

Cervical Cancer Screening

PHAC Scientific Officers:
S. Pollock/L. Dunfield

Consultant: L. Elit

D. Ciliska & D. Fitzpatrick-Lewis
And project staff
McMaster Evidence Review and Synthesis Centre
McMaster University
Hamilton Ontario Canada

CFTPHC Working Group Lead:
J. Dickinson
Members: R Birtwhistle, M. Joffres, G Lewin, E. Shaw, H. Singh
Partners: V Mai, M McLachlin

FINAL: February 25, 2011

Work Plan

Contents:

1. Purpose and Background
2. Previous Review and CTFPHC Recommendations
3. Analytic Framework
4. Key and Contextual Questions
5. Literature Search and Review
6. Inclusion/Exclusion Criteria
7. Quality and Strength of Evidence Criteria
8. Appendix 1: Search Strategy

1. Purpose and Background

Purpose

This is a revision of the previous Canadian Task Force Recommendations, last updated in 1991 and reviewed in 1999.¹

Cervical cancer screening using Pap smears is a well accepted intervention that lowers deaths from cervical cancer. Many recommendations are for annual screening² and “the annual pap smear” has become a regular part of medical care and articles in the popular press in North America. However, few other countries have recommended such frequent screening, and many start at a later age.³⁻⁷

Studies from across Canada and around the world show that most invasive cervical cancer arises in women who have never had a Pap test or who have allowed a long interval to elapse since having one. Consequently, some policies linked the screening interval and the presence of registries, asserting that the interval must be short until registry programs are available to remind women who do not have their Pap test “on time”² The Society of Obstetrics and Gynecology of Canada recommended that provincial and territorial governments should implement a publicly funded, organized, population-based cervical cancer screening system in order to move from opportunistic towards organized screening.⁸

In the last 5 years, with better understanding of the infectious nature of the disease and a change in screening test technology, there has been pressure to change screening policy. Many Canadian pathology laboratories have changed over to liquid-based technology, from the old slide-based technology, to reduce the number of unsatisfactory smears, to allow reflex human papillomavirus (HPV) testing of the supernatant if that is part of the protocol, and to reduce the work-pressure on their cytotechnologists.⁸ Given this, we need to understand how liquid-based testing affects the process of screening and to what extent it changes the diagnostic yield and performance measures of the Pap test.

There is recognition that particular populations have low Pap test rates, and high incidence of cancer. These include populations from some countries that are the source of

substantial immigration to Canada, where the cervical cancer rates are high but Pap tests are not used. There are questions about how to reach out to women with low Pap test rates and high risk for cervical cancer. The movement for change has been further accentuated with development of papillomavirus technology, with questions about the need for Pap tests in young women who have been immunized, and the role of HPV testing to decide whether cancer is likely to develop.

Thus there are questions in the medical and wider community that need answers in the Canadian context. The Canadian Partnership Against Cancer has supported the Pan-Canadian Cervical Screening Initiative (PCCSI) to work on these issues. Consequently the Task Force has partnered with PCCSI to develop a consistent approach to cervical cancer screening. Given the apparent success of many European countries in reducing the burden of cervical cancer through less frequent testing that starts later in life and that women prefer less frequent testing, the question arises of how few Pap tests can be done and how late they can be started without losing the preventive benefit.

Common questions that are asked by doctors and community members include:

1. For which groups do Pap tests reduce death from cervical cancer? Who should be screened?
2. At what age should screening start and stop?
3. How often should we screen?
4. Should we require 3 annual Pap tests before going to a longer screening interval?
5. What is the effect of changing to liquid-based cytology? Should this change our policies?
6. Is the number of sexual partners, or a recent change in sexual partners a reason to change the recommendations?
7. What screening is needed after hysterectomy?
8. Does having HPV immunization change the recommendations?
9. Does HPV testing change screening recommendations?
 - a) In women <30 years?
 - b) In women >30 years?

Condition Background

a. Definition

Cervical cancer is a proliferation of malignant cells that arise in cervical tissue and represents a continuum of conditions ranging from noninvasive to invasive carcinoma. The most common form is squamous cell carcinoma, but there are a number of other subtypes of noninvasive and invasive lesions.⁹

Preinvasive lesions, otherwise known as dysplasia, cervical intraepithelial neoplasia (CIN) or intraepithelial lesions, are epithelial proliferation of atypical cells as a result of infection with oncogenic HPV. Either the squamous and/or the glandular epithelium of the transformation zone can be affected. The transformation zone is an area of dynamic cellular turnover when the squamous cells cover the glandular cells as a result of hormonal changes during the woman's lifetime. These preinvasive lesions can be very early and only involve the basal cells near the basement membrane. Other preinvasive lesions can involve half (CIN 2) or the whole thickness of the epithelium (CIN 3) in which case there is an increasing risk that the lesion will progress to cancer over time. This earlier classification of smears, describing dysplasia, has largely been superseded since 1998 by Bethesda terminology, which classifies smears as atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesions (LSIL), and high grade squamous intraepithelial lesions (HSIL). The histology classification is similar, but based on the structural detail available in biopsy material.

