Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection

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Abstract

ORGANIZED SCREENING HAS CONTRIBUTED TO A DECLINE in cervical cancer incidence and mortality over the past 50 years. However, women in developing countries are yet to profit extensively from the benefits of screening programs, and recent trends show a resurgence of the disease in developed countries. The past 2 decades have witnessed substantial progress in our understanding of the natural history of cervical cancer and in major treatment advances. Human papillomavirus (HPV) infection is now recognized as the main cause of cervical cancer, the role of coexisting factors is better understood, a new cytology reporting terminology has improved diagnosis and management of precursor lesions, and specific treatment protocols have increased survival among patients with early or advanced disease. Current research has focused on the determinants of infection with oncogenic HPV types, the assessment of prophylactic and therapeutic vaccines and the development of screening strategies incorporating HPV testing and other methods as adjunct to cytology. These are fundamental stepping stones for the implementation of effective public health programs aimed at the control of cervical cancer.

An estimated 371 000 new cases of invasive cervical cancer are diagnosed world wide each year, representing nearly 10% of all cancers in women. In frequency, it is the seventh cancer site overall and third among women, after breast and colorectal cancer.[1] In developing countries, cervical cancer was the most frequent neoplastic disease among women until the early 1990s, when breast cancer became the predominant cancer site.[2,3]

Fig. 1 shows age-standardized incidence and mortality rates for cervical cancer in Canada, the United States and the cancer surveillance regions of the World Health Organization (WHO). The highest risk areas are in Central and South America, southern and eastern Africa, and the Caribbean, with incidence rates of at least 30 new cases per 100 000 women per year. In general, there is a correlation between incidence and mortality across all regions, but some areas, such as Africa, seem to have a disproportionately higher mortality. Incidence and mortality rates in North America are relatively low. The mortality rate in Canada is the lowest among all regions.

Table 1 shows Canada's incidence and mortality rates for cervical cancer (averages for latest 5-year reporting periods) and estimated numbers of new cases and deaths for 2000. Nearly 1500 new cases of cervical cancer were estimated to have been diagnosed in Canadian women in 2000, and an estimated 430 women died from the disease in the same year.[4] The provinces with the highest incidence rates are Nova Scotia, Newfoundland and Prince Edward Island.

Cervical cancer takes a particularly heavy toll in North American Aboriginal, black and Hispanic populations. Among the Canadian Inuit, it accounts for nearly 15% of all cancers among women. The proportion is even greater among Aboriginal Canadians in Saskatchewan (29%), with an age-standardized rate 6 times higher than the national average.[5]

Incidence and mortality have declined in North America during the last 50 years because of increased availability of Papanicolaou smear screening programs and a decline in fertility rates over the last 4 decades. Fig. 2 shows the decline in age-standardized incidence and mortality rates in Canada since 1960. There is an indi-

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cation that the marked declines seen until the mid-1980s have been slowing in recent years. This can be more easily seen by examining incidence rates by age in Canada and in the United States (Fig. 3). There seems to be a trend of increasing incidence during the last few years among white women less than 50 years old living in the United States in areas covered by the Statistics, Epidemiology, and End Results (SEER) program of the National Cancer Institute. This trend, suggestive of a resurgence in cervical cancer,

has also been observed in many European countries and could reflect increased cancer detection by the use of new diagnostic techniques, such as human papillomavirus (HPV) testing and cervicography, or it could be the result of a cohort effect. Another factor potentially affecting incidence trends is the increase in rates of adenocarcinomas and adenosquamous carcinomas, which account for about 10% of all cervical cancers in Western populations.[6,7]

