INSIGHT ON CANCER

news and information on cervical cancer

HIGHLIGHTS

- Cervical cancer is the tenth most common cancer in Ontario females of all ages, but it is the second most common among women under 50 years
- Incidence and mortality rates declined between 1981 and 2002 in all age groups
- ▶ In 2002, incidence rates for squamous cell carcinoma, the most common form of cervical cancer, were about half what they were in 1981
- Incidence rates for adenocarcinoma (about 20% of cervical cancers) increased between 1981 and 1995 then declined annually thereafter until 2002
- Five-year survival has improved slightly since 1981, particularly for adenocarcinoma
- > Screening with regular Pap tests is the most important determinant of the declines in incidence and mortality and the improvement in survival
- > High-risk (oncogenic) human papillomavirus (HPV) is the primary causal factor in the development of cervical precancerous lesions and invasive cancer
- Risk factors that enhance the carcinogenic effect of HPV infection include smoking tobacco, having a high number of live births, and presence of other sexually transmitted infections (HIV, chlamydia, HSV-2)
- > Although cervical cancer is almost entirely preventable with regular Pap test screening, only 81% of Ontario women have had a recent Pap test
- Screening is most effective if delivered through an organized program that includes $\mathbf{>}$ a comprehensive information system. Action is urgently required in Ontario to overcome the barriers to creating such a system



Insight on Cancer is a series of joint Cancer Care Ontario and Canadian Cancer Society (Ontario Division) publications, designed to provide up-to-date information for health professionals and policy-makers about cancer and cancer risk factors in the province.







www.cancer.ca



www.cancercare.on.ca



This monograph could not have been produced without the technical support and graphic skills of Sandrene Chin Cheong.

The authors are grateful to the many other colleagues who also reviewed earlier drafts:

D. Bryant, L. Kells, Simcoe Muskoka District Health Unit; T. Colgan, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital; L. Elit, Juravinski Cancer Centre; E. Franco, McGill University; L. Gillespie, Public Health Services of the City of Ottawa; P. Holowaty, Halton Region Health Department; R. Kyle, Durham Region Health Department; C. McDowell, Group Health Centre; S. Bahl, E. Halapy, L. Kiefer, J. Mangles, C. Naugler, and B. Theis, Cancer Care Ontario.

The operations staff of the Ontario Cancer Registry and the Registry Support Group (Information Technology) are acknowledged for their ongoing efforts to ensure the generation of high-quality cancer incidence data for Ontario. Published and distributed by the Canadian Cancer Society (Ontario Division). The information was analyzed and interpreted by staff of Cancer Care Ontario's Division of Preventive Oncology:

Loraine D. Marrett Michael Innes Robbi Howlett Michelle Cotterchio

With input from: W.K. (Bill) Evans, Juravinski Cancer Centre, Hamilton Health Sciences Barry Rosen, Princess Margaret Hospital, University Health Network

Citation: Material appearing in this report may be reproduced or copied without permission; however, the following citation to indicate the source must be used:

Cancer Care Ontario: *Insight on Cancer*. News and Information on Cervical Cancer. Toronto: Canadian Cancer Society (Ontario Division), 2005.

Disclaimer

The tables and charts in this report contain information derived from the Ontario Cancer Registry. Cancer Care Ontario made efforts to ensure the completeness, accuracy and currency of this information at the time of writing this report. This information changes over time, however, as does our interpretation of it. Accordingly, Cancer Care Ontario makes no representation or warranty as to the completeness, accuracy or currency of this information.





insight on cancer

volume five • october 2005

Canadian Soc Cancer can Society du G

canadienne du cancer

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society www.cancer.ca

CERVICAL CANCER DEFINED

The *cervix uteri* is the narrow lower end of the uterus that connects the uterus to the vagina. The part of the cervix closest to the body of the uterus is called the endocervix. The part next to the vagina is the ectocervix. Most cervical cancers occur where the endo- and ecto- cervix meet (transformation zone); these have a **squamous cell morphology**. Cervical cancers that arise from the mucin-producing glandular cells of the endocervix are generally **adenocarcinomas** (including adenosquamous cancers).

Sexually transmitted infection with a high-risk (*oncogenic*) type of *human papillomavirus* (HPV) is the primary cause of cervical cancer.^{1,2}

The majority of cervical cancers develop slowly, with normal cervical cells gradually changing to *precancerous* lesions. If left untreated, these precancerous lesions may progress to cervical cancer, typically over several years. Cancer can, however, sometimes develop more rapidly.^{3,4}

Regular **Papanicolaou (Pap) test** screening is an effective way to control cervical cancer. Pap tests can identify precancerous lesions, which can then be treated so that cancer does not arise. They can also identify cancers at an early stage, when treatments are most effective.

See Glossary of Terms, Data Sources and Methods.



Cancer Care Ontario, The Ontario Cervical Screening Program

Canadian Cancer Society

CERVICAL CANCER IN CONTEXT



Annual number of new cases and deaths for the most common cancers in Ontario females, 2002

Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)



Cervical cancer age-adjusted incidence rates* for selected countries, 1993–1997

Source: Parkin et al., 2002⁸

*Standardized to the 1991 Canadian population

How common is cervical cancer?

In Ontario females of all ages, cervical cancer is the 10th most common newly diagnosed cancer, with 522 new cases and 130 deaths in 2002. Among women aged 20–49, cervical cancer incidence ranks second to breast cancer [data not shown]. Cervical cancer is relatively uncommon in Ontario because most women have regular Pap tests, which substantially reduces the risk of this cancer. However, the incidence of cervical cancer worldwide ranks second after breast cancer.⁵

In 2002, approximately 5,560 Ontario women were living with a previous diagnosis of cervical cancer [refer to glossary for **prevalence**]. Cervical cancer accounts for 2% of the **potential years of life lost** due to cancer among Ontario females.

Geographic variation

During 1993–1997, the *age-standardized incidence rate* of cervical cancer in Ontario was among the lowest in the world and similar to rates in the USA and New Zealand. A few populations, such as those in Finland and Spain, have lower incidence. Many developing countries, such as Colombia and India, have much higher rates. These international variations are likely the result of differences in both the prevalence of high-risk HPV infection⁶ and the extent and quality of Pap test screening.⁷

The incidence of cervical cancer in Ontario is similar to the national average; however, there is geographic variation across Canada.⁸ The lowest rates are observed in British Columbia (8/100,000), which has the oldest *organized screening program* in the country (since 1960). Newfoundland and Labrador have the highest provincial incidence (12/100,000).

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society

IMPACT OF AGE

Age at diagnosis or death

The *median age at diagnosis* of cervical cancer is 47, which is much younger than for many cancers. The median age at diagnosis for all types of cancer in Canadians is between 60 and 69 years.⁹

Because they no longer have a cervix, women who have had a total **hysterectomy** are not at risk of getting cervical cancer. By age 60, nearly 30% of Ontario women report having had a hysterectomy.¹⁰ When women with total hysterectomies are excluded (as they should be) from the **population at risk for cervical cancer** [refer to glossary for hysterectomy-corrected population at risk for cervical cancer], the incidence rate rises continuously with age until age 65, after which it declines. If the population at risk was not adjusted for prior hysterectomies, cancer incidence rates would appear to level appear to level off or decline slightly after age 45.

Rates of mortality (corrected for hysterectomy) are low among younger women, but increase steeply after age 40, to a rate of 16 per 100,000 among women 80 and older. *Median age at death* from cervical cancer is 60 years.

Cervical cancer incidence and mortality rates by age, 1998–2002



---- Mortality uncorrected for hysterectomy

Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

The *median age at diagnosis* of cervical cancer is 47, which is much younger than for many cancers: the median age at diagnosis for all types of cancer in Canadians is between 60 and 69 years.

Median age at death from cervical cancer is 60 years.

Canadian Cancer Society

TIME TRENDS



^{*}Calculated with hysterectomy-corrected population at risk

The long-term declines in both incidence and mortality are related to widespread use of the Pap test, which can detect both early cancer and cancer precursors that, if treated, do not typically progress to cancer.