Table 1. Classification systems

Dysplasia (cytology)	CIN (histology)¹⁰	Bethesda (cytology)¹¹
Atypia	Atypia	ASCUS
HPV effect	HPV effect	LSIL
Mild Dysplasia	CIN 1	
Moderate Dysplasia	CIN 2	HSIL
Severe Dysplasia	CIN 3	
Carcinoma in Situ		
Cancer	Cancer	Cancer

CIN: Cervical Intraepithelial Neoplasia: in 3 grades according to extent

ASCUS: Atypical Squamous Cells of Undetermined Significance

LSIL: Low grade Squamous Intraepithelial Lesion.

HSIL: High grade Squamous Intraepithelial Lesion. Also used for histological diagnoses: CIN 2,3 and Carcinoma in Situ.

Invasive lesions have metastatic potential as they invade the basement membrane into the adjacent stroma. The most common sites of metastasis include adjacent lymph nodes, vagina, and ultimately bladder, bowel, and lung. Approximately 80% of invasive cervical cancers are squamous cell carcinoma and 15% are adenocarcinoma, followed by a combination of both types, adenosquamous carcinoma. The remainder are rarer types (e.g., small cell neuroendocrine).¹²

b. Prevalence and burden of disease

Cervical cancer is the second leading cause of death in women worldwide. In Canada in 2010, there will be an estimated 1300 new cases of cervical cancer and 370 deaths from cervical cancer.¹³ For women aged 15-44 years, other estimates have cervical cancer as the third most common form of cancer accounting for 10% of cases.^{14,15} The peak age of

women with cervical cancer tends to be a decade younger than for other cancers thus affecting women in their reproductive and economically productive years.

The current age standardized incidence of cervical cancer in Canada is 7/100,000 and for mortality it is 2/100,000.¹⁶ Of note, age standardized incidence rates have declined from 21.6 per 100,000 in 1969 to 7 per 100,000 in 2010; age-standardized mortality rates from invasive cervical cancer have similarly declined from 7.4 per 100,000 females in 1969 to 2 per 100,000 females in 2010 (stable since 1992).¹⁷ Since the mid-70s the rate of decline in incidence rates has slowed, particularly among women under 50 years.^{15,17,18}

Data from British Columbia indicate that while mortality and incidence rates of invasive cancer have decreased since the introduction of an organized program of cervical screening in 1949, there has been an increase in the number of cases of in-situ carcinomas from 12.3 per 100,000 in 1955 to 133.6 per 100,000 in 1985.^{17,19} The increased uptake of cervical screening over this period has led to this apparent increase in incidence, but part of the increase may be due to changing lifestyles (e.g. early onset of sexual activity, multiple partners).

c. Etiology and natural history

Cervical cancer develops as a result of loss of cell cycle regulation. This is caused by incorporation of parts of the HPV (i.e., E6 and E7 regions) into the nucleus of an epithelial cell. There are more than 100 HPV types; more than 30 types are known to cause genital infection. These types are broadly classified as high or low risk for cervical cancer, and some 18 types are considered high-risk or oncogenic. HPV 16 and 18 are responsible for 70% of all cervical cancers. Currently 10% of Canadian women harbor HPV at any point in time.^{15,20}

d. Risk factors

Oncogenic HPV is the etiologic agent for cervical cancer. Infection with oncogenic HPV is related to long known risk factors for cervical cancer including: smoking,^{21,22} early age of intercourse, multiple sexual partners, a partner with a history of multiple partners, and long term use of oral contraceptive pills.²³ HPV is a necessary but insufficient precursor to cancer. Cofactors that may modulate the incorporation of the HPV DNA into the host cervical cell include: age, other sexually transmitted infections (e.g., *C. trachomatis*), immunosuppression (e.g., HIV), nutritional deficits (e.g., vitamin A) and possibly silent genetic polymorphisms.²⁴

e. Consequences of untreated pre-invasive disease

In an unethical clinical study which took place in New Zealand between 1965 and 1974, women with CIN 3 (severe dysplasia or HSIL) were not offered treatment. After a judicial inquiry, the results of this medical practice were later published.²⁵ From 1955-1976, 1063 women had CIN 3 on biopsy. Of the 143 who were not treated, 31.3% (95% CI 22.7-42.3) went on to invasive cervical or vaginal cancer at 30 years and 50.3% (37.3-64.9) had persistent disease within 24 months. In the group that had appropriate treatment, only 0.7% (0.3-1.9) went on to cancer.

More recently, Sankaranarayanan (2009) conducted a cluster-randomized study of 131,746 women age 30 to 59 years old in rural India. They were randomized to either the current standard of care (no screening) or one of three once in a life-time screening strategies. He showed that no screening had the highest rate of death from cervical cancer.²⁶ Thus it is clear that a proportion of preinvasive cervical disease progresses to cancer if left untreated, and that screening can prevent death from cervical cancer.

f. Rationale for screening

There is widespread acceptance of the value of regular cervical cancer screening as the single most important public health strategy to reduce cervical cancer mortality. The implementation of the Pap test in the 1950s was never evaluated using a randomized study. Rather, population based assessments showed that cervical cancer incidence and mortality (for example in British Columbia) fell by 60-90% once this screening strategy was implemented.^{27,28} Cervical cytology identifies preinvasive disease which if treated prevents the occurrence of cancer (or leads to identification of the cancer at an earlier stage permitting more effective treatment). The only prospective randomized study evaluating the Pap test was conducted in India. As mentioned above (Sankaranarayanan, 2009), women were randomized into one of 4 groups. There was a trend for decreased mortality for cervical cancer with a once in a lifetime Pap test but this did not reach statistical significance (HR 0.89 95% CI 0.62-1.27).²⁶ The studies that evaluate one-time testing do not reflect the impact of routine repeated screening over time.