Survival

Table 2 shows relative survival rates in some Canadian provinces, US populations and selected developed and de-
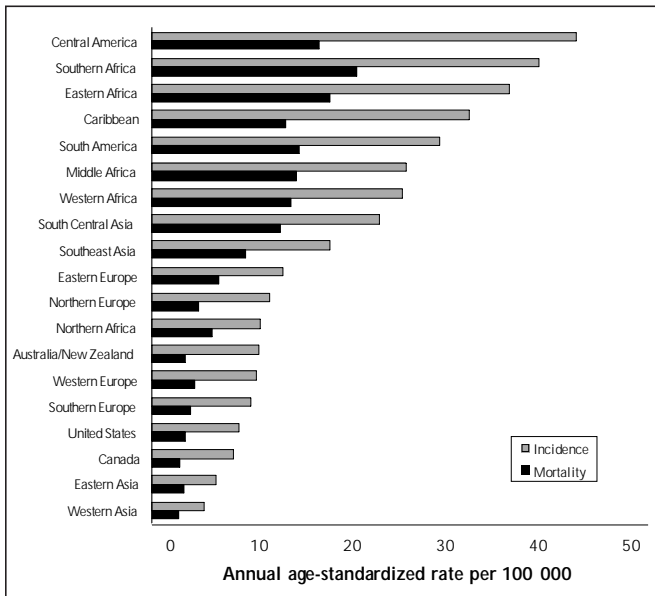

Fig. 1: Annual incidence and mortality rates (per 100 000 women) of invasive cervical cancer in Canada, the United States and cancer surveillance regions of theWorld Health Organization. Rates are standardized according to age distribution of world population in 1960. Source: Ferlay et al.[3]
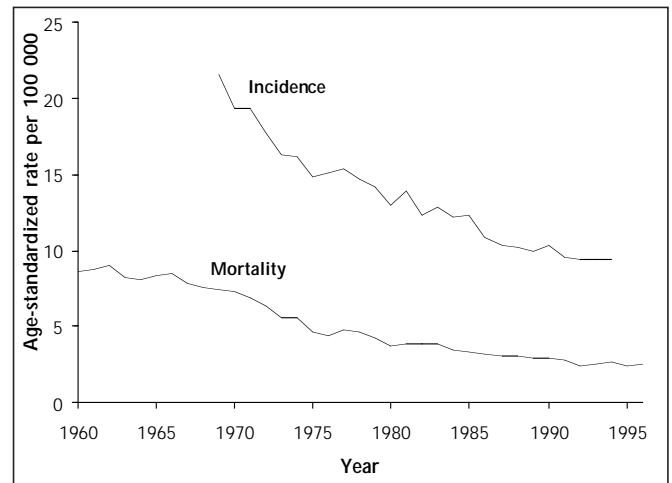

Fig. 2: Annual incidence and mortality rates (per 100 000 women) of invasive cervical cancer in Canada. Rates are standardized according to age distribution of Canadian population in 1991. Source: Cancer Bureau, Population and Public Health Branch, Health Canada.

Table 1: Average annual incidence and mortality rates for cervical cancer* and estimated new cases and deaths in 2000 in Canada

Province	Annual incidence rate per 100 000†	Annual mortality rate per 100 000‡	Estimated no. of new cases in 2000	Estimated no. of deaths in 2000
Newfoundland	12.6	3.6	30	10
Prince Edward Island	12.0	4.0	10	5
Nova Scotia	13.0	3.7	55	20
New Brunswick	8.3	2.2	35	10
Quebec	8.4	2.0	300	90
Ontario	10.2	2.7	610	170
Manitoba	10.7	3.2	60	20
Saskatchewan	9.5	2.3	45	15
Alberta	10.7	2.9	130	40
British Columbia	8.5	2.3	180	60
Canada	9.7	2.5	1450	430

*Rates are age-standardized according to the 1991 Canadian population.
†Average annual rate for 1990–1994.
‡Average annual rate for 1992–1996.
Source: Cancer Bureau, Population and Public Health Branch, Health Canada; Statistics Canada; National Cancer Institute of Canada.

veloping countries. Patients diagnosed and treated in Canada have had somewhat better long-term (5-year) survival than those in the United States. Although survival among US women improved dramatically until the mid-1970s, these gains did not continue in recent years. Moreover, 5-year survival rates among black women have actually declined, widening the gap between races.