The steeper drop in incidence beginning in 1996 coincides with the dissemination of information to Ontario health care practitioners, aimed at improving Pap test screening.

Incidence and mortality

Incidence rates were much higher than mortality rates throughout the period 1981 to 2002. Incidence fell by 1.6% per year [refer to glossary for **average annual percent change in rate**] between 1981 and 1996, and by 4.5% per year thereafter, for a total drop of 39% over the 22-year period. Mortality decreased by 3.2% per year over this period, for a total drop of 53%. Cervical cancer incidence and mortality have been declining in Ontario since at least 1964.¹¹ Similar decreases in incidence and mortality have been reported in many developed countries.⁷

The long-term declines in both incidence and mortality are related to widespread use of the Pap test, which can detect both early cancer and cancer precursors that, if treated, do not typically progress to cancer.^{12,13}

The steeper drop in incidence beginning in 1996 coincides with the dissemination of information to Ontario health care practitioners, aimed at improving Pap test screening. Included were provincial cervical screening guidelines, and a reference card with instructions for specimen collection and slide preparation. Additional quality assurance efforts and the introduction of liquid-based cytology have resulted in further improvements in the quality of Pap testing, including specimen collection, interpretation and reporting.^{14,15}

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society



Incidence and mortality by age group

Since 1981, incidence rates have fallen by about the same average annual percentage (2.0%–2.5% per year) in every age group. (Rates of decline may appear to differ between age groups because of the arithmetic scale used in the graph.) The consistent rates of decline suggest that Pap testing has had a positive impact at all ages.

Mortality also fell in every age group. Between 1981 and 2002, mortality rates declined by 1.6% per year in those aged 20–34, 3.6% in those aged 35–49, 3.6% in those aged 50–64 and 2.8% among women 65 and over.

In most age groups, declines in mortality were slightly larger than those in incidence. This may be because cancers have been detected earlier, primarily through screening. The survival rate for early cervical cancer exceeds 90%.¹⁶ Further mortality reductions are likely in the future due to the introduction of **chemotherapy** in combination with **radiotherapy**.¹⁷



Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

*Calculated with hysterectomy-corrected population at risk





Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

*Calculated with hysterectomy-corrected population at risk

insight on cancer volume five • october 2005 Canadian Cancer Society



Morphology distribution for cervical cancer, 2002

Adenocarcinoma (including adenosquamous carcinoma)

Other morphologies

Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)



Cervical cancer incidence rates* by morphologic subgroups, 1981-2002

*Calculated with hysterectomy-corrected population at risk

Morphology

About 64% of cervical cancers are squamous cell carcinomas, while about 26% are adenocarcinomas. The remaining 10% of cervical cancers are of unspecified or other rare morphologies.

In the early 1980s, the incidence rate for squamous cell carcinoma was more than 6 times that for adenocarcinoma; by the year 2000, the ratio of the two incidence rates was less than 3. This reflects the consistent decline in squamous cell carcinoma incidence (3.1% per year between 1981 and 2002), accompanied by a 3% annual rise in adenocarcinoma incidence through to 1995 followed by a 3.9% annual decline thereafter.

For many decades, specimen collection for Pap test screening was done using a spatula, which is effective in sampling cells from the outer surface of the cervix where squamous cell carcinomas typically develop. Thus Pap testing has been most effective at reducing the incidence of squamous cell carcinoma.

The rising incidence of adenocarcinoma through to the mid-1990s may indicate increasing detection of prevalent cases of cervical cancer with gradual improvements in screening, followed by a decline in incidence as uptake of improved screening increased and the number of prevalent cases diminished.¹⁸

An alternative explanation for the observed trend is that it reflects an increase in the true rate of disease in the absence of significant changes in screening until around 1996, when significant improvements to screening occurred, resulting in detection of more adenocarcinoma precursors and therefore less cancer.

Finally, the trend in adenocarcinoma may be due to a true change in disease caused by a **cohort effect**, or some combination of all of these possibilities.

Cancer Care Ontario www.cancercare.on.ca **Canadian Cancer Society** www.cancer.ca

Morphology by age group

Declines in the incidence of squamous cell carcinoma are similar across the age groups, ranging between 2.9% and 3.2% per year.

Between 1981 and 2002, the incidence of adenocarcinoma rose by 3.1% per year among women aged 20-34. Among those aged 35-49, incidence rose by 5.2% annually until 1992, and declined by 3.1% per year thereafter. The trends among women aged 50-64 and 65+ appear to rise and then fall in a pattern similar to that for women 35-49 years of age. Small numbers of adenocarcinoma account for the apparent fluctuations for some age groups.

The rising incidence of adenocarcinoma through to at least the early 1990s, particularly in those under age 50, has been noted in many other parts of the world. This increase appears to be restricted to women born since the 1930s.¹⁸ These are the women who experienced the sexual revolution of the 1960s and 1970s. Increased sexual activity among these cohorts would be expected to increase rates of infection with HPV, including its high-risk forms.18



Incidence rates* for squamous cell carcinoma** of the cervix

*Calculated with hysterectomy-corrected population at risk Including microinvasive

Incidence rates* for adenocarcinoma** of the cervix by age group, 1981-2002



Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

*Calculated with hysterectomy-corrected population at risk Including adenosquamous

Canadian Cancer Society www.cancer.ca

Cancer Care Ontario www.cancercare.on.ca

SURVIVAL



Cervical cancer 5-year relative survival, 1981-2000

Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

 \mathbf{T} = 95% confidence intervals



Cervical cancer 5-year relative survival by age group, 1981-2000

Five-year relative survival

Estimated five-year relative survival has improved very slightly over the last two decades from 69% in 1981-1985 to 73% in 1996-2000.

Survival is influenced by stage at diagnosis and treatment. Earlier detection through Pap testing may have increased slightly the percentage of diagnoses that are made at an early stage, resulting in somewhat improved survival. The Ontario Cancer Registry does not include sufficient stage and treatment information to directly examine changes in these factors.

Although there were no major treatment advances likely to impact survival of women diagnosed during the time period, new evidence for a beneficial effect of adjuvant chemotherapy is expected to improve survival among women with more recent diagnoses.17

Five-year relative survival by age

Five-year survival is highest amongst younger women, ranging from 85% in those aged 20-34 at diagnosis to about 50% among women diagnosed at age 65 or older. Over time, survival appears to have improved among women aged 35-49 and 65 or older; it has remained constant for other age groups.

\mathbf{I} = 95% confidence intervals

Five-year relative survival by morphology

Five-year relative survival was similar for diagnoses of squamous cell carcinoma and adenocarcinoma of the cervix diagnosed in the most recent time period, 1996–2000 (74% and 75%, respectively).

Survival following a diagnosis of squamous cell carcinoma has improved minimally over the past two decades. Survival for adenocarcinoma has risen substantially, from 61% among women diagnosed in 1981–1985 to 75% for those diagnosed most recently.

Slight improvements in survival for squamous cell carcinoma probably reflect marginal improvements in diagnosis and staging for a disease that has for decades been relatively well-controlled by effective screening.

Increased survival for adenocarcinoma may be due to earlier detection related to improvements in Pap test screening (e.g., use of a brush in addition to a spatula to collect cells, along with increased awareness of adenocarcinoma among clinicians and cytopathologists), and may partly reflect *lead time bias*.

Cervical cancer 5-year relative survival by morphologic subgroups, 1981–2000



* Including adenosquamous

Canadian Cancer Society

T = 95% confidence intervals

REGIONAL VARIATION IN ONTARIO

Cervical cancer incidence and mortality rates* by region, 1998–2002



Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

* Uncorrected for hysterectomies \mathbf{I} = 95% confidence intervals

NW = Northwest NE = Northeast SW-W = Southwest-Windsor SW-L = Southwest-London CS = Central South CW-K = Central West-Kitchener CW-P = Central West-Peel CE = Central East E-K = East Kingston E-O = East Ottawa

Incidence and mortality

Regional data are not calculated with hysterectomycorrected population at risk because reliable estimates of hysterectomy prevalence required for such adjustment are unavailable.