g. Screening strategies

The screening strategies considered in this review are the Pap test and primary oncogenic HPV testing. Conventional Pap test screening has a moderate sensitivity (60-80% for high grade lesion and lower for low grade lesions)²⁹ and specificity of 91%³⁰ and is acceptable to most women. Pap test screening in clinical practice is currently moving away from using conventional cytology methods in favor of liquid-based cytology. Primary HPV testing is performed on a swab taken from the cervix. When liquid based cytology is abnormal, the remaining aliquot can be sent for HPV testing (called Reflex testing).

The presence of an oncogenic HPV may represent a transient infection in young women but the persistence of an oncogenic HPV as a woman approaches 30 years of age increases the likelihood of progressive disease.³¹ Thus the use of the HPV test in women over 30 has been evaluated as a possible screening test. The use of Hybrid capture II test (which identifies the presence of 15 oncogenic oncology HPV types) has a sensitivity for HSIL of 82% and a specificity of 78%.²⁹

Outcomes of cervical cancer screening such as identification of preinvasive or early invasive disease and decreased mortality must be put into the context of costs to the individual and the health care system, as well as the individual and health care system costs of overdiagnosis and over-treatment. Consideration of benefits, harms and costs is complicated by variations in risk factors, type and stage of cancer. At younger ages, (under 25 years), there are much higher rates of early abnormalities and therefore referral

for further investigation and biopsy, although the incidence of cancer is very low.³² Such positive findings on screening produce emotional costs such as anxiety and worry for patients and their families, and financial costs to the individual and health care system as a result of additional diagnostic tests. Procedures may also cause harm through scarring of the cervix, and the effects this may have on fertility and pregnancy outcomes. Starting screening at later ages therefore reduces the burden on both women and the health care system, at a small risk of missing some early disease.

Using a modeling approach, Kulasingam showed that for Canada, efficiency curves indicate that the current screening strategy of Pap tests beginning at 18 years of age was the most costly strategy at \$221,322 per life year gained (LYG).³³ Screening beginning at age 25 years with HPV testing every five years or every three years had a cost of \$6,720 or \$24,257 per LYG respectively. Screening with HPV beginning at 18 years and Pap triage cost \$47,319 per LYG. Screening with Pap at 18 years with HPV triage was \$79,481 per LYG. All strategies of HPV test with Pap triage had incremental cost effectiveness ratios (ICERS) of < \$50,000 per LYG.³³

h. Interventions/treatments

On first glance, the Pap test appears to be a low cost strategy by which cells are retrieved from the cervix. The test is sent to the cytology lab where roughly 8% of Canadian women are found to have a varying degree of abnormalities. However, women with abnormalities require follow-up with either a repeat Pap test, HPV testing, which is more sensitive, or colposcopy, which can be the diagnostic test. Thus considering the costs of Pap tests alone underestimates the true costs of screening for cervical cancer. Given that HPV testing is not funded by most Canadian provincial Ministries of Health, the majority of women who require more than a repeat Pap test are referred for colposcopy. Here the cervix is inspected with a microscope that enlarges the view of the cervix 5-15 fold. After the application of 3-5% acetic acid, visually abnormal areas are identified and biopsied. The cumulative results of the Pap test, the inspected cervix and the biopsy help the physician determine the next step in management. The goal of therapy is to remove CIN 2 or 3 lesions so as to prevent progression to cervical cancer.¹⁰

Removal of the preinvasive disease is usually outpatient therapy using freezing (cryotherapy), evaporation of abnormal cells (Laser), removal of abnormal cells with a hot wire through a loop electrosurgical excision procedure (LEEP), or surgical excision (cold knife cone biopsy). Each of these techniques is associated with their own benefits and side effects. Close follow-up is required following treatment to ensure that the disease has been successfully eliminated.¹⁰

In the event that early stage cervical cancer is identified by one of the excisional techniques, further assessment to determine the extent of disease is required including a chest x-ray, lab tests (e.g. complete blood count, renal function tests) and sometimes a CT scan and/or MRI of the abdomen and pelvis. If the disease is confined to the cervix, radical surgery (radical hysterectomy and pelvic lymph node dissection) or radical radiation therapy with adjuvant chemotherapy is recommended. If the woman wishes to preserve her fertility, in some situations it is possible to retain the uterus by conducting a

radical trachelectomy and pelvic node dissection. As the treatment becomes more radical, the side effects of treatment are more complex. However, the goal is to cure the patient of her cervical cancer. Close follow-up is required to determine if the disease has been eliminated, define early recurrence, deal with complications, and survivorship issues.³⁴

i. Current clinical practice guidelines

In their 2003 recommendations, the U.S. Preventive Services Task Force (USPSTF)³⁵ found strong evidence for conducting cervical cancer screening on women who have been sexually active and who have a cervix. There was limited evidence for any benefit of screening women older than age 65 years if they had adequate recent screening with normal Pap tests and were not otherwise at high risk for cervical cancer. Thus the USPSTF recommend against screening this population. There was fair evidence to recommend against routine Pap test screening of women who have had a hysterectomy for benign disease. They USPSTF felt the evidence was insufficient to recommend for or against the routine use of new technologies (i.e., liquid-based cytology) to screen for cervical cancer and they also felt the evidence was insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer.