Ability to pay for health care could be a determinant for why survival rates differ substantially between white and black women in the United States and between the United States and Canada. A recent study comparing cancer survival between Detroit and Toronto revealed that socioeconomic status was associated with survival in Detroit but not in Toronto. Furthermore, survival among the poorest patients in Toronto was significantly better than that among
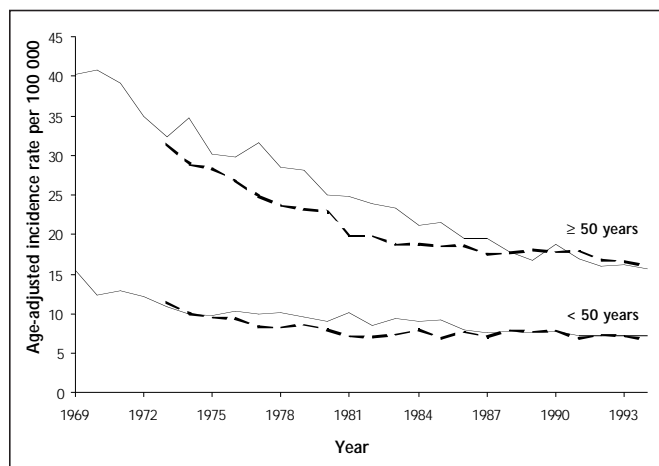
Fig. 3: Annual incidence rates (per 100 000 women) of invasive cervical cancer among women less than 50 years of age and among those 50 years or older in Canada (solid line) and in the United States (broken line). Rates are standardized according to age distribution of Canadian population in 1991. Source: Cancer Bureau, Population and Public Health Branch, Health Canada, and the National Cancer Institute Statistics, Epidemiology, and End Results (SEER) program.

Factors influencing the magnitude of survival rates in different populations

- Relative proportions of patients with advanced versus early-stage disease.
- Age distribution of the cohort of patients.
- Access to surgery, radiation therapy and chemotherapy.

These 3 factors, particularly the first and third, are strongly correlated with socioeconomic status. Patients of lower economic means will have their diagnosis delayed, which may lead to more advanced disease at the time of treatment and consequently to poorer survival.

Table 2: Relative survival rates by time since diagnosis of invasive cervical cancer in Canada and selected countries

Country/population	Year of diagnosis	Relative survival rate, %		
		1 year	2 years	5 years
Canada				
Quebec	1984–1986	88	78	74
British Columbia	1970–1988	87	76	72
Alberta	1974–1978	89	75	69
Ontario, British Columbia and Saskatchewan	1970–1984	88	76	72
United States				
SEER, all races	1984–1986	87	72	67
SEER, all races	1989–1991	89	75	71
SEER, white	1986–1993	–	–	71
SEER, black	1986–1993	–	–	57
Australia	1977–1994	88	76	72
China (Shanghai)	1988–1991	76	58	52
Cuba	1988–1989	77	59	56
Denmark	1983–1984	82	68	64
England	1983–1984	82	65	60
France	1983–1985	86	70	67
India (Bangalore)	1982–1989	78	53	40
Philippines (Rizal)	1987	70	38	29
Poland	1978–1984	75	59	54

Note: SEER = Statistics, Epidemiology, and End Results program, National Cancer Institute.
Source: Ministère de la Santé et des Services sociaux du Québec; SEER program; National Cancer Institute of Canada; International Agency for Research on Cancer.

the poorest ones in Detroit for most types of cancer, including cervical cancer.[8]

Risk factors

Epidemiological studies conducted during the past 30 years have consistently indicated that cervical cancer risk is strongly influenced by measures of sexual activity: number of sexual partners, age at first sexual intercourse and sexual behaviour of the woman's male partners.[9,10] Circumstantial evidence for sexual transmission of an infectious agent comes from studies showing that wives of patients with penile cancer are at an increased risk of cervical cancer later in life.[11] Such findings are further supported by results from correlation studies, in which strong associations were found between cervical and penile cancer mortality and incidence.[12,13]

Tobacco smoking has been a well-known risk factor for cervical cancer.[14] A direct carcinogenic action of cigarette smoking on the cervix has been upheld on the grounds that nicotine metabolites can be found in the cervical mucus of women who smoke.[15] Since smoking is associated with sexual behaviour, it is difficult to determine whether this association is spurious given the impossibility of effectively eliminating confounding through adjustment for measures of sexual activity.

