screening imposes a substantial economic burden. In most Western countries, for each new case of invasive cancer found by Pap cytology approximately 50–100 other cases yield abnormal smears consistent with precursor lesions requiring clinical management, such as squamous intraepithelial lesions (SIL), low- (LSIL) and high-grade (HSIL) lesions. Further, twice as many cases are found of equivocal or borderline atypias, known as atypical squamous cells of undetermined significance (ASC-US). ASC-US and SIL findings account for up to 10% of all Pap smears processed in screening programs in Western countries.⁵

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 transformation zone cells. The highly repetitive nature of screening many smears leads to fatigue and invariably to errors in interpretation. A recent meta-analysis of studies unaffected by veri-

fication bias indicated that the average sensitivity of Pap cytology to detect CIN was 51% and average specificity was 98%.⁶ The high false-negative rate has been the Pap test's most critical limitation, as false-negative diagnoses have important medical, financial and legal implications. In North America false-negative smears are among the most frequent reasons for medical malpractice litigation.⁷ The advent of liquid-based cytology has helped mitigate the problem of efficiency in processing smears but the limitations of cytology remain. To compensate for the low sensitivity of individual testing, women whose initial smear is negative should be retested at least twice over the next 2–3 years, before they can be safely followed at 2- or 3-year intervals. This brings the screening program sensitivity to acceptable levels but requires safeguards to ensure compliance, 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.

Of the molecular-based technologies for cervical cancer screening, HPV testing is eliciting the greatest interest, with 2 main technologies. The hybrid capture (HC) assay, currently the most widely used in clinical and screening settings, is a nucleic acid hybridization assay with signal

amplification. It uses microplate chemiluminescence for the qualitative detection in cervical specimens of HPV DNA of 13 high oncogenic-risk genotypes associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Different polymerase chain reaction (PCR) protocols have also been used to detect HPV. Based on target amplification with type-specific or consensus (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 it to be a suitable and cost-effective option in deciding whether or not such cases need to be referred for colposcopy.⁸ Several studies assessing the value of HPV testing compared to the Pap test as a cervical cancer screening tool in European, African, Asian, Latin American and North American populations have found HPV testing to have 25% to 35% higher sensitivity than cytology in absolute terms but 5% to 10% lower specificity for detecting high-grade lesions.⁹⁻¹¹ Screen-

ing of women more than 30 years old 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 in younger women. Importantly, the combination of cytology and HPV testing attains very high sensitivity and negative predictive values approaching 100%, which could potentially make longer screening intervals of 3–5 years safe (depending on the population). The drawback of this approach is that an initially excessive number of patients would need to be referred for colposcopy, with many turning out to be lesion-free. Over time this dual-testing screening approach should be cost-saving because it will extend the screening interval for women who are cytology- and HPV-negative, reducing patient flow in primary screening clinics.

A few large randomized controlled trials (RCTs) of HPV testing in primary cervical cancer screening are currently ongoing. Of note are the UK HART (HPV in Addition to Routine Testing) investigation,¹² the UK ARTISTIC trial (A Randomized Trial In Screening To Improve Cytology),

TABLE 1. Technologies used for cervical cancer screening and their characteristics

Approach	Technology	Features
Morphological, recognition of cellular level abnormalities	Pap test	Standard, oldest medical test, proven effectiveness in reducing incidence and mortality. 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. Dependent on proprietary technology. Suitable for high- and middle-income countries.
	Automated cytology	Useful in settings with mandated quality control of conventional cytology. Dependent 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, because high-false positive rate leads to a high rate of referrals.
	Visual inspection with acetic acid (VIA). Synonyms and variations: 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. Investigations ongoing to obtain proof of effectiveness in reducing incidence and mortality.
	Cervicography	Sensitivity lower and specificity comparable or lower (setting-dependent) than conventional cytology. Dependent on proprietary technology. Suitable for high-income countries as an ancillary method but has lost favour in recent years.
Morphological, recognition of tissue level abnormalities based on physical/optical properties	Spectroscopy and speculoscopy	Experimental, real-time. Promising, but lacks adequate evidence of comparative efficacy. Sensitivity and specificity seems comparable to VIA (speculoscopy).
	Polar probe	Experimental, real-time. Promising but lacks evidence of comparative efficacy.
Molecular testing	HPV testing	More sensitive but slightly less specific than conventional or liquid-based cytology. In combination with cytology may allow safely increasing screening intervals, thus lowering costs. Can be automated. Dependent on proprietary technology. Suitable for high- and middle-income countries and possibly for low-income countries with no screening programs.

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and the CCCaST (Canadian Cervical Cancer Screening Trial).¹³ Embedded in ongoing opportunistic or organized screening programs, these RCTs 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.