In Canada, several guidelines of varying quality address various aspects of the cervical cancer screening program. Since health care is primarily a provincial responsibility, most are provincial in scope. There is a Health Canada Programmatic Guideline for screening for cancer of the cervix, published in 1998. The goal of this document was to address quality management in the cervical screening program in each province of Canada. While this is the only national document available, the recommendations in this document are stated as being “based on opinion and expertise” of the panel of members. For this reason and the fact the document is more than a decade old, it will not be discussed here.¹⁷

Adherence to guideline recommendations has not been ideal. Recently the Project for an Ontario Women’s Health Evidence-Based Report (POWER) (2010) independently reviewed the quality of cervical screening in Ontario³⁶ There were 3.7 million women 18-70 years of age eligible for screening between 2003-2005 in Ontario, of whom 69% had a Pap test in the prior three years. This is lower than the Cancer Care Ontario target for cervical screening of 85%.³⁷ In an earlier 2003 Canadian Health Survey, Ontario women age 18-69 years self reported that 73.9% had undergone a Pap test within the prior three years and 11.7% had never had a Pap test.³⁸ This patient reported rate is slightly higher than, but in keeping with the POWER study 3 year Pap test rate. Keeping in mind variations in study designs, the POWER study rate is actually lower than the 1998/1999 Pap test rates of 82.2%³⁹ or the 2001-2003 rate of 78.7%⁴⁰ for hysterectomy corrected women age 20-69 years. The rates reported in the POWER study varied by age, income and region ($p < 0.0001$). Only 44% of those with a low-grade abnormality had a repeat Pap test or colposcopy within six months and this varied by age, income and region ($p < 0.0001$). Among women with an unsatisfactory Pap test, only 35% were retested within four months and this varied by age with 31% of women 45 to 70 years of age having follow-ups compared to 38% of 18-24 year olds and 42% of 25 to 44 year olds.⁴⁰

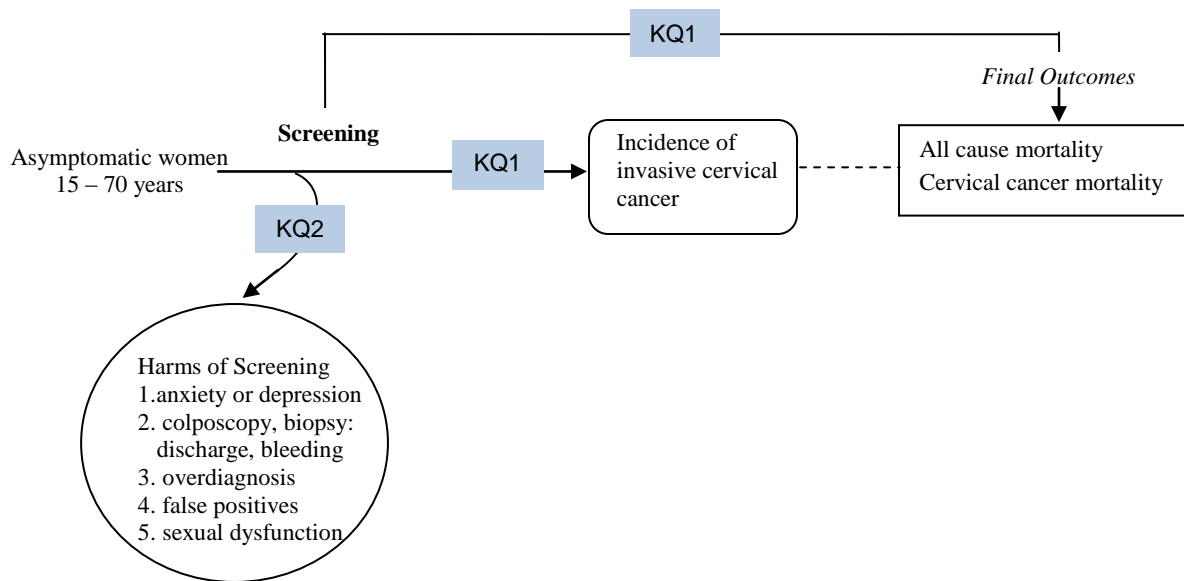
2. Previous Review and CTFPHC Recommendations

The previous Canadian Task Force recommendations were last updated in 1991 and reviewed in 1999.¹ At that time, annual screening was recommended following initiation of sexual activity or at age 18 years. After two normal screens, screening was then recommended every three years to age 69 years. Risk factors for increasing frequency were age of first intercourse <18 years of age, many sexual partners, smoking, or low socioeconomic status.

3. Analytic Framework

The analytic framework illustrating the key questions and related outcomes is depicted below in Figure 1.