The number of live births is a consistent risk factor for cervical cancer. There is a linear trend in the association between parity and risk, as seen in studies in North America and Central and South America.[16] Apart from issues of screening coverage and quality, the high parity and deficient diets of women in developing nations may be contributory factors for the high incidence rates of cervical cancer observed in these regions.

> ### Human papillomaviruses
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> - The epithelial lining of the anogenital tract is the target for infection by a group of mucosotropic viruses, the human papillomaviruses (HPVs).
> - Subclinical and clinical genital warts, also known as condylomata acuminata, and virtually all squamous cell cancers of the anogenital tract are caused by specific HPV types.
> - HPVs are DNA viruses with a genome size of about 8000 base-pairs.
> - There are more than 100 HPV types defined on the basis of DNA homology, of which more than 40 infect the anogenital tract.
> - Genital HPV types are typically divided into groups according to their presumed oncogenic potential.[21,22]
> - HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered to be of oncogenic risk.
> - The remaining genital types — types 6, 11, 42, 43 and 44 — are considered of low or no oncogenic risk.

There is an excess risk of cervical cancer associated with long-term use (12 years or more) of oral contraceptives. The association is somewhat stronger for adenocarcinomas than for squamous cell carcinomas.[17] The association with oral contraceptive use observed in studies in which precancer was an outcome may have been due to detection bias, since women who use oral contraceptives undergo more frequent gynecological examinations, and are thus more likely to have disease detected early, than those who do not use them. The difficulty in properly assessing the effect of oral contraceptive use stems from the fact that this variable is highly associated with other risk factors, such as sexual activity and history of Pap smear screening.[10]

The evidence for an effect of diet on risk of cervical cancer indicates that a high intake of foods containing beta carotene and vitamin C and, to a lesser extent, vitamin A may reduce the risk of cervical cancer.[18,19] The results from studies using diet recall methods have generally been corroborated by laboratory surveys assaying dietary constituents in plasma.[20] As with reproductive factors, it is likely that diet may influence between-country differences in cervical cancer incidence rates.

HPV infection and cervical cancer

The WHO's International Agency for Research on Cancer (IARC) classified HPV infection as "carcinogenic" to humans (HPV types 16 and 18), "probably"
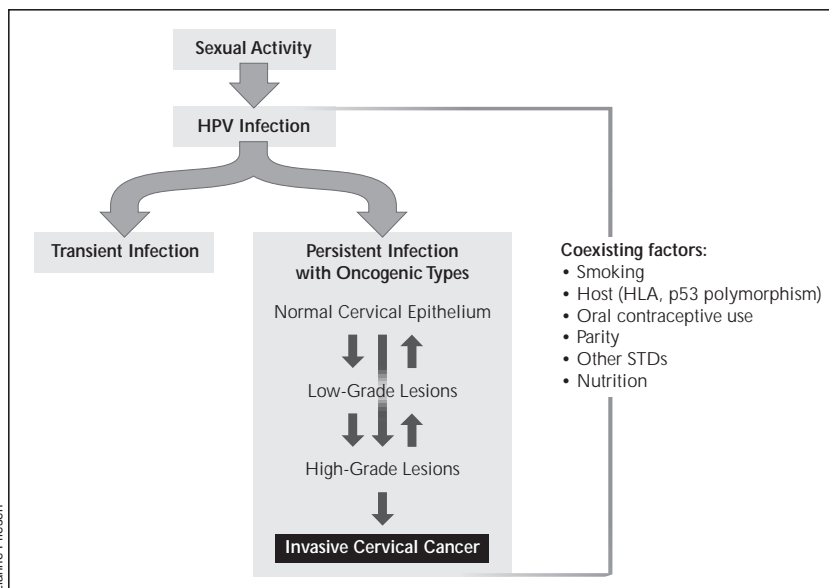

Fig. 4: Etiological model of human papillomavirus (HPV) infection and cervical cancer, illustrating probable role of remote behavioural risk factors for persistent infection and of coexisting factors that mediate lesion progression.

carcinogenic (HPV types 31 and 33) and "possibly" carcinogenic (other HPV types except 6 and 11).[23]

Clinical and subclinical HPV infections are the most common STDs today. Asymptomatic cervical HPV infection can be detected in 5%–40% of women of reproductive age.[24] HPV infection is a transient or intermittent phenomenon; only a small proportion of women positive for a given HPV type are found to have the same type in subsequent specimens.[25,26] Risk of subsequent cervical intraepithelial neoplasia (CIN) is proportional to the number of specimens testing positive for HPV,[27] which suggests that carcinogenic development results from persistent infections.