PREVENTION VIA HPV VACCINATION

Vaccination is among the most successful and least costly of all public health interventions. Primary prevention of cervical cancer can be achieved through prevention and control of genital infection with oncogenic HPV types. Two 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. The latter vaccine type has not shown encouraging results and cannot be considered a primary prevention strategy because it targets existing lesions. Here, we consider only progress with prophylactic vaccines.

HPV DNA-free virus-like particles (VLPs) synthesized by self-assembly of fusion proteins of the major capsid anti-

gen L1 (or of both L1 and L2) induce a strong humoral response with neutralizing antibodies. VLPs have thus become the best candidate immunogen for HPV vaccine trials.¹⁴ In electron microscopy preparations, VLPs are indistinguishable from real viruses. Initial results indicate that protection against development of persistent infection with HPV types 16 and 18 is nearly 100% in up to 5 years of followup.¹⁵⁻¹⁹ **Table 2** summarizes the characteristics of the Phase II trials published to date. Ongoing Phase III studies will likely corroborate the preliminary findings concerning the efficacy of prophylactic HPV vaccines against high-grade preneoplastic cervical lesions. Mathematical models of their impact have also suggested a substantial public health benefit in most geographical areas.²⁰⁻²³

INCORPORATING HPV VACCINATION IN EXISTING CERVICAL CANCER PREVENTION PROGRAMS

The 2 candidate vaccines now nearing commercialization (GardasilTM and CervarixTM) protect against the 2 main HPV types that together cause about 75% of all cervical cancers, HPVs 16 and 18.²⁴ Although a small degree of

TABLE 2. Characteristics and key findings for prophylactic HPV vaccines

Study feature or finding	Vaccine type		
	bivalent HPV-16 and HPV-18 VLPs L1 capsid component only (Cervarix TM)	monovalent HPV-16 VLP L1 capsid component only (will not be commercialized)	quadrivalent HPV 6, 11, 16, 18 L1 VLP capsid component (Gardasil TM)
Reference (study type)	Harper et al, 2004 ¹⁶ Harper et al, 2006 ¹⁹ (Phase II)	Koutsky et al, 2002 ¹⁵ Mao et al, 2006 ¹⁸ (Phase II)	Villa et al, 2005 ¹⁷ (Phase II)
Expression system	insect cells (baculovirus)	yeast	yeast
Concentration	20 µg HPV 16, 20 µg HPV 18	40 µg HPV 16	20 µg HPV 6, 40 µg HPV 11, 40 µg HPV 16, 20 µg HPV 18
Adjuvant	AS04 (proprietary)	aluminum hydroxy phosphate sulfate	aluminum hydroxy phosphate sulfate
Dose, administration and schedule	0.5 mL IM; 0, 1 and 6 months	0.5 mL IM; 0, 2 and 6 months	0.5 mL IM; 0, 2 and 6 months
Trial size, age range of participants and trial site	560 vaccinees, 553 placebo; 15-25 years; US, Canada, Brazil	768 vaccinees, 765 placebo; 16-23 years; US	277 vaccinees, 275 placebo; 16-23 years; US, Brazil, Europe
Key eligibility requirements	No history of cervical lesions, few sexual partners	No history of cervical lesions, few sexual partners	No history of cervical lesions, few sexual partners
Duration	Up to 54 months	Up to 48 months	Up to 36 months
Efficacy data (95% confidence intervals)			
• Preventing incident/transient infections	97% (89% to 100%)	91% (80% to 97%)	Not provided
• Preventing persistent infections	100% (77% to 100%)	100% (90% to 100%)	89% (70% to 97%)
• Preventing cytological abnormalities	97% (84% to 100%)	100% (84% to 100%)	Not provided
• Preventing pre-invasive lesions	100% (42% to 100%)	100% (85% to 100%)	100% (32% to 100%)
Immune response data			
• Sustained seroconversion	100%	100%	100%
• Specific titers compared to natural infection	50-80 times greater	60 times greater	10-20 times greater
Adverse events			
• acceptable rate	yes	yes	yes
• serious	no	no	no

cross-protection against other oncogenic HPVs may be expected,¹⁹ a gradual change may potentially arise in the distribution of HPV types in vaccinated populations, reflecting the vacated ecologic niches following the elimination of HPVs 16 and 18 (a yet unproven phenomenon known as type replacement). Also, the type-specific immunity conferred by vaccination may wane over periods extending much beyond 5 years. Other areas of concern that will take many years to be settled via scientific evidence include the choice of the ideal age for vaccination, whether women who have been previously exposed to HPV can be protected, and whether men should be vaccinated to achieve herd immunity. While much is yet to be learned about these and other vaccine-related issues, substantial streamlining or restructuring of screening programs are clearly needed to keep cervical cancer prevention cost-effective following the incorporation of HPV vaccination.