Figure 1. Analytic framework: screening for cervical cancer



4. Key and Contextual Questions

Key Questions

KQ1. What is the effect of cervical cancer screening on incidence of and mortality from invasive cervical cancer?

KQ1a. Do liquid-based methods of cytology reduce incidence of or mortality from invasive cervical cancer compared to slide-based techniques?

KQ1b. Does either primary or reflex HPV testing reduce incidence of or mortality from invasive cervical cancer compared to conventional cytologic screening?

KQ1c. Does computer assisted screening reduce incidence of or mortality from invasive cervical cancer compared to conventional cytologic screening?

KQ1d. How does varying the screening interval affect the incidence and mortality of invasive cervical cancer?

KQ1e. How does varying the age at which screening is started or stopped reduce the risk and mortality of invasive cervical cancer?

KQ2. What are the harms of cervical cancer screening? (Including: colposcopy and biopsy procedures, anxiety/depression, sexual dysfunction, over diagnosis and false-positives)

KQ2a. At what rates do these harms occur, by age, and with different screening intervals?

Contextual Questions

CQ1. What are the harms of treatment of cervical cancer?

CQ1a. Harms of total hysterectomy: incontinence, infection, hospitalization

CQ1b. Harms of radiotherapy.

CQ1d. Harms of cone biopsy (immediate and late): preterm labour, miscarriage

CQ1e. Harms of LEEP: immediate and late effects

CQ1f. Effects of treatment such as anxiety, depression and sexual dysfunction

CQ2. What is the effect of cervical cancer screening in subgroups: reduction in mortality and/or morbidity, and harms? Subgroups include:

i) aboriginal populations,

ii) rural populations,

iii) immigrants,

iv) pregnant women,

v) women who have sex with women,

vi) immunocompromised women (eg with HIV),

vii) women who have had a hysterectomy,

viii) women who have received the HPV vaccination, and

ix) women who have multiple partners or a change in partners (they may be at a higher risk of HPV infection and progression)

Is there evidence that women from any of these groups have a higher risk of invasive cervical cancer, or greater risk of harms (of screening), and if so, is there evidence that screening policies should be different for any of these groups: more or less frequent or with different starting/stopping rules?

- CQ3. What are the resource implications and cost effectiveness of cervical cancer screening in Canada?
- CQ4. What are patients' values and preferences regarding cervical cancer screening?
- CQ5. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of cervical screening?
- CQ5a. What is the evidence of the value of organized programs for cervical cancer screening?
- CQ6. What is the evidence on using different categories of healthcare professionals to perform Pap smears in medical or different settings?
- CQ7. What is the evidence of the value (acceptability, participation rates) of women self-sampling for HPV testing?

5. Literature Search and Review

The USPSTF last updated its review on cervical cancer screening in 2003. For this review, Medline, EMBASE and Cochrane Central will be searched from 2000 to November 2010. EMBASE was not searched in the USPSTF, and most of the contextual questions were not searched; therefore, all searches will go back to 2000. There are three separate search strategies. The first search (KQ1) focuses generally on cervical cancer screening and includes both RCTs and observational studies. The second search (KQ2) focuses on adverse events for cervical cancer screening. The third search focuses on the contextual questions, including adverse events of cervical cancer treatment. All three search strategies combine subject heading and text word terms for cervical cancer and screening adapted to be appropriate for each database. The fourth search will be a grey literature search of websites to find relevant Canadian statistics.

6. Inclusion/Exclusion Criteria

Population: *Inclusion:* Women who are at risk for cervical cancer, between ages of 15 and 70 years, who are sexually active. (Studies that examine age groups separately will be of great value).

Country: *Any:* Consideration will be given to studies that can be generalized to the context of the Canadian Health Care System.

Screening methods: Conventional Pap tests, liquid-based Pap tests, HPV DNA testing

Comparison: No screening, conventional Pap tests, liquid-based Pap tests, HPV DNA testing

Studies of celibate or single partner groups can be included as low risk comparison groups

Outcomes: *Of screening:* Incidence of invasive cervical cancer (squamous and adenocarcinoma); cervical cancer mortality and all cause mortality

Exclude: corpus uteri cancer

Harms: *Of screening:* anxiety and/or depression; sexual dysfunction; colposcopy and biopsy procedures (discharge, bleeding); over diagnosis (high grade lesions and early “cancer” that would otherwise not have developed into invasive potentially fatal cancers); false positives

Timing of
outcome

measurement: Two years or greater

Setting: Generally whole of population studies

Study design: Meta-analyses, RCTs, observational studies (cohort studies), case control studies

Language: English, French

7. Quality and Strength of Evidence Criteria

To answer the questions we will use a staged approach, looking first for RCT studies but using lower grade evidence where RCTs are not available. We will first search for studies of the final outcomes (reduced mortality) and then the intermediate outcome (incidence of invasive cancer). If such studies are not available or not sufficient, only then will we look for studies that report high grade disease and early cancers (which have been histologically proven) as their outcome, bearing in mind that there may be a larger number of these outcomes reported, and that their relationship to invasive cancer and cancer mortality is less clear. We will therefore search for any studies that demonstrate the exact level of this relationship.