It is now well established that HPV infection is the central causal factor in cervical cancer.[28,29] The thrust of epidemiological research in recent years has focused on the understanding of the role of risk factors that influence acquisition of persistent HPV infection or of coexisting factors that mediate progression in the continuum of lesion grades (Fig. 4).

The relative risks for the association between HPV infection and cervical neoplasia are of high magnitude, typically in the 20–70 range. This range is greater than that for the association between smoking and lung cancer and is comparable only to that of the association between chronic hepatitis B and liver cancer, causal relations that are undisputable.[30] Recent evidence using meticulous testing by polymerase chain reaction of a large international collection of cervical cancer specimens has shown that HPV DNA is present in 99.7% of cases.[22,31,32] This finding indicates that HPV infection could be a necessary cause of cervical neoplasia — the first instance in which this causal link would have been shown in cancer epidemiology — a realization that has obvious implications for primary and secondary prevention.[33]

Cytology screening

Despite its success, cytology has important limitations, false-negative results being the most important. Nearly half of specimens yield false-negative results; about one-third of these results are attributable to errors in interpreting slides and two-thirds to poor sample collection and slide preparation.[34] The solution to minimize errors in cytology is to improve the quality of sample taking, slide processing and overall diagnostic performance of cervical cytology. False-negative results have important medical, financial and legal implications; the last is an acute problem in North America, where false-negative cytology specimens are a leading reason for medical malpractice litigation.

The Canadian Task Force on Preventive Health Care (formerly the Canadian Task Force on the Periodic Health Examination)[35] and various consensus workshops[36–39] have provided national recommendations that have been reaffirmed on separate occasions by provinces or by cancer prevention coalitions. The Cervical Cancer Prevention Network, which brings together federal and provincial representatives and clinical professional bodies, is the most important of these coalitions. This network spawned from a national workshop held in Ottawa in 1995 to identify barriers, needs and new directions in the development of organized cytology screening. The empirical basis for the soundness of these management guidelines was recently published.[40]

A new terminology for reporting results of cervical cytology — the Bethesda system — considers the information on

HPV as part of the cytologic criteria to define lesion grade (Table 3). In addition, a new category for borderline lesions — atypical squamous cells of undetermined significance (ASCUS) — was created. These changes result in an increased proportion of low-grade lesions, which, combined with ASCUS, can account for up to 13% of smears in certain ethnic groups.[42] On follow-up, most of these abnormalities revert to normal, and in some cases women have persistent minor grade lesion or hidden high-grade squamous intraepithelial lesion (HSIL) (20% of those with low-grade intraepithelial lesion [LSIL] and 10% of those with ASCUS).[40] There is much debate over whether management of LSIL should be conservative or interventionist.[43] The National Institutes of Health is conducting a large trial to assess whether HPV testing could improve the detection of missed HSIL among women with an initial diagnosis of ASCUS or LSIL.

HPV testing as an adjunct screening method

If HPV infection is an early precursor of cervical neoplasia, should HPV testing be used in screening for cervical cancer? Opponents to HPV testing have claimed that cytology screening alone has been very successful in decreasing invasive cervical cancer morbidity and mortality in many countries. An additional criticism is that HPV infection is highly prevalent among women of reproductive age and that it would be impractical to follow-up all positive cases. On the other hand, proponents of HPV testing claim that it would represent a scientifically sound approach for secondary prevention, particularly in developing countries, where high-quality cytology screening is difficult to implement, and that any pending issues could be evaluated by intervention trials. Consensus panels of the IARC and WHO have concluded that there is enough justification to evaluate HPV testing as an adjunct to Pap smear screening in cervical cancer.[44,45]

Treatment

Management options for LSIL (CIN grade 1) on histology vary widely across North America, ranging from simple observation to excisional therapies. Patients with persistent LSIL should be treated, chiefly with the use of office-based ablative therapies. Management guidelines for HSIL (CIN grade 2 or 3) are well established and recommend colposcopy-directed biopsy with or without endocervical curettage. Cold-knife conization or electroconization should be performed in all patients with biopsy-confirmed HSIL in order to exclude invasive disease.