Indeed, assuming that HPV vaccination will become an accepted approach for primary prevention of cervical cancer, it is essential to consider the impact on screening practices. Implementation of HPV vaccination will likely be a gradual and diverse process reflecting specific health policy environments. In some countries, vaccination may be adopted as universal policy for all adolescents and young women and covered by a centrally managed healthcare system. In other settings, the costs of vaccination may be shared between the public sector and individuals. It is also conceivable that some countries may not opt at all for covering the costs of vaccination and may leave the decision to healthcare providers and their patients. Finally, some may not even consider vaccination due to other pressing healthcare priorities. Individual countries' perceptions regarding the cost-effectiveness of vaccination as a primary prevention measure will no doubt be the main deciding factor for whether or not to adopt vaccination, a decision requiring careful consideration of different possible modifications to existing screening programs.

Short-term impact

In most Western countries, widespread vaccination of young women may decrease rates of referral to colposcopy to 60% or less of the existing caseloads.²⁵ A small proportion of currently-referred cases are associated with low oncogenic-risk HPVs, such as HPVs 6 and 11. The quadrivalent Gardasil vaccine, which includes the latter 2 types as immunogens, may thus lead to a more pronounced reduction in abnormalities than the bivalent Cervarix vaccine, perhaps by an extra 10% in absolute terms. These reductions will no doubt translate into initial savings but may entail untoward consequences related to personnel training and degradation of performance standards in Pap cytology. The positive predictive value of Pap cytology will decline in populations with high vaccine uptake because clinically relevant lesions will become less common. Vaccination may also lead to a decline in the performance of cytology by causing a decrease in the signal (squamous abnormalities) to noise (inflammation and reactive atypias) ratio for those reading and interpreting smears: the lower abnormality rate may lead to fatigue and missing less conspicuous lesions, reducing sensitivity, while fear of this may lead to more over-calls of benign abnormalities, reducing specificity.

Reduction in caseloads will be a function of 2 factors: the overall uptake of HPV vaccination by successive cohorts of adolescents and young women targeted by vaccination, and the time it takes for protected women to reach the age when they become clients of screening. In countries without a centrally managed healthcare system (e.g. the US) uptake of vaccination will require much effort in educating the public and healthcare providers. While women may welcome HPV vaccines there may be dissent as well, mostly stemming from the parental perception that vaccination may foster permissive behaviour among adolescents.^{26,27} Vaccinated adolescents will reach the age of cervical cancer screening within 3 years after the onset of sexual activity. Therefore, the impact on screening and management caseloads will initially be minimal for women vaccinated between the ages of 10 and 18 years. The benefits in risk reduction among young adult women receiving the vaccine, however, will be realized almost immediately because of the short latency between the averted acquisition of HPV infection and the appearance of low-grade or equivocal cervical abnormalities.

Possible long-term public health outcomes of HPV vaccination

Even with high uptake, a statistically noticeable reduction of the burden of cervical cancer via HPV vaccination is unlikely for at least a decade or longer because of the latency required for averted high-grade lesions to progress to invasive disease. A paradoxical situation may arise if high vaccine uptake occurs primarily among adolescents and young women who also comply with screening recommendations, because reduced ASC-US and SIL abnormalities would likely be seen nearly exclusively among such women. With fewer abnormalities identified on screening, triage and management caseloads would be reduced. But because of their high compliance with screening these women would not be the ones destined to develop cervical cancer. On the other hand, if non-vaccinated women are less likely to be screened their cervical lesions will progress undetected until invasion occurs, with no precancerous lesions averted.

PROSPECTS


Given the potential problems in Pap cytology performance due to a reduction in lesion prevalence, HPV testing would be an ideal primary cervical cancer-screening test, with Pap cytology reserved for triage settings, i.e. to assist management of HPV-positive cases. Another key advantage of using HPV testing as the primary screening tool in prevention programs is the opportunity to create HPV infection registries with the ability to link test results from the same women over time, thus allowing an efficient and low-cost strategy for monitoring long-term protection among vaccinated women.

In conclusion, much has been achieved during the last 10 years from research on screening and prevention of cervical cancer. Progress has been grounded on the recognition that HPV infection is the central, necessary cause of this important neoplastic disease. To permit cost-effective reductions in the burden of cervical cancer, however, screening and other

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preventive strategies must be adapted to one another. The next 5–10 years will bring many changes in practice standards and guidelines, as research on the subject continues to provide acceptable evidence for public health action. Canadian oncologists and primary care providers will do well to observe closely the unfolding story of cervical cancer prevention. 

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