Although the ‘timing of the outcome measurement’ is stated as two years or greater for both the final outcome (mortality) and the intermediate outcome (incidence of invasive cervical cancer), the ERSC will also search for studies where the follow-up time is less than two years. This group of studies will be set aside and only reviewed if: i) there is not enough evidence using a follow-up period of two years or greater, and ii) the cervical cancer working group decides on the appropriate revised follow-up period.

The retrieved included studies will be reviewed according to the criteria set out in the CTFPHC Procedure Manual.

8. Appendix 1: Search Strategy

Question 1

MERSC_CervicalScreen_Q1_medline

Nov 1 2010

1. Cervix Uteri/
2. Uterine Cervical Neoplasms/
3. ((cervix or cervical) adj2 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
4. Cervical Intraepithelial Neoplasia/
5. Uterine Cervical Dysplasia/
6. Papillomavirus Infections/ or Papillomaviridae/
7. or/1-6
8. "Early Detection of Cancer"/
9. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
10. vaginal smears/
11. (early adj (detection or diagnosis)).ti,ab.
12. mass screening/ or screen*.ti,ab.
13. DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
14. or/8-13
15. 7 and 14
16. (hpv adj3 (screen* or test*)).tw.
17. 15 or 16
18. limit 17 to (english or french)
19. limit 18 to yr="2000 -Current"
20. limit 19 to (comment or editorial or letter or newspaper article)
21. 19 not 20
22. exp randomized controlled trials as topic/
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. (random* or sham or placebo*).tw.
26. placebos/
27. random allocation/
28. single blind method/
29. double blind method/
30. ((singl* or doubl* or trebl* or tripl*) adj25 (blind* or dumm* or mask*)).ti,ab.
31. (rct or rcts).tw.
32. (control* adj2 (study or studies or trial*)).tw.
33. or/22-32
34. 21 and 33
35. Epidemiologic studies/
36. exp case control studies/
37. exp cohort studies/
38. Case control.tw.
39. (cohort adj (study or studies)).tw.
40. Cohort analy\$.tw.

41. (Follow up adj (study or studies)).tw.
42. (observational adj (study or studies)).tw.
43. Longitudinal.tw.
44. Retrospective.tw.
45. Cross sectional.tw.
46. Cross-sectional studies/
47. or/35-46
48. (animals not humans).sh.
49. 47 not 48
50. 21 and 49
51. 50 not 34
52. 34 or 51

Question 2

MERSC_CervicalScreen_Q2ae_medline

Nov 2 2010

1. Cervix Uteri/
2. Uterine Cervical Neoplasms/
3. ((cervix or cervical) adj2 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
4. Cervical Intraepithelial Neoplasia/
5. Uterine Cervical Dysplasia/
6. Papillomavirus Infections/ or Papillomaviridae/
7. or/1-6
8. "Early Detection of Cancer"/
9. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
10. vaginal smears/
11. (early adj (detection or diagnosis)).ti,ab.
12. mass screening/ or screen*.ti,ab.
13. DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
14. or/8-13
15. 7 and 14
16. (hpv adj3 (screen* or test*)).tw.
17. 15 or 16
18. exp diagnostic errors/
19. (adverse adj2 (effect? or event?)).tw.
20. (overtest\$ or overdiagnos\$ or over-test\$ or over-diagnos\$).mp.
21. misdiagnos\$.mp.
22. (false\$ adj (positiv\$ or negativ\$)).mp.
23. ((incorrect\$ or false\$ or wrong\$ or bias\$ or mistake\$ or error\$ or erroneous\$) adj3 (result\$ or finding\$ or test\$ or diagnos\$)).mp.
24. ((inappropriat\$ or unnecess\$ or unneed\$) adj3 (treat\$ or Surg\$ or therap\$ or regimen\$)).mp.
25. (observ\$ adj3 bias\$).mp.
26. exp Abortion, Spontaneous/
27. exp Obstetric Labor, Premature/
28. Anxiety/

29. Sexual Dysfunctions, Psychological/ or Sexual Dysfunction, Physiological/
30. Depression/
31. or/18-30
32. 17 and 31
33. LEEP.tw.
34. 31 and 33
35. Colposcopy/ae, ct [Adverse Effects, Contraindications]
36. Vaginal Smears/ae, ct [Adverse Effects, Contraindications]
37. mass screening/ae, ct
38. Laser Therapy/ae, ct [Adverse Effects, Contraindications]
39. Electrosurgery/ae, ct [Adverse Effects, Contraindications]
40. cryosurgery/ae, ct
41. or/34-40
42. 7 and 41
43. 32 or 42
44. limit 43 to (english or french)
45. limit 44 to yr="2000 -Current"

Context Questions

MERSC_CervicalScreen_ContextQ_medline

Nov 2 2010

1. Cervix Uteri/
2. Uterine Cervical Neoplasms/
3. ((cervix or cervical) adj2 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
4. Cervical Intraepithelial Neoplasia/
5. Uterine Cervical Dysplasia/
6. Papillomavirus Infections/ or Papillomaviridae/
7. or/1-6
8. "Early Detection of Cancer"/
9. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
10. vaginal smears/
11. (early adj (detection or diagnosis)).ti,ab.
12. mass screening/ or screen*.ti,ab.
13. DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
14. or/8-13
15. 7 and 14
16. (hpv adj3 (screen* or test*)).tw.
17. 15 or 16
18. Indians, North American/
19. first nations.tw.
20. native canadian?.tw.
21. (aboriginal? and canada).tw.
22. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian).mp.
23. exp Canada/
24. or/18-23
25. 17 and 24

26. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
27. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
28. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
29. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
30. willingness to pay.tw.
31. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
32. or/26-31
33. 17 and 32
34. exp "Costs and Cost Analysis"/
35. 17 and 34
36. Radiotherapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
37. Hysterectomy/ae, ct, co, mo [Adverse Effects, Contraindications, Mortality]
38. Uterine Cervical Neoplasms/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]
39. Cervical Intraepithelial Neoplasia/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]
40. Cervix Uteri/de, dt, ra, su, th [Drug Effects, Drug Therapy, Radiography, Surgery, Therapy]
41. 36 or 37
42. 7 and 41
43. (adverse adj2 (effect? or event?)).tw.
44. ((inappropriat\$ or unnecess\$ or unneed\$) adj3 (treat\$ or Surg\$ or therap\$ or regimen\$)).mp.
45. exp Abortion, Spontaneous/
46. exp Obstetric Labor, Premature/
47. Anxiety/
48. Sexual Dysfunctions, Psychological/ or Sexual Dysfunction, Physiological/
49. Depression/
50. ae.fs.
51. exp Urinary Incontinence/
52. infection/ or pelvic infection/ or surgical wound infection/
53. or/43-52
54. 38 or 39 or 40
55. 53 and 54
56. 42 or 55
57. Papillomavirus Vaccines/
58. 7 and 57
59. Immunocompromised Host/
60. exp HIV/
61. 59 or 60
62. 7 and 61
63. Homosexuality, Female/
64. 7 and 63
65. Hysterectomy/

- 66. 15 and 65
- 67. 25 or 33 or 35 or 56 or 62 or 64 or 66
- 68. limit 67 to (english or french)
- 69. limit 68 to yr="2000 -Current"

Reference List

1. Morrison, B. J. Screening for cervical cancer. In: Canadian Task Force on the Periodic Health Examination Canadian Guide to Clinical Preventive Health Care Ottawa: Health Canada. 1994. 870-881. Accessed 2010 Nov 23. at <http://www.198.103.98.77/publicat/clinic-clinique/pdf/s10c73e.pdf>.
2. McLachlin CM, Mai VMJ, Fung Kee Fung M, Chambers A, and Members of the Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program and the Gynecology Cancer Disease Site Group of Cancer Care Ontario. Cervical screening: a clinical practice guideline. Toronto, ON: Program in evidence-based care; a cancer care ontario program; 2005. Available at http://www.cancercare.on.ca/pdf/pebc_cervical_screen.pdf.
3. American College of Obstetricians and Gynecologists (ACOG). Cervical cytology screening. Washington, DC: American College of Obstetricians and Gynecologists (ACOG); 2009. (ACOG practice bulletin; no. 109). Available at <http://www.guideline.gov/content.aspx?id=15274>.
4. Institute for Clinical Systems Improvement (ICSI). Preventive services for adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI). Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); 2009.
5. Kaiser Permanente National Cervical Cancer Screening Guideline Development Team. Cervical cancer screening guideline: October 2006. Oakland CA: Kaiser Permanente Care Management Institute; 2006.
6. Michigan Quality Improvement Consortium. Adult preventive services (ages 50-65+). Southfield, MI: Michigan Quality Improvement Consortium; 2008.
7. Michigan Quality Improvement Consortium. Adult preventive services (ages 18-49). Southfield, MI: Michigan Quality Improvement Consortium; 2008. Available at [www.mqic.org/.../MQIC_2008%20Adult_Preventive_Services_Guideline_\(Ages_18-49_Yrs.\).pdf](http://www.mqic.org/.../MQIC_2008%20Adult_Preventive_Services_Guideline_(Ages_18-49_Yrs.).pdf).
8. Murphy KJ and Howlett R. Screening for cervical cancer. In: Canadian consensus guidelines on human papillomavirus. *J Obstet Gynaecol Can.* 2007;8(Suppl 3):s27-36.
9. What is cancer: defining cancer. 2010. Available at: <http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer>.
10. Wright TC, Jr., Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, and Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol.* 2007;197(4):340-5.
11. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T, Jr., and Young N. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002;287(16):2114-9.