In women with invasive cancer, additional tests are required to establish the stage of the disease. Treatment depends primarily on the extent of the lesion, but it also depends on factors such as the patient's age, her desire to preserve fertility and the presence of other medical conditions.[46] Virtually all patients with stage IA disease are cured with either simple hysterectomy or, if fertility preservation is desired, by conization if margins are free of disease. For women with stage IB disease without involvement of the lymph nodes, prognosis is best after radical hysterectomy. Recent randomized phase III trials involving women with stage IB or stage II disease and metastatic pelvic node involvement demonstrated significant survival benefits for the combined use of cisplatin chemotherapy and radiation at the time of primary surgery, with a reduction in risk of death of 30%–50%.[47–49] More advanced clinical stages are associated with relatively lower survival rates, even after radiation or chemotherapy, or both.

Current and future research

Recognition that HPV infection is the central cause of cervical neoplasia has created new research fronts in primary and secondary prevention of this disease.

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 behaviour targeting all STDs of public health significance can be effective in preventing genital HPV infection.[50] Although there is consensus that symptomatic HPV infection (genital warts) should be managed by way of treatment, counselling and partner notification, active case-finding of

Table 3: Corresponding dysplasia, CIN and SIL terminologies used to report cervical cancer precursors

Dysplasia terminology	CIN terminology	SIL terminology (Bethesda system)
Mild dysplasia or dyskaryosis, koilocytotic atypia, flat condyloma (old Papanicolaou class III)	CIN grade 1	Low-grade SIL
Moderate dysplasia or dyskaryosis (old Papanicolaou class IV)	CIN grade 2	High-grade SIL
Severe dysplasia or dyskaryosis (old Papanicolaou class IV)	CIN grade 3	High-grade SIL
Carcinoma in situ (old Papanicolaou class V)	CIN grade 3	High-grade SIL

Note: CIN = cervical intraepithelial neoplasia, SIL = squamous intraepithelial lesion.

asymptomatic HPV infection is currently not recommended as a control measure. Further research is needed to determine the effectiveness of such a strategy.

Vaccination 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. Two main types of vaccine are currently being developed: prophylactic vaccines to prevent HPV infection and consequently the various HPV-associated diseases, and therapeutic vaccines to induce regression of precancerous lesions or remission of advanced cervical cancer.

DNA-free virus-like particles synthesized by self-assembly of fusion proteins of the major capsid antigen L1 have been found to induce a strong humoral response with neutralizing antibodies. These virus-like particles are thus the best candidate immunogen for HPV vaccine trials. Pro-

tection seems to be type specific, which will require the production of virus-like particles for a variety of oncogenic types. Such vaccines are already being evaluated in phase I and II trials in different populations.

Organized cytology screening programs have been successful in developed countries, but in developing countries these programs lack coverage, accessibility, effectiveness and acceptability — conditions that are not likely to change soon because of competing public health priorities. General improvement in socioeconomic status and educational level of the population tends to have a positive effect on the risk of cervical cancer by altering some of the known risk factors such as age at marriage, parity and health-care seeking behaviour. Other strategies such as low-intensity cytology screening (e.g., 1 Pap smear every 10 years after age 35) and visual inspection need to be better evaluated in randomized controlled trials to determine their cost-effectiveness.[54]

In recent years, 3 new laboratory tests have been developed for primary and secondary screening for cervical cancer and its precursors (Boxes 1, 2 and 3). These are thin-layer liquid-based cytology, HPV DNA testing and computer-assisted automated cytology. All have been approved by the US Food and Drug Administration for clinical use and by Health Canada.

Although there is enthusiasm concerning the possible application of HPV testing as an adjunct to Pap screening, there are several problems that need to be solved before any secondary prevention programs can be augmented. Ongoing research on the epidemiology of viral persistence will help to determine the utility of HPV testing as a screening tool for cervical cancer.