In 1998–2002, the incidence of cervical cancer varied significantly among *regions* of the province. In particular, rates in the Northwest and Northeast regions were significantly higher than the overall provincial rate of 7.8 per 100,000, while the Central West–Peel and East–Ottawa regions had significantly lower incidence.

The regional variation may reflect differences in the uptake and quality of Pap testing (see **Screening**), or in the prevalence of high-risk HPV or its co-factors (for example, smoking rates are highest in women living in northern parts of the province and lowest in Toronto¹⁹).

In contrast, mortality rates were similar across the regions.

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society





Source: Cancer Care Ontario (Ontario Cancer Registry, 2005) SAS, 1999-2001²⁰

Survival

Five-year relative survival was similar in every Ontario region to the estimate of 73% for the province as a whole.



Source: Cancer Care Ontario (Ontario Cancer Registry, 2005)

* Period of diagnosis = 95% confidence intervals

insight on cancer volume five • october 2005 Canadian Cancer Society

Cancer Care Ontario www.cancercare.on.ca

HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER

verwhelming epidemiologic evidence has shown that the main cause of cervical cancer and its precursors is infection with a high-risk form of human papillomavirus (HPV).^{1,2}

There are more than 100 types of HPV of which about 40 types infect the genital region. These have been subdivided as to their potential to cause cancer (oncogenic potential). High-risk viral types are frequently associated with invasive cervical cancer and precursor lesions (types 16 and 18 in particular), while low-risk types are mainly found in genital warts.²¹ Highrisk types have also been implicated as a cause of other cancers, including anal, penile, skin and oral-pharyngeal cancers.^{22–25}

Infection with high-risk HPV types appears to be necessary for the development of cervical cancer. HPV infection is transmitted through intimate contact (predominantly sexual intercourse) and is common among both women and men; at least 50% of sexually active women will be infected with one or more types at some point in their life.²⁶

HPV infection status can change in a relatively short time. For example, in a community-based sample of Ontario women aged 15–49, 9% tested positive for high-risk HPV type and 4% for a low-risk type in 1998–1999.²⁷ Upon retesting 9–21 months later, half of those with a high-risk HPV initially had no HPV infection, while 11% of those with no HPV initially were positive for high-risk HPV.²⁸

Most HPV infections will resolve spontaneously in healthy individuals (i.e., enter a *latent phase* or be suppressed by the host *immune response*).²⁹ *Persistent infections*, however, if left untreated, may lead to cervical precancerous lesions (low-grade and high-grade squamous or glanduar intraepithelial lesions) or *invasive carcinoma* (squamous cell carcinoma or adenocarcinoma). In addition to viral type, other viral characteristics, such as the level of HPV **DNA** found in cervical specimens (viral load) and particular HPV intratype variants (non-European versus European variants of HPV 16) have been found to influence the likelihood that cervical cancer will develop.^{30,31}

Sexual behaviour is the key determinant of HPV infection among both women and men: lifetime number of partners, early age at first sexual intercourse and the likelihood that at least one sexual partner was an HPV carrier increase the probability of infection.³² Men play an important role in the transmission of HPV to women.^{33,34} There is a significant correlation in men between number of sexual partners and prevalence of penile HPV DNA.³³ The probability that a woman will become infected with HPV and her risk of developing cervical cancer are associated with the presence of HPV DNA in the penis of her male partner.^{7,35}

A number of behaviours appear to act as co-factors with HPV, enhancing the likelihood that cervical cancer will develop. These are discussed under **Risk Modifiers**.



HPV infections in Ontario women aged 15–49, sampled 1998–1999

Source: Data from Sellors et al., 2000,²⁷ weighted to reflect distribution for the age groups tested

Cancer Care Ontario

Canadian Cancer Society

RISK MODIFIERS & PREVENTION

Factors modifying cervical cancer risk

Although high-risk (oncogenic) HPV infection is the primary cause of cervical cancer, several co-factors may increase a woman's susceptibility to HPV infection and subsequent risk of developing cervical cancer:

Smokers are about twice as likely as non-smokers to develop cervical cancer.³⁶ Direct carcinogenic action of cigarette smoking on the cervix, as well as suppression of the local immune response, are plausible mechanisms.³⁷

High parity, especially with 5 or more full-term pregnancies, puts a woman at increased risk.³⁸ The association is stronger for squamous cell carcinoma than for adenocarcinoma.

No definitive evidence links **oral contraceptives** with cervical cancer, although some data indicate that long-term use (5 or more years) may increase a woman's risk, particularly for adenocarcinoma.³⁹

Co-infection with HIV, *Chlamydia trachomatis* or herpes simplex virus-2 (HSV-2) facilitates the establishment of an HPV infection.^{40–42} The associations seem more important for squamous cell carcinoma than adenocarcinoma.

More research is needed to examine the association between nutritional status and cervical cancer. Some studies have shown an inverse relationship between cervical carcinogenesis and some dietary nutrients, such as lycopene,⁴³ tocopherols⁴⁴ and folates.^{43,45}

Prevention

Having regular Pap tests is the most important way to prevent cervical cancer.⁴⁶ (See **Screening**).

Reducing behaviours that increase the likelihood of infection with HPV among both women and men (for example, lifetime number of partners and early age at first sexual activity) would decrease the risk of cervical cancer.

Condom use is known to reduce the risk of a number of important sexually transmitted infections.^{47,48} Although it may reduce the risk of HPV transmission, studies have been inconsistent regarding its effectiveness.⁴⁹

Some evidence indicates that male circumcision is associated with reduced risk of penile HPV infection and a reduced risk of cervical cancer in men's current female partners.⁵⁰

Phase III clinical trials of a preventive HPV 16 and 18 vaccine will soon conclude; these vaccines show great promise with an extremely high rate of efficacy (100%) in the short term.^{51,52} HPV immunization could offer a long-term solution to cervical cancer, particularly in jurisdictions where it is difficult to implement screening and treatment programs. Although commercial vaccines may be available in the near future, long-term protection has not been established. The effect of a vaccine on cervical cancer rates will not be measurable until years after its introduction. Nonetheless, vaccines have the potential to significantly reduce the incidence of cervical cancer.⁵³

HPV immunization could offer a longterm solution to cervical cancer, particularly in jurisdictions where it is difficult to implement screening and treatment programs.

Canadian Cancer Society

SCREENING

he Pap test for cervical cancer screening (developed by Dr. Papanicolaou) has been available in Ontario for more than 40 years. The conventional Pap test involves scraping some cells from the surface of the cervix with a wooden spatula and from the endocervix with a brush, spreading the cells on a glass slide and applying a chemical coating to protect the cells. The slide is sent to a laboratory for microscopic examination by a cytotechnologist and/or cytopathologist to determine whether abnormal cells are present.

Liquid-based cytology (LBC) is a variant of the conventional Pap test. With LBC, the collected cells are placed into a vial containing cell-preserving fluid. The laboratory uses an automated system to prepare slides for analysis. Although more expensive, LBC has greater *sensitivity* and *specificity* and a lower percentage of

unsatisfactory specimens compared to the conventional Pap test.¹⁴ It also offers the potential for HPV DNA testing using residual cells in the LBC fluid.

There is sufficient evidence that screening women with Pap tests in a high-quality screening program reduces cervical cancer incidence and mortality by at least 80%.⁷ Efficacy has been adequately demonstrated only for squamous cell carcinoma,⁷ although the addition of the endocervical brush for cell collection is expected to result in improved efficacy for adenocarcinoma.

HPV DNA analysis of cervical cells for high-risk HPV types may be used as part of a screening regimen in two ways: for **triage** and for primary screening. Triage HPV DNA testing is carried out as follow-up to selected Pap test results (e.g., atypical squamous cells of unknown significance, or ASC-US) to differentiate

Cervical screening recommendations for women at risk*					
Ontario Cervical Screening Program Practice Guidelines (2005) ⁵⁴	Pan-Canadian Forum on Cervical Screening (2003) ⁵⁵	International Agency for Cancer Research (2005) ⁷			
Women of all ages who are, or ever have been, sexually active should be screened.	Both LBC and conventional Pap are acceptable.	Women aged 25–65 should be screened.			
After 3 annual normal Pap tests screening should be continued every 2–3 years.	Scientific evidence supports the efficacy of HPV testing in	Women aged 25–49 should be screened every 3 years,			
Discontinue after age 70 if 3+ normal Pap tests in the previous 10 years.	but knowledge about	5 years.			
Immunocompromised/HIV positive women should be screened annually.	implementation is insufficient.	HIV positive women should			
Pregnant women and women who have sex with women should follow	Scientific and clinical	be screened more trequently.			
same regimen as non-pregnant women and women who have sex with men.	evidence supports HPV triage for women 30+ years with	Both LBC and conventional cytology are acceptable.			
LBC is the preferred tool; conventional Pap is acceptable.	ASC-US Pap test result				
HPV triage is acceptable for women 30+ years with ASC-US Pap test result.	methods used).				

* Screening can be discontinued in women who have had a total hysterectomy and have no history of a cervical cancer precursor or high-risk HPV. Women who have had a subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines above.

HIV = human immunodeficiency virus; LBC = liquid-based cytology; HPV = human papillomavirus; ASC-US = atypical squamous cells of unknown significance

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society



women who would likely benefit from *colposcopy* from those who would be unlikely to benefit. This is particularly useful if the initial cytology was liquidbased (*reflex HPV testing*); the cells for HPV DNA analysis are then drawn from the residual LBC medium. Studies have shown triage HPV DNA testing to be efficacious.^{56,57}

Although there is sufficient evidence that HPV DNA analysis can be expected to be at least as effective as conventional cytology as a primary screening modality,⁷ further research is necessary, especially to determine whether HPV DNA testing can be used alone versus as an adjunct to conventional cytology, age of initiation, and the method of DNA analysis to be used.

Practice guidelines for screening

Specific screening recommendations vary, but the Ontario Cervical Screening Program (OCSP) recommends that all sexually active women be screened annually until they have had 3 successive normal Pap tests, and every 2–3 years thereafter until age 70. Reflex HPV testing is a recommended triage intervention for women over 30 years of age with an ASC-US Pap test.

Practice guidelines for follow-up of abnormalities

There are standardized guidelines for next steps when an abnormality is identified on a Pap test. In particular, cellular changes that suggest an abnormality (with a

Cellular abnormality*	Description/Definition	Practice guidelines for follow-up
ASC-US	Atypical squamous cells of unknown significance	Repeat cytology for women <30 years HPV DNA testing for women 30+ years **
ASC-H	Atypical squamous cells in which high-grade lesions cannot be excluded	Colposcopy
Atypical glandular cells	Atypical cells from the endocervix or endometrium	Repeat cytology and/or endometrial sampling
LSIL	Low-grade squamous intraepithelial lesions; epithelial abnormality that is unlikely to act as cervical cancer precursor. Equivalent to mild dysplasia or CIN 1	Repeat cytology
HSIL	High-grade squamous intraepithelial lesions; associated with persistent infection with high-risk types of HPV and significant risk of progressing to cervical cancer. Equivalent to moderate to severe dysplasia, or carcinoma in <i>situ</i> , or CIN 2 or 3	Colposcopy
Squamous cell carcinoma, adenocarcinoma and other malignant neoplasms		Colposcopy

OCSP Practice Guidelines for follow-up of abnormalities identified on a Pap test

Source: http://www.cancercare.on.ca/documents/CervicalScreeningGuidelines.pdf (June 2005)

* Ontario classifies abnormalities identified on a Pap test according to the revised Bethesda System 2001.58

** Repeat cytology if HPV DNA testing is not available.

OCSP = Ontario Cervical Screening Program

insight on cancer volume five • october 2005 Canadian Cancer Society



moderate to high risk of progressing to cancer if left untreated) should be referred for colposcopy. A physician then examines the cervix under magnification (using a colposcope) and removes some tissue from the area of apparent abnormality, so that it can be examined under a microscope by a pathologist and a diagnosis made.

Organized screening

Screening is most effective and cost-effective if delivered through an organized program with components that cover all aspects of the screening process.⁵⁹ These comprise comprehensive practice guidelines for screening and for follow-up of test results; initiatives to increase and maintain a high level

Components of organized screening

	OCSP
Screening and follow-up guidelines	•
Initiatives to increase and maintain screening participation	
Routine recall for next screening test	
Procedures to ensure follow-up of abnormal test results	
Quality assurance	•
Regular monitoring and evaluation of screening program	
Information system	

= Yes

🔺 = Partial

= No

OCSP = Ontario Cervical Screening Program

of screening participation; procedures to ensure that women are regularly re-screened (following a normal test result) or followed-up (when a test result suggests an abnormality) according to practice guidelines; and programs to ensure high standards of quality for all screening-related activities.⁷ The Ontario Cervical Screening Program (OCSP) currently includes some of these components.

The OCSP does not have a comprehensive information system that includes data on all Pap tests, follow-up procedures and results, and outcomes. This is the required foundation of an organized program, which facilitates optimal implementation of screening as well as continuous monitoring and evaluation.

Screening is most effective and costeffective if delivered through an organized program with components that cover all aspects of the screening process.

The OCSP does not have a comprehensive information system that includes data on all Pap tests, follow-up procedures and results, and outcomes. This is the required foundation of an organized program, which facilitates optimal implementation of screening as well as continuous monitoring and evaluation.

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society www.cancer.ca

PRESENTATION AND TREATMENT

Presentation and diagnosis

Although cervical cancer most often has no noticeable symptoms (especially early in development), sometimes vaginal bleeding, unusual vaginal discharge, pelvic pain, or pain during sexual intercourse may be present. The surface of the cervix may appear ulcerated.

As the tumour extends more widely, it may invade adjacent organs such as the bladder or the rectum, and may obstruct the drainage tubes from the kidney causing the backup of urine into the kidneys (hydronephrosis) and even renal failure. Cancer of the

cervix can also spread through the regional lymphatics or blood stream resulting in *metastases* in the pelvic lymph nodes, lungs, liver, or bone.

If a lesion that is suspicious for cancer is suggested by either a Pap test or symptoms, a woman is referred for colposcopy. With the aid of a colposcope, the cervix is examined visually, and a small piece of tissue from the area suspicious for cancer is taken for microscopic examination by a pathologist, who will make the diagnosis.

Staging and treatment for cervical cancer					
Stage	Description	Treatment			
0	Carcinoma <i>in situ</i> , preinvasive carcinoma There is no stromal invasion	Localized treatment: cryotherapy, LEEP, laser therapy, or conization			
I	Invasive carcinoma confined to the cervix				
ΙΑ	Invasive carcinoma identified microscopically Subdivided as (1) measured invasion of stroma \leq 3.0 mm in depth and \leq 7.0 mm in horizontal spread; or (2) measured invasion of stroma more than 3.0 mm in depth, but no greater than 5.0 mm and 7.0 mm in horizontal spread	Conization for women wishing to preserve ability to have children or for <i>microinvasive</i> cancer. Radical hysterectomy is acceptable for post-reproductive age women or if the depth is between 3.0 mm and 5.0 mm			
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than stage IA2 Subdivided as (1) clinical lesions of \leq 4.0 cm in size; or (2) clinical lesions >4.0 cm in size	Radical hysterectomy and pelvic <i>lymphadenectomy</i> for lesions ≤4.0 cm in diameter. In young women wishing to preserve fertility radical <i>trachelectomy</i> and laparoscopic lymphadenectomy. Radiotherapy for lesions >4.0 cm			
II	Carcinoma that extends beyond the cervix, but not onto the pelvic wall. It may involve the vagina, but not as far as the lower third of the vagina Subdivided as to (A) no parametrial involvement, or (B) parametrial involvement				
111	Carcinoma that extends to the pelvic wall, or involves the lower third of the vagina Includes all patients with hydronephrosis or non-functioning kidney, excluding other causes	Radiotherapy (both external and intracavity methods) and concurrent chemo-radiotherapy			
IV	Carcinoma that extends beyond the true pelvis, or has clinically involved the mucosa of the bladder or rectum				

Sources: IARC, 20057: FIGO, 200060; NCI, 200561

LEEP = loop electrosurgical excision procedure

insight on cancer volume five • october 2005 **Canadian Cancer Society** www.cancer.ca

Cancer Care Ontario www.cancercare.on.ca

Treatment strategies

If a precursor lesion is diagnosed, removal of the entire lesion by one of a number of techniques–*cryotherapy, laser therapy, loop electrosurgical excision procedure* (LEEP), or a knife cone biopsy (*conization*)–may be required.

The treatment for cervical cancer depends primarily on the extent of spread, or stage, of the cancer. In addition, factors such as invasion of tumour cells into the vascular or lymphatic spaces, the bulk of the primary tumour, and whether tumour is evident at the edges of the surgically removed tissue, determine the most appropriate treatment strategy.

Surgery to remove the tumour and part (or all) of the cervix is typically the initial treatment for cervical cancer. Radical hysterectomy is the surgical procedure to remove the uterus, cervix, part of the vagina, some of the tissue surrounding the cervix (parametrium), and the regional pelvic lymph nodes. Depending on the age of the patient and the type of cancer, sometimes it is recommended that the ovaries also be removed. Surgery is usually performed for small stage IB cancers, or for post-reproductive women with stage 0 or IA carcinoma. Women who wish to maintain the ability to have children may have fertility-sparing surgery, including removal of the regional lymph nodes and the tumour from the cervix. The uterus and ovaries are not removed, and the individual has the opportunity of having children after the surgery. This can only be done for early or small cervical cancers.

Radiotherapy is most commonly used for more advanced stages (large stage IB (>4 cm) and higher), and at earlier stages for women who are not candidates for surgery. Radiation treatment may be given either externally or through intracavitary methods.

Chemotherapy may be combined with radiotherapy concurrently to improve effectiveness. Cisplatin is believed to sensitize tumour cells to radiation and to assist in the eradication of *micrometastases*. In women whose cervical cancer is being treated with radiotherapy because it is locally advanced disease, bulky, or associated with lymph nodes or positive resection margins, chemotherapy with cisplatin has been shown to improve survival.¹⁷ Cisplatin plus topotecan is a new regimen that appears to be highly effective for recurrent or advanced stage cervical cancer.⁶²

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society



Complications of treatment

Complications of treatment can affect quality of life. Conization, undertaken for carcinoma in situ or very early invasive cancer, can occasionally lead to **cervical** *incompetence* during pregnancy. It is rare for other surgical techniques to impact at all on fertility. As with any abdominal surgery, hysterectomy can be associated with infection, deep vein thrombosis, pulmonary embolism, or blood loss requiring transfusion, as well as injury to surrounding structures. Other side effects occur with surgery but for the most part are rare or short-lived. Rare complications of lymph node removal include *lymphedema* of the legs or *lymphocyst* formation.

External beam radiotherapy can be associated with fatigue, redness of the skin at the site where the treatment is given, loss of appetite, nausea and vomiting. It can also cause injury to structures that surround the cervix, such as the bladder and rectum. Some late side effects from radiation are possible, the worst being bowel *strictures* or *fistulas*, which ultimately require surgery for repair. Injury to the blood vessels in the lining of the rectum or bladder may result in bleeding from the lining of the rectum and/or the bladder. *Atrophy* or *stenosis* of the vagina may also occur.

Chemotherapy administered concurrently with radiotherapy can increase the acute side effects of radiation, including inflammation of the bladder, rectum or vagina. Chemotherapy administered for metastatic disease may be associated with nausea and vomiting, diarrhea, anorexia and lowering of the white blood cell count.

Supportive and palliative care

Patients with cervical cancer frequently require psychosocial support to deal with the diagnosis of cancer and changes in sexual function. For those whose disease becomes metastatic and resistant to treatment, a palliative medicine team consultation may be necessary to manage pain or other symptoms from bone, liver or retroperitoneal lymph node metastases, or renal failure, a common terminal event in patients with uncontrolled cancer in the pelvis.

Canadian Cancer Society

CONCLUSIONS AND ACTIONS

100% Ontario Age-standardized percentage 80% 60% 40% 20% 0% SWIN CWH Toronto CWLR SWIL 4.D 12 St. ු Ś ext Source: Canadian Community Health Survey 2000/2001 - Cycle 1.1

Percentage* of Ontario women aged 20–69 who had a Pap test within the previous 3 years, by region**, 2000

The Ontario Cervical Screening Program (OCSP)

Cervical screening in Ontario

recommends that all women who have ever been sexually active (and have not had a total hysterectomy) have a Pap test every 2–3 years until age 70. In 2000, only 81% of Ontario women reported having had a test within the previous 3 years.¹⁰ This ranged from a low of 73% in Toronto to a high of 85–86% in Southwest–London, Central South, Central East, East–Kingston and East–Ottawa regions of the province. Women who are not screened regularly tend to have a low level of education, live in poverty, be newcomers to Canada, be over 50 years of age, or be of Aboriginal descent.⁶³

Call to Action!

Cancer Care Ontario, in consultation with its stakeholders, has set cancer prevention targets for the year 2020.⁶⁴ The current level of participation in cervical screening in Ontario is well below the Cancer 2020 target of 95%. Furthermore, the province does **not** include all components of an organized screening program. Ontario lags behind other provinces in progress towards organized screening.

A high-quality organized cervical screening program with high rates of participation can reduce the incidence of and mortality from cervical cancer by 80–90%, compared to no screening. The maximum benefit of cervical screening will be realized in Ontario only by achieving the Cancer 2020 targets.

(Statistics Canada, 2002) * Excluding women who reported having had a hysterectomy ** Refer to key map on page 13

Ontario cancer prevention target for cervical cancer screening

Measure% women who have ever been
sexually active who participate in
organized screeningCancer 2020 target95%

Source: Cancer 2020 Steering Committee, 200364

Cancer Care Ontario www.cancercare.on.ca Canadian Cancer Society

These goals are attainable. The highest priority at this time is the development of a comprehensive information system to permit optimal implementation of all components of organized screening. This will require access to data from a variety of sources, including laboratories, hospitals, physicians, and the Ontario Cancer Registry. Achieving such access will necessitate concerted action from a variety of stakeholders to overcome legislative and other barriers.

Percentage* of Ontario women aged 20–69 who had a Pap test within the previous 3 years, 2000, compared to Cancer 2020 target



Source: Canadian Community Health Survey 2000/2001 – Cycle 1.1 (Statistics Canada, 2002)

* Excluding women who reported having had a hysterectomy

Canadian Cancer Society

GLOSSARY OF TERMS, DATA SOURCES AND METHODS

Adenocarcinoma

Cancer in cells that have glandular (secretory) properties.

Adenosquamous cancer

Cancer of the mucosa consisting of a mixture of malignant squamous and glandular cells.

Age-standardized rate

The number of new cases of cancer or cancer deaths per 100,000 person-years that would have occurred in the standard population (1991 Canadian population) if the actual age-specific rates observed in a given population had prevailed in the standard population.

Age-specific rate

The number of new cases of cancer or cancer deaths, expressed as a rate per 100,000 person-years, in a given age group.

Atrophy

An abnormal decrease in size of an organ or tissue.

Average annual percent change in rate

A measure to assess the rate of change over time of an incidence or mortality rate, calculated by fitting a linear model to the annual rates after applying a logarithmic transformation. The estimated slope is then transformed back to represent a percentage increase or decrease per year. The method used allows for a series of straight line segments with different slopes to be fit to long-term trend data. This measure estimates both the specific years at which the slope (rate of change) changes significantly and the slope of each line segment.

Carcinoma in situ

Cancer that involves only the cells in which it began and that has not spread to nearby tissues.

Cervical incompetence

Inability of the cervix to remain closed during pregnancy.

Chemotherapy

Treatment with drugs that kill cancer cells.

Cohort effect

Variation in health status that arises from the different causal factors to which each birth cohort in the population is exposed as the environment and society change. Each consecutive birth cohort is exposed to a unique environment that coincides with its life span.

Colposcopy

Visual examination of the cervix using an instrument called a colposcope (a low-power stereoscopic binocular field microscope with a powerful light source) that magnifies the surface of the cervix.

Conization

A surgical procedure involving the removal of a cone-shaped section of the cervix using a "cold knife" (scalpel) under local or general anesthesia. This procedure may be used to diagnose or to treat a cervical condition. It is also called knife cone biopsy or cold knife cone.

Cryotherapy

24

A treatment that uses extremely low temperatures to freeze and destroy abnormal tissue.

Deoxyribonucleic acid (DNA)

The molecules inside cells that carry genetic information and pass it from one generation to the next.

Fistula

An abnormal passage or opening between two internal organs or from an internal organ to the surface of the body.

Five-year relative survival

A measure of the reduction in life expectancy due to a diagnosis of cervical cancer. Relative survival is estimated from life tables as the ratio of the observed survival of cervical cancer cases five years after diagnosis to the expected survival of women in the general population who are the same age. The ratio is expressed as a percentage. Deaths from all causes occurring in Ontario through 2002 were used.

Human papillomavirus (HPV)

A member of a family of viruses that can cause abnormal tissue growth (for example, genital warts) and other changes to cells. Infection with certain (high-risk oncogenic) types of HPV may increase the risk of developing some types of cancer, such as cervical cancer.

Hysterectomy

Surgery to remove the uterus and, sometimes, the cervix. When the uterus and part or all of the cervix are removed, it is called a total hysterectomy. When only the uterus is removed, it is called a partial hysterectomy. Surgery to remove the uterus, cervix and upper vagina (and, sometimes, the ovaries, fallopian tubes and nearby lymph nodes) is called a radical hysterectomy.

Hysterectomy-corrected population at risk for cervical cancer

Ontario women at risk for cervical cancer are those who have not had a hysterectomy that includes removal of the ectocervix. Rates of cervical cancer providing a more accurate assessment for Ontario as a whole are based on total women minus the number estimated to have had a prior hysterectomy. Adjusted population counts were derived by multiplying the cumulative probability of not having had a hysterectomy for a woman of a given age by the total number of women in Ontario of that age in each year.⁶⁵ Hysterectomy data were provided by the Hospital Medical Records Institute (HMRI)/Canadian Institute for Health Information (CIHI) for 1980–1996. For 1997–2002, hysterectomy counts were imputed from the available data for five years prior to each of these years.

Immune response

The activity of the immune system against foreign substances (antigens).

Invasive carcinoma

Cancer that has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues.

Laser therapy

The use of an intensely powerful beam of light to kill cancer cells.

Latent HPV infection

HPV infections causing no morphologic cervical abnormalities and identified only by HPV DNA detection.

Cancer Care Ontario

Canadian Cancer Society



Lead time bias

Overestimation of survival time, due to the backward shift in the starting point for measuring survival that arises when cancer is detected early, as by screening.

Liquid-based cytology (LBC)

A screening method similar to the Pap test in that cells are collected from the cervix with a spatula, but then rather than being smeared onto a microscope slide as for a Pap test, the cells are rinsed into a small container of liquid and treated to remove obscuring material before being deposited onto a slide and read under a microscope in the usual Pap test way. This method reduces the number of unsatisfactory specimens.

Loop electrosurgical excision procedure (LEEP)

A surgical technique that uses electric current passed through a thin wire loop to remove abnormal tissue.

Lymph node

A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (lymphatic fluid), and store lymphocytes (white blood cells). They are located along lymphatic vessels.

Lymphadenectomy

A surgical procedure in which the lymph nodes are removed and examined to see whether they contain cancer. For a regional lymph node dissection, some of the lymph nodes in the tumour area are removed; for a radical lymph node dissection, most or all of the lymph nodes in the tumour area are removed. Also called lymph node dissection.

Lymphedema

A condition in which excess fluid collects in tissue and causes swelling. Lymphedema may occur in the arm or leg after lymph vessels or lymph nodes in the underarm or groin are removed or treated with radiation.

Lymphocyst

A cystic mass containing lymph following surgical trauma.

Median age at diagnosis/death

The age for which 50% of the diagnoses or deaths occur in younger individuals and 50% occur in older individuals.

Metastases

The spread of cancer from one part of the body to other parts, usually through the vascular or lymphatic systems.

Microinvasive carcinoma

The earliest stage of invasive squamous cell carcinoma. Cancers that have invaded no more than 5 mm deep and 7 mm wide into the underlying cervical stroma.

Micrometastases

Small numbers of cancer cells that have spread from the primary tumour to other parts of the body and are too few to be picked up in a screening or diagnostic test.

Morphology

Refers to the type of cell that has become neoplastic. The morphologic data have been coded according to the First Edition of

the International Classification of Diseases for Oncology (ICD-O).^{66,67} The grouping scheme for this analysis was a variant of Parkin and coauthors' groups for comparative studies.⁶⁸

Moving average rate

Rate calculated using the sum of the new cases of cancer or cancer deaths for a three-year period and the population estimates for those same years. Three-year moving average rates are shown on all graphs describing trends in order to smooth out annual fluctuations.

Oncogenic

Physiologic processes, viruses, and other biological agents or events that promote the formation or development of cancerous tumours.

Ontario Cancer Registry (OCR)

The population-based database that includes information on all diagnoses of cancer reported in residents of Ontario since 1964. The Registry includes limited data about diagnosis (date, type of cancer), death (date, cause), treatment, and the individual (date of birth, sex, census division of residence at diagnosis or death) for all cancer patients. The Registry does not include data on risk factors, stage, grade, or basal or squamous cell skin cancers.

Opportunistic screening

Screening outside an organized or population-based screening program, as a result of (for example) a recommendation made during a routine medical consultation, consultation for an unrelated condition, on the basis of a possibly increased risk for developing cancer or by self-referral.

Organized screening program

Screening organized at the national or regional level, with an explicit policy that includes several essential elements, from identification of target population, through recruitment into screening, to treatment.

Papanicolaou (Pap) test

A procedure in which cells are scraped from the cervix for examination under a microscope. It is used to detect cancer and changes that may lead to cancer. The test was named after its inventor, Dr. Papanicolaou.

Persistent HPV infection

When the same type of HPV DNA is detected at least twice over a period of one or more years.

Population data

Population counts used as denominators of rates. Statistics Canada, which conducts the National Population Census every five years, provides annual population estimates by five-year age groups and census divisions.

Potential years of life lost (PYLL)

A method that helps to describe the extent to which life is cut short by cancer. It is calculated by multiplying the number of deaths from a particular cancer at each individual age by the life expectancy of survivors.

Precancer/precancerous/cancer precursor

A cellular abnormality that may progress to cancer.

insight on cancer volume five • october 2005 Canadian Cancer Society

Prevalence

The number of individuals alive and diagnosed with cervical cancer in the previous 15 years, according to the Ontario Cancer Registry. This number is probably an overestimate, because deaths that occur outside Ontario may not be reported to the Registry.

Radiotherapy

The use of high-energy radiation from X-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (intracavitary radiation, internal radiation therapy, implant radiation or brachytherapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body.

Reflex HPV testing

A protocol for routine triage of equivocal cervical cytological interpretations, by HPV testing either the residual liquid cytology specimen or an additional specimen collected at the same time as the original sample.

Regions

Cancer planning regions that correspond to aggregations of census divisions, and are to some extent defined by the locations of specialized cancer treatment centres.

Regional variation

Incidence and mortality rates and relative survival for each region compared to those of all Ontario. Region-specific values are considered significantly different from Ontario if the 95% confidence interval excludes the overall provincial value.

Sensitivity

A characteristic of a screening test that measures the ability of a test to detect a disease (or condition) when it is truly present. Sensitivity is the proportion of all truly diseased patients for whom there is a positive test, determined as the number of true positives divided by the sum of true positives + false negatives.

Specificity

A characteristic of a screening test that measures the ability of a test to exclude the presence of a disease (or condition) when it is truly not present. Specificity is the proportion of truly nondiseased patients for whom there is a correctly negative test, expressed as the number of true negatives divided by the sum of true negatives + false positives.

Squamous cell carcinoma

Cancer that begins in squamous cells, which are thin, flat, irregularlyshaped cells that cover the outer cervix.

Stage/staging

The size and extent of spread of cancer. Staging is a method of determining and describing a cancer's site and extent.

Stenosis/stricture

An abnormal narrowing of a passageway or body opening.

Stroma

Adult connective tissue, which forms the structure of organs. In the case of most visceral organs, including the cervix, the stroma is composed predominantly of smooth muscle.

Trachelectomy

Surgical removal of the cervix (but not the rest of the uterus). A radical trachelectomy involves removal of the cervix and the surrounding tissues, including some pelvic lymph nodes.

Triage cytology

A second screening test that is performed when the first test is neither normal nor definitively indicative of need for treatment. Triage further stratifies individuals according to their risk for the disease state.

Unsatisfactory Pap test specimen

A specimen in which not enough cells were retrieved for proper evaluation, or for which there was a problem with the preparation or staining of the slide containing the cervical cell sample.

REFERENCES

- Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12–9
- Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55:244–65
- 3. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst. 1999;91:252–8
- Schiffman M, Kruger Kjaer S. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr. 2003; 31:14–19
- Ferlay J, Bray F, Pisani P, Parkin DM. J. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide, IARC CancerBase No. 5. version 2.0. Lyon, France: IARC Press, 2004
- 6. Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer. 2004;111:278–85
- International Agency for Research on Cancer Working Group. IARC handbooks of cancer prevention: cervix cancer screening. Vol 10. Lyon: IARC Press, 2005
- 8. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds). Cancer incidence in five continents. Volume VIII. Lyon, FR: International Agency for Research on Cancer, 2002
- 9. National Cancer Institute of Canada. Canadian Cancer Statistics 2005. Toronto, Canada, 2005
- 10. Statistics Canada. Canadian Community Health Survey Cycle 1.1, 2000–2001. Ottawa, 2002
- Holowaty EJ, Marrett LD, Fehringer G. Cancer incidence in Ontario: trends and regional variations. Toronto: Ontario Cancer Treatment Research Foundation, 1995
- Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999;318:904–8
- Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet. 2004;364:249–56
- 14. Colgan TJ, McLachlin CM, Cotterchio M, Howlett R, Seidenfeld AM, Mai VM. Results of the implementation of liquid-based cytology-SurePath in the Ontario screening program. Cancer. 2004;102:362–7
- 15. Ontario Cervical Screening Program. Program Report, 2001–2003. Toronto: Cancer Care Ontario, In Press
- Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, et al. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. Cancer. 2004;101:3–27
- Lukka H, Hirte H, Fyles A, Thomas G, Fung Kee Fung M, Johnston M. Cancer Care Ontario Program in Evidence-Based Care. Primary treatment for locally advanced cervical cancer: concurrent platinum-based chemotherapy and radiation. Practice guideline report #4–5. June 2004 http://www.cancercare.on.ca/pdf/pebc4–5f.pdf

Accessed 30 March 2005

- Vizcaino AP, Moreno V, Bosch FX, Munoz N, Barros-Dios XM, Parkin DM. International trends in the incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. Int J Cancer. 1998;75:536–45
- Adlaf EM, lalomiteanu A. CAMH Monitor eReport: Addiction and mental health indicators among Ontario adults in 2001, and changes since 1997. CAMH Research Doc. Series No. 12. Toronto, ON: Centre for Addiction and Mental Health http://www.ocat.org/pdf/CAMH_report_prevalence.pdf Accessed 7 May 2004
- 20. SAS Institute Inc. SAS/Stat Software: changes and enhancements through Release 8.02. Cary, NC: SAS Institute Inc, 1999–2001
- Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348:518–27
- 22. Frisch M. On the etiology of anal squamous carcinoma. Dan Med Bulletin. 2002;49:194–209
- Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WG, Pirog EC. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol. 2001;159:1211–8
- 24. Herrero R. Chapter 7: Human papillomavirus and cancer of the upper aerodigestive tract. [43 refs] J Natl Cancer Inst Monogr. 2003;31:47–51
- 25. Pfister H. Chapter 8: Human papillomavirus and skin cancer. J Natl Cancer Inst Monogr. 2003;31:52–6
- 26. Winer RL, Koutsky LA. The epidemiology of human papillomavirus infections. In: Rohan TE, Shah KV, eds. Cervical Cancer: from Etiology to Prevention. Dordrecht, The Netherlands: Kluwer Academic Publishers, 2004;143–87
- Sellors JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. Survey of HPV in Ontario Women (SHOW) Group. CMAJ. 2000;163:503–8
- Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. A survey of HPV in Ontario Women Group. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ. 2003;168:421–5
- Mao C, Hughes JP, Kiviat N, Kuypers J, Lee SK, Adam DE, Koutsky LA. Clinical findings among young women with genital human papillomavirus infection. Am J Obstet Gynecol. 2003;188:677–84
- Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, et al. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. JAMA. 2001;286:3106–14
- Villa LL, Sichero L, Rahal P, Caballero O, Ferenczy A, Rohan T, Franco EL. Molecular variants of human papillomavirus types 16 and 18 preferentially associated with cervical neoplasia. J Gen Virol. 2000;81:2959–68
- 32. Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). Cancer Epidemiol Biomarkers Prev. 2001;10:101–6

Canadian Cancer Society

- 33. Castellsague X, Ghaffari A, Daniel RW, Bosch FX, Munoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. J Infect Dis. 1997;176:353–61
- Lazcano-Ponce E, Herrero R, Munoz N, Hernandez-Avila M, Salmeron J, Leyva A, et al. High prevalence of human papillomavirus infection in Mexican males: comparative study of penile-urethral swabs and urine samples. Sex Transm Dis. 2001;28:277–80
- Thomas DB, Ray RM, Kuypers J, Kiviat N, Koetsawang A, Ashley RL, et al. Human papillomaviruses and cervical cancer in Bangkok. III. The role of husbands and commercial sex workers. Am J Epidemiol. 2001;153:740–8
- 36. Kjellberg L. Hallmans G. Ahren AM. Johansson R. Bergman F. Wadell G. et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. Br J Cancer. 2000;82:1332–8
- Plummer M, Herrero R, Franceschi S, Meijer CJ, Snijders P, Bosch FX, et al. IARC Multi-centre Cervical Cancer Study Group. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case-control study. Cancer Causes Control. 2003;14:805–14
- Munoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. International Agency for Research on Cancer. Multicentric Cervical Cancer Study Group. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric casecontrol study. Lancet. 2002;359:1093–101
- 39. Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet. 2003;361:1159–67
- 40. Smith JS, Munoz N, Herrero R, Eluf-Neto J, Ngelangel C, Franceschi S, et al. Evidence for Chlamydia trachomatis as a human papillomavirus co-factor in the etiology of invasive cervical cancer in Brazil and the Philippines. J Infect Dis. 2002;185:324–31
- 41. Smith JS, Herrero R, Bosetti C, Munoz N, Bosch FX, Eluf-Neto J, et al. International Agency for Research on Cancer (IARC) Multicentric Cervical Cancer Study Group. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J Natl Cancer Inst. 2002;94:1604–13
- Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, Wright TC Jr. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. JAMA. 2000;283:1031–7
- Palan PR, Mikhail MS, Goldberg GL, et al. Plasma levels of betacarotene, lycopene, canthaxanthin, retinol, and alpha- and tautocopherol in cervical intraepithelial neoplasia and cancer. Clin Cancer Res. 1996;2:181–5
- 44. Kwasniewska A, Charzewska J, Tukendorf A, Semczuk M. Dietary factors in women with dysplasia colli uteri associated with human papillomavirus infection. Nutr Cancer. 1998;30:39–45
- Liu T, Soong SJ, Alvarez RD, Butterworth CE Jr. A longitudinal analysis of human papillomavirus 16 infection, nutritional status, and cervical dysplasia progression. Cancer Epidemiol Biomarkers Prev. 1995;4:373–80

- National Cancer Institute. Cervical cancer prevention. http://www.nci.nih.gov/cancertopics/pdq/prevention/cervical/ Patient/page2 Accessed 3 November 2004
- Smith JS, Bosetti C, Munoz N, Herrero R, Bosch FX, Eluf-Neto J, et al. Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. Int J Cancer. 2004; 111:431–39
- Wald A, Langenberg AG, Link K, Izu AE, Ashley R, Warren T, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA. 2001; 285:3100–6
- Gerberding JL. Report to Congress: prevention of genital human papillomavirus infection. Department of Health and Human Services. Centers for Disease Control and Prevention. 2004. http://www.cdcnpin.org/scripts/std/HPV%20ReportJan% 202004.pdf Accessed 1 August 2004
- Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med. 2002;346:1105–12
- Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. New Engl J Med. 2002;347:1645–51
- 52. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364:1757–65
- Lowry DR, Frazer IH. Chapter 16: Prophylactic human papillomavirus vaccines. J Natl Cancer Inst Monogr. 2003;31:111–6
- 54. Ontario Cervical Screening Program. Ontario Cervical Screening Practice Guidelines. Toronto: Cancer Care Ontario, 2005
- Stuart G, Gregory T, Bancej CM, Colgan T, Franco EL, Kropp RY, et al. Report of the 2003 Pan-Canadian forum on cervical cancer prevention and control. J Obstet Gynaecol Can. 2004;26:1004–14
- 56. Arbyn M, Buntinx F, Van Ranst M, Paraskevaidis E, Martin-Hirsch P, Dillner J. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst. 2004;96:280–93
- 57. Wright TC Jr., Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287:2120–9
- Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. Forum Group Members. Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114–9

Cancer Care Ontario www.cancercare.on.ca



- Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer. 2004;101:1201–13
- FIGO Committee on Gynecologic Oncology. Staging classifications and clinical practice guidelines of gynaecologic cancers. Benedet JL, Hacker NF, & Ngan HYS, (eds). Elsevier: 2000
- National Cancer Institute. Cancer Topics: Cervical cancer (PDQ): treatment. http://www.nci.nih.gov/cancertopics/pdq/treatment/cervical/ healthprofessional/ Accessed 10 March 2005
- 62. Monk BJ, Huang H, Wenzel L, Cella D, Long HJ. Quality of life outcomes from a phase III trial of cisplatin versus cisplatin plus topotecan in stage IVB, recurrent or persistent carcinoma of the cervix: results of GOG Protocol 179. Proceedings from the 35th annual meeting of the American Society of Gynecologic Oncologists. February 2004
- 63. Ontario Cervical Screening Program. Program Report, 1997–2000. Toronto: Cancer Care Ontario, 2002
- 64. Cancer 2020 Steering Committee. Targeting cancer: an action plan for cancer prevention and detection. Cancer 2020 Summary Report. Toronto: Canadian Cancer Society, 2003
- 65. Holowaty P. The natural history of cervical dysplasia [dissertation]. Toronto: University of Toronto, 1996
- 66. World Health Organization. Manual of the International Classification of Diseases for Oncology, First Edition. Geneva: World Health Organization, 1976
- 67. Percy C, Van Holten V, and Muir C, eds. International Classification of Diseases for Oncology, Second Edition. Geneva: World Health Organization, 1990
- Parkin DM, Shanmugaratnam K, Sobin L, Ferlay J, Whelan S. Histological groups for comparative studies. Lyon, France: International Agency for Research on Cancer. (IARC Technical Report No. 31), 1998

CERVICAL CANCER RESOURCES

Ontario Cervical Screening Practice Guidelines

The practice guidelines represent a convenient and upto-date source of the best available evidence on cervical screening developed through systematic review, evidence synthesis, and input from practitioners in Ontario. It is intended to promote evidence-based practice.

http://www.cancercare.on.ca/documents/ CervicalScreeningGuidelines.pdf

The Ontario Cervical Screening Program (OCSP) has developed a wide range of materials to educate the general public about cervical cancer. These materials are distributed with the help of the Canadian Cancer Society.

Materials can be ordered free of charge by contacting a Canadian Cancer Society Cancer Information Specialist at 1 888 939-3333.

The OCSP Resource Catalogue can be viewed and downloaded from the Cancer Care Ontario Web site at http://www.cancercare.on.ca/prevention_ cervicalScreening.htm

Some materials are available in multiple languages.

Ontario Cervical Screening Practice Guidelines

vised June 20

Initiation of Screening	All women who are, or have ever been, sexually active should be screened. Cervical cytology screening should be initiated within three years of first vaginal sexual activity, i.e., vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity.			
Screening Interval	Screening should be done annually until there are three consecutive negative Pap tests. After three annual negative Pap tests, screening should continue every two to three years. (These recommendations do not apply to women with previous almornal Pap tests) – See over for management of almornal cytology. – Screening at a three year interval is recommended, supported by an adequate recall mechanism. – Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests.			
Cessation of Screening	 Screening may be discontinued after the age of 70 if there is an adequate negative screening history in the previous 10 years (i.e., 3 or more negative tests). 			
Screening Women	with Special Circumstances			
Immunocompromised or HIV positive women should receive annual screening. Examples of situations where women may be immunocompromised include women who have received transplants, or women who have undergone chemotherapy.				
 Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or human papillomavirus (HPV). -Women who have undergose ablotal hysterectomy (with an htact cervix) should continue screening according to the guidelines. 				
 Indications for screening frequency for pregnant women should be the same as for women who are not pregnant. Manufacturer's recommendations for the use of individual screening tools in pregnancy should be considered. 				
Women who have sex with women should follow the same cervical screening regimen as women who have sex with men.				
Optimal Cervical S • Liquid-based cytology • Conventional smear cy Optimal Screening • A province-wide cervice	creening Tool (LBC) is the preferred tool for cervical cyclology screening. tology remains an acceptable alternative. Circumstances al screening program with an adequate recall mechanism is recommended.			
For more detail on t	he guidelines, please refer to: www.cancercare.on.ca/index_cervicalScreening.htm			
06/2005	See reverse			
returning control of the second				

Human Papillomavirus (HPV) and Cancer of the Cervix

This fact sheet offers clear, concise information about HPV and its implications for cervical health.

Make a Pap Test Part of Your Regular **Health Check Up**

This brochure provides information about the who, what and why of the Pap test.







Maixe a Pap Test Part of Your Regula Health Check-up

C



G

Understanding Your Pap Test Results

This brochure explains what happens if a Pap test is abnormal, what the abnormality classifications are and what they mean. It includes questions to ask of health care providers and explains that not all abnormal test results are cancer.

The Canadian Cancer Society's Cancer Information Service, a national, bilingual, toll-free service, offers comprehensive information about cancer and community resources to cancer patients, their families, the general public and health care professionals. The Canadian Cancer Society also has information for people living with cancer. Call 1 888 939-3333 or go to their Web site at http://www.cancer.ca







Understanding Your Pap Test Results

G

Canadian Cancer Society www.cancer.ca

Cancer Care Ontario www.cancercare.on.ca

INSIGHT ON CANCER news and information on cervical cancer



Cancer Care Ontario is dedicated to improving the quality of care for cancer patients by creating a seamless journey for them as they access the highest quality programs in cancer prevention, early detection, treatment, supportive care, palliative care and research. Working with partners, including the Cancer Quality Council of Ontario, CCO will measure, evaluate and report on quality improvement in the cancer system. Cancer Care Ontario is a policy, planning and research organization that advises government on all aspects of provincial cancer care.

Insight on Cancer can be found on both the Canadian Cancer Society's and Cancer Care Ontario's websites. Please visit the "library section" of the Ontario pages of the Canadian Cancer Society's website located at www.cancer.ca, or visit www.cancercare.on.ca.



Canadian Société Cancer canadienne Society du cancer

The Canadian Cancer Society is a national, communitybased organization of volunteers whose mission is the eradication of cancer and the enhancement of the quality of life of people living with cancer.

The Canadian Cancer Society, in partnership with the National Cancer Institute of Canada, achieves its mission through research, education, patient services and advocacy for healthy public policy. These efforts are supported by volunteers and staff and funds raised in communities across Canada.