12. Stehman FB, Perez CA, Kurman RJ, and Thigpen JT. Uterine cervix. In: Hoskins WJ, Perez CA, Young RC, editors, Principles and practice of gynecologic oncology. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1997. Chapter 29, p. 785-857805.
13. Canadian Cancer Society's Steering Committee. 2010. Available at: <http://www.mentalhealthcoalition.ca/steeringcommittee.html>.
14. Cancer Care Ontario. Cancer in young adults in Canada. Toronto, ON; 2006. Available at <http://www.phac-aspc.gc.ca/publicat/cyac-cjac06/index-eng.php>.
15. WHO/ICO (Institut Català d'Oncologia) Information Centre on HPV and Cervical Cancer. 2010. Available at: <http://www.who.int/hpvcentre/en/>.
16. Canadian Cancer Society, Statistics Canada PTCR, and Public Health Agency of Canada. Canadian Cancer Statistics 2010. 2010. Available at <http://www.cancer.ca>.
17. Health Canada and Society of Gynecologic Oncologists of Canada. Programmatic guidelines for screening for cancer of the cervix in Canada. 1998. Cat. No: H39-436/1998E. Available at www.phac-aspc.gc.ca/cd-mc/pdf/screening.pdf.
18. Laboratory Centre for Disease Control. 2010. Unpublished Work
19. Anderson GH, Boyes DA, Benedet JL, Le Riche JC, Maticic JP, Suen KC, Worth AJ, Millner A, and Bennett OM. Organisation and results of the cervical cytology screening programme in British Columbia, 1955-85. *Br Med J (Clin Res Ed)*. 1988;296(6627):975-8.
20. International Agency for Research on Cancer and World Health Organization. Globocan 2008: cancer incidence and mortality worldwide in 2008. [http://www globocan iarc fr/](http://www.globocan.iarc.fr/). 2010.
21. de Vet HC, Sturmans F, and Knipschild PG. The role of cigarette smoking in the etiology of cervical dysplasia. *Epidemiology*. 1994;5(6):631-3.
22. Lyon JL, Gardner JW, West DW, Stanish WM, and Hebertson RM. Smoking and carcinoma in situ of the uterine cervix. *Am J Public Health*. 1983;73(5):558-62.
23. Vaccarella S, Herrero R, Dai M, Snijders PJ, Meijer CJ, Thomas JO, Hoang Anh PT, Ferreccio C, Matos E, Posso H, de SS, Shin HR, Sukvirach S, Lazcano-Ponce E, Ronco G, Rajkumar R, Qiao YL, Munoz N, and Franceschi S. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev*. 2006;15(11):2148-53.
24. Wang SS, Zuna RE, Wentzensen N, Dunn ST, Sherman ME, Gold MA, Schiffman M, Wacholder S, Allen RA, Block I, Downing K, Jeronimo J, Carreon JD, Safaeian M, Brown D, and Walker JL. Human papillomavirus cofactors by disease progression and human papillomavirus types in the study to understand cervical cancer early endpoints and determinants. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):113-20.

25. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, and Skegg DC. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008;9(5):425-34.
26. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, and Dinshaw KA. HPV screening for cervical cancer in rural India. *N Engl J Med.* 2009;360(14):1385-94.
27. IARC Working Group On Evaluation Of Cervical Cancer Screening Programmes. Screening For squamous cervical cancer: duration Of low Risk after negative results of cervical cytology and Its implication for screening policies. *British Medical Journal (Clinical Research Edition).* 1986;293(6548):659-64.
28. Sasieni PD, Cuzick J, and Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. *Br J Cancer.* 1996;73(8):1001-5.
29. McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, Myers E, and Nanda K. Evaluation of cervical cytology. Rockville, MD: Agency for Health Care Policy and Research (US); 1999. 5. Available at PM:11925972.
30. University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. <[11] Journal> 1999;353(9156):869.
31. Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, Roberts C, Desai M, and Peto J. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health Technol Assess.* 2009;13(51):1-iv.
32. Towards Optimized Practice Program. Screening for cervical cancer. 2009. Available at: http://www.topalbertadoctors.org/informed_practice/cpgs/cervical_cancer.html.
33. Kulasingam SL, Rajan R, St PY, Atwood CV, Myers ER, and Franco EL. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. *BMC Med.* 2009;7:69.
34. Hoskins WJ, Perez CA, and Young RC. Principles And Practice Of Gynecologic Oncology. 2nd ed. Hagerstown, MD: Lippincott Williams & Wilkins; 1996.
35. Hartmann KE, Hall SA, Nanda K, Boggess JF, and Zolnoun D. Screening for cervical cancer: U.S. Preventive Services Task Force evidence syntheses, formerly systematic evidence reviews. Rockville, MD: Agency for Healthcare Research and Quality (US) TI - U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews; 2002. Prepared for: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.1 Contract No. 290-97-0011, Task Order No. 3. Technical Support of the U.S. Preventive Services Task Force. Prepared by: Research Triangle Institute/University of North Carolina.2. Available at <http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm>.

36. Krzyzanowska MK, Barbera L, Elit L, Kwon J, Lofters A, Saskin R, Yeritsyan N, and Bierman AS. Project for an Ontario Women's Health Evidence-Based Report (POWER) Study: Cancer Chapter 4. Toronto, ON: The POWER Study: Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital; 2010. Volume 1. Available at <http://www.powerstudy.ca/the-power-report/the-power-report-volume-1/cancer>.
37. Angus H, Nadalin V, and Greenberg A. The quality of cancer services for women in Ontario: summary report. Toronto, ON: Ontario Women's Health Council; 2006. Available at <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13712>.
38. Cancer System Quality Index. 2010. Available at: <http://www.cancercare.on.ca/ocs/qpi/csqi/>.
39. Cancer Care Ontario. 2010. Available at: <http://www.cancercare.on.ca/>.
40. Ontario Cervical Screening program. 2010. Available at: http://www.cancer.ca/ontario/prevention/get%20screened/od-ontario%20cervical%20cancer%20screening%20programs.aspx?sc_lang=en.