Box 1: Thin-layer liquid-based cytology
(ThinPrep Pap Test, Cytyc Canada Ltd., Lucan, Ont.; AutoCyte PREP System, TriPath Imaging Inc., Burlington, NC)

Use: The cervical sample is suspended in a cell-preserving solution rather than placed on a glass slide. As a result, virtually all cellular material is made available to the laboratory. With a conventional Pap smear, only 20% of the cells harvested from the cervix are placed manually on the slide.[51] With liquid-based cytology, excess blood and inflammatory cells are lysed, and about 50 000 diagnostic cells are randomly selected by machine and transferred onto a slide in a thin-layer fashion by a robotic cell processor. The slides are read by cytotechnologists.

Promise: The technique improves slide quality by reducing obscuring blood (99.8%) and inflammatory exudate (94.3%). In one study, the ThinPrep Pap Test increased detection rates of high-grade precancerous lesions among 154 872 women at low and high risk of cervical cancer by 26% to 233% compared with historical controls from a year earlier.[52] The technique also permits panel testing for HPV DNA and *Chlamydia trachomatis*. The US Food and Drug Administration approved the ThinPrep Pap Test (1996) and the AutoCyte PREP System (1999) as being significantly superior and equivalent, respectively, to the conventional Pap smear for the detection of precancerous and cancerous lesions of the cervix.[53]

Problems: Additional large-scale prospective studies using histological verification of cervical samples from women at low and high risk of cervical cancer who had negative results with liquid-based cytology are needed to estimate the test's diagnostic performance. The data will help to assess the impact of liquid-based cytology for cervical cancer screening and to solve perceived problems with its additional costs and validity that are currently slowing its greater widespread use.

Box 2: Computer-assisted automated cytology
(AutoPap Primary Screening System, TriPath Imaging Inc., Burlington, NC)

Use: A high-speed video camera is used to scan about 200 conventional Pap smears daily. Morphometric algorithms interpret images and indicate to the cytotechnologists which slides to screen manually. The slides least likely to contain abnormal cells (about 25% to 50%) are filed without the need for human review.

Promise: The device outperforms human review of manually screened negative smears (for quality control) by a factor of 5 to 7; in a primary screening mode of populations at low risk, it performs as well as humans with a sort rate (no review of smears needed) of up to 50%.[55] It has the potential to alleviate shortages of qualified personnel in cytopathology.

Problems: The device is cumbersome, its pay-per-slide system may require additional administrative costs, service charges may be high, and its large throughput requires it to be located in high-volume laboratories. Approval for automated reading of thin-layer samples is pending.

Box 3: HPV DNA testing

(Hybrid Capture / HC-II, Digene Corporation, Gaithersburg, Md.)

Use: Detects, by means of signal amplification and immunocapture of DNA and RNA hybrids, the 13 most frequent oncogenic HPV types in cervical samples. Cervical samples are obtained by cytobrush and placed in tubes containing transport medium and sent to the laboratory. Alternatively, the residual cell suspension used in the liquid-based cytology collection vial may be used for HPV DNA testing.

Promise: Clinical trials involving women with borderline cytologic abnormalities have shown that HPV DNA testing combined with liquid-based cytology detects 100% of high-grade cancer precursors and defers up to 60% of unnecessary colposcopies and biopsies.[56] In a population-based screening mode, double testing (HPV testing and Pap smear) in women aged 35 years and older detected 90%–100% of high-grade cancer precursors, compared with 40%–78% detected by conventional cytology, and had a false-positive rate of only 5%.[57–59] Conversely, the negative predictive value of a single double test is close to 100% for high-grade cancer precursors.[56,57,60,61] Double testing should permit the institution of longer screening intervals, safely. The test is also cost effective and suitable for self-sampling,[62] which may improve participation rates in screening programs.

Problems: The social and medical costs of identifying HPV-positive, cytology-negative women must be considered because of potential patient anxiety and clinical management problems. Indeed, it becomes problematic to identify such women if the timing of HPV testing and the clinical significance of the HPV latency period are not addressed appropriately. Consensus guidelines have yet to be developed for the management of women aged 35 years and older who are positive for high-risk HPV types but have negative cytology results